Draft Guidance for Industry and Food and Drug Administration Staff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 Artificial Pancreas 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DRAFT GUIDANCE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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Contains Nonbinding Recommendations
Draft - Not for Implementation

Draft Guidance for Industry and Food and Drug Administration Staff

The Content of Investigational Device Exemption (IDE) and Premarket Applications for Artificial Pancreas Device 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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance is intended to provide recommendations to Sponsors or Applicants[1] planning to develop and submit an Investigational Device Exemption (IDE) or premarket approval (PMA) application for an Artificial Pancreas Device System (APDS) for single patient use in the home environment. FDA recognizes the need for guidance on the least burdensome means of development for these innovative device systems. Due to the evolving nature of these device systems, it is expected that they will develop incrementally. The recommendations contained in this guidance are intended to provide adequate guidance and instruction to facilitate the development and marketing of the APDS while, at the same time, adopting a flexible approach.

This guidance discusses the development and evaluation of APDS. We describe both nonclinical and clinical approaches to establishing the safety and effectiveness of an APDS, and suggest areas where there is flexibility in the pathway to market for these devices. Specifically, Section VII and Appendix A of this guidance provide detailed information to

[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.

assist Sponsors in assembling information to support an IDE submission, while Sections IV – VI set out the criteria FDA will use in evaluating an APDS for premarket approval (PMA).

This document does not provide guidance on the evaluation of low glucose suspend (LGS) systems. We issued draft guidance in June 2011 that provided recommendations for Sponsors or Applicants planning to develop and submit an IDE or PMA for an LGS system for use in the home environment.

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.

II. Background

A. Overview

This guidance lays out many of the possible options for the design, testing and marketing of an APDS, but it is by no means all-inclusive. Our intent is to provide the most flexible recommendations to guide Sponsors in designing and testing these devices that are consistent with the least burdensome principle to provide options while assuring that testing is adequate to support marketing approval. In particular, the guidance:

- Provides an approach to allow Sponsors to proceed to outpatient studies as quickly as possible;
- Provides maximum flexibility in determining appropriate size and duration of clinical studies;
- Gives Sponsors the option to prove non-inferiority to standard therapy, but also describes study criteria to support superiority claims if the Sponsor prefers to make a superiority claim; and
- Describes approaches to leveraging existing data about the safety and effectiveness of the devices already on the market collected from studies done within and outside of the US, which minimizes the need for preclinical data.

Use of Continuous Glucose Monitor Data in the Evaluation of APDS. We have placed the primary focus for glucose measurement on a Continuous Glucose Monitor (CGM). Because patients currently need to periodically calibrate their CGM using a blood glucose measurement from a blood glucose device (BGD), we have kept the BGD as part of the APDS, but not the primary focus. Recognizing that, over time, improved CGM performance may obviate the need for periodic blood glucose checks with a BGD, we have built in the flexibility to eventually allow for the approval of APDS that do not use a BGD.

Flexibility with respect to Endpoints. We have also introduced a number of suggested examples of primary endpoints that can be used to measure the safety and effectiveness of an APDS and support a successful PMA. In addition to these endpoints, we believe that there may be alternative acceptable primary endpoints. We encourage Sponsors to discuss their choice of primary endpoint and study design with us.

Flexibility with respect to Indication. We give examples of indication statements that we believe will be the most likely indications for early APDS, and those that would be supported by the endpoints we suggest, but do not foreclose the possibility of other indication statements that can be appropriately supported. We have also set out criteria that would support superiority claims for Sponsors who wish to be able to claim that their device improves outcomes compared to other therapies.

Reasonable Study Progression allowing for Quick Outpatient Use. We have set out a clinical study progression that will move the APDS to outpatient use as quickly as possible. Each step is designed to test specific aspects of the APDS functionality and performance. The guidance describes how sponsors who believe they already have sufficient, valid scientific evidence that fulfills the purpose of a particular study phase and that justifies moving to the next study phase may do so, using clinical and non-clinical evidence, and evidence that was obtained from studies performed outside the US.

Flexibility with respect to Study Size and Duration. We have built in maximum flexibility regarding the size and duration of each study phase, while also aiming to take the least burdensome approach. We recognize that study size and duration is entirely dependent on the design and features of the APDS and its proposed indication. We recognize that each APDS will likely have unique features that affect study design. In addition, because some APDS may be composed of parts that have already been approved or cleared by FDA, we encourage Sponsors to leverage what we already know about the safety and effectiveness of the individual components to streamline the clinical testing of such a system.

We believe the recommendations contained in this guidance will, when finalized afford Sponsors the flexibility they need to design innovative, safe and effective systems to treat diabetes mellitus (DM). If you believe an alternative, less burdensome approach to investigating and developing premarket applications for these devices can satisfy regulatory requirements for investigation and approval of APDS, we encourage you to discuss that approach with the FDA.

B. Currently Marketed Devices to Treat DM

Today, patients with DM utilize a variety of devices to monitor and manage their blood glucose levels:

- Hand-held portable **BGDs** which have been cleared by FDA for home-use, allow patients to determine their blood glucose levels using blood from a finger stick. Patients use BGDs multiple times a day to help make decisions regarding insulin administration and diabetes management around meals, exercise, and other activities of daily living.

- Some patients also use continuous subcutaneous insulin infusion (CSII) via an **insulin pump** to manage their disease.

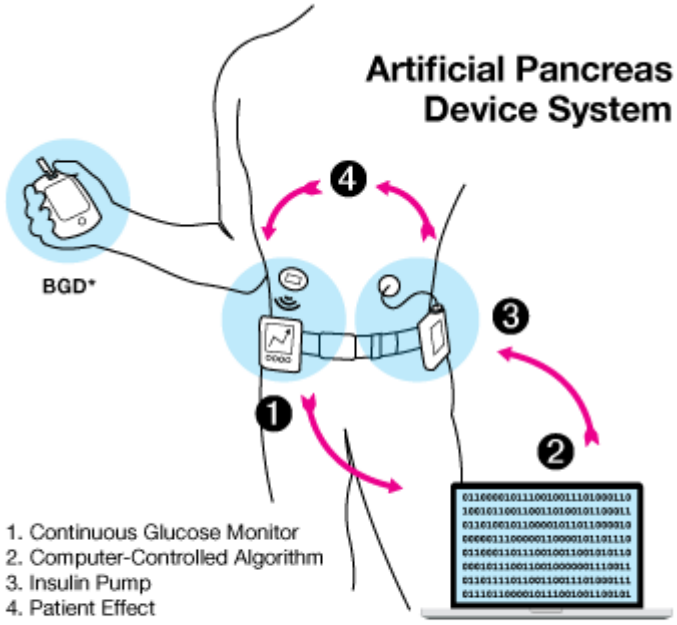
- Some patients use a **CGM system**, which uses a sensor inserted into the subcutaneous tissue and continuously (meaning, at a consistent interval) measures the concentration of glucose in the interstitial fluid. While CGM devices have not yet reached a performance level that would make them an adequate substitute for BGDs, they do allow patients to monitor trends and patterns of glucose levels in their bodies.

Even with the aid of these devices, maintaining blood glucose concentrations within a suggested optimal range is a daily struggle for people living with DM, and the risk of hypoglycemia associated with attempts at improved glycemic control remains an ever-present danger.

C. Basic Design of an APDS

APDS link a CGM to an insulin pump and automatically reduce or increase insulin infusion based upon specified thresholds of measured interstitial glucose. The APDS parts are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a specified target or range and minimize the incidence and severity of hypoglycemic (dangerously low blood sugar) and hyperglycemic (dangerously high blood sugar) events.

The illustration below describes the parts of an APDS and depicts how they work together.



(1) **Continuous Glucose Monitor (CGM).** A CGM provides a steady stream of information that reflects 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) which has been found to correlate with blood glucose levels. A small transmitter sends information to a receiver. A CGM continuously displays both an estimate of blood glucose levels and their direction and rate of change of these estimates.

> **Blood Glucose Device (BGD).** Currently, to get the most accurate estimates of blood glucose possible from a CGM, the patient needs to periodically calibrate the CGM using a blood glucose measurement from a BGD; therefore, the BGD still plays a critical role in the proper management of patients with an APDS. However, over time, we anticipate that improved CGM performance may obviate the need for periodic blood glucose checks with a BGD.

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

(3) **Infusion pump.** Based on the instructions sent by the controller, an infusion pump adjusts the insulin delivery to the subcutaneous tissue.

(4) **The Patient.** The patient is an important part of the APDS. The concentration of glucose circulating in the patient's blood is constantly changing. It is affected by the patient's diet, activity level, and how his or her body metabolizes insulin and other substances.

D. Different APDS Types

Although the fundamental parts described above are common to all APDS, different device designs, algorithms, and patient management strategies create the potential for different APDS types including:

- A **Control-to-Range (CTR) system** that reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person's glucose levels approaches predetermined thresholds. When a patient's blood glucose concentration is within the specified range, the infusion pump will not take any action based upon CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump and give pre-meal bolus insulin to maintain control of their glucose levels.

- A **Control-to-Target (CTT) system** that sets target glucose levels and tries to maintain these levels at all times. This system is fully automated and requires no interaction from the user (except for calibration of the continuous glucose monitoring system). There are two subtypes of CTT systems currently being investigated (i.e., insulin-only and bi-hormonal) and a hybrid system option (patient administration of a pre-meal or partial pre-meal insulin bolus) that can be used in either of the system types.
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CTR and CTT System Subtypes are dependent upon the drug or drugs being delivered and how each drug affects blood glucose concentrations. Subtypes may include:

- An **insulin-only system** that achieves a target glucose level by increasing or decreasing the amount of insulin infused.

- A **bi-hormonal control system** that achieves a target glucose level by using two algorithms to instruct an infusion pump to deliver two different hormones — one hormone (insulin) to lower glucose levels and another (glucagon) to increase blood glucose levels. The bi-hormonal system mimics the glucose-regulating function of a healthy pancreas more closely than an insulin-only system.

III. Scope

This guidance is focused on the development, investigation and approval requirements for APDS – autonomous systems that administer insulin to maintain blood glucose concentrations within a prespecified range to maintain glycemic control and minimize the risk of hypoglycemia or hyperglycemia – for use outside a health care facility. The guidance was written to both accommodate APDS utilizing current technologies, and permit application of the principles described in this guidance to newer technologies.

As described in Section II above, the wide variety of CGMs, BGDs, insulin pumps, and control algorithms available allows for a number of different types and designs of APDS. We anticipate that some APDS will utilize already cleared or approved components. Others may utilize components that have been modified in some way. The information needed and the studies required when changes are made to the different components, or when components are substituted into an already approved APDS, will depend on the effect the change is anticipated to have on system performance. For example, additional clinical studies may not be needed if a Sponsor is able to demonstrate that a newly introduced component is similar to the previously approved version, e.g., its accuracy, susceptibility to interferences, human factors, etc.

For purposes of this document, FDA defines an APDS as including the following components:

- **Glucose Monitoring Devices – a CGM** and **BGD** used for calibrating the CGM (where applicable) plus associated reagents/test strips;
- **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); and
- **Network** (i.e., any device or system physically or wirelessly connected to the APDS)

The primary product code for an APDS is 'LHE' (controller closed-loop blood glucose), which is regulated as a class III device system.

This guidance applies only to APDS that use insulin products that have been approved by the FDA for delivery via an infusion pump, and that are used in accordance with their FDA-approved labeling. This guidance does not address data requirements for a drug labeling modification such as approval of a new drug formulation or drug delivery method. Also, this guidance may not apply to APDS that utilize synthetic or artificial cells, tissues or organs nor does it address issues that are unique to combination products.[2] Although

[2] 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,

elements of this guidance may be applicable to these circumstances, additional considerations outside the scope of this guidance may also need to be addressed.

IV. Device Description

APDS currently consist of a number of device components that communicate to form a complete system. The unique qualities of these systems stem from the interaction of the various device components to achieve the system's intended use. To unify the device description for all types of APDS, Applicants should describe: (i) the device system as a whole, and (ii) each of the functional components within the device system. FDA recommends Applicants provide the following information as part of the APDS device description:

A. APDS System Level Description

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

- A clear statement of the intended use and indications for use (see 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 system (including model numbers).
- Because the system is intended for ambulatory use, a description should be provided on features of the system designed to address issues such as 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 of features of the system designed to address how the device has been designed to be safely and effectively used by the lay population, which often have limited or no clinical background and may have functional limitations.
- Detailed description of the technological features of the system (e.g., alarms, etc.).

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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.

- Detailed description of the training for all persons involved with an APDS. See Part 8 of Section VI below for a full discussion of Human Factors and other training considerations.

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

B. Glucose Monitoring Functional Components

Applicants should provide the following information for the functional components of the APDS that serve to monitor glucose levels in the patient.

1. CGM Component

- Applicants should indicate the regulatory status of the CGM component.
  - If a modified version of an approved CGM is used, the Applicant should provide a comprehensive list and description of the modifications to the CGM and provide the rationale for the change(s). This might include instructions for use, such as the required run in period or calibration, or changes to the algorithm or physical structure.
  - If it is an already approved CGM, applicants should provide:
    - The name of the CGM and the FDA document number under which it was approved (noting the appropriate Supplement number and the date of the Supplement).
    - If the Applicant wishes to rely on information previously submitted by a different Applicant, a letter of authorization granting access to the information.

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

- Description of the methodology employed for glucose measurement (e.g., electrochemical measurement).

- Description of the sample matrix analyzed (e.g., interstitial fluid)

- Description of the anatomical site(s) into which the sensor is inserted.

- Description of the information provided by the CGM, such as the frequency of reported glucose values, trending information and alarms.

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

2. BGD Component (if applicable[3])

- The regulatory status of the BGD.
- If modified, a comprehensive list and description of all modifications and a rationale for the change(s).
- Description of the 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 or stores data or quality control results.
- A summary description of the measurement method utilized by the BGD (e.g., electrochemical, spectrophotometric measurement).
- A description of the test principle, i.e., all chemical reactions and concentration of all reagent components.
- Matrix of blood sample to be analyzed (e.g., fingerstick capillary blood).

C. Control Algorithm & Signal Processing Functional Component

The description of the control algorithm functional component should include all computational steps, including CGM signal and changes in the command for insulin delivery. The control algorithm should include the following information.

- 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 artifact or real (in addition to processing performed as part of the CGM algorithm).
- 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:

[3] Currently, to get the most accurate readings possible from a CGM, the patient needs to periodically calibrate the CGM using a blood glucose measurement from a BGD; therefore, the BGD still plays a critical role in the proper management of patients with an APDS. However, over time, we anticipate that improved CGM performance may obviate the need for periodic blood glucose checks with a BGD.

  - 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 parameters) 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 and the smallest increment that the parameter can be adjusted.
    - 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 minimum and maximum insulin delivery dose recommendation of the control algorithm.

- If applicable, a description of any safety check that the system performs to ensure insulin infusion has delivered the appropriate dose.

- Description of the signal processing from the dosing recommendation to the raw signal pump current command.

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

If the CGM is not already approved or if the algorithm has been modified and not previously reviewed by FDA, the Applicant should also provide a 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 signal processing that is performed for the calibration method.

D. Infusion Pump Functional Component

The description of the infusion pump functional component should include the following information:

- 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
  - 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

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

- Identification and description of particular infusion sets or cassettes that will be provided or recommended for use with the APDS, if any.

- 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.

- A detailed design description of the software utilized by the device, if any, including all key elements.[4]

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

E. Communication Pathway Functional Component

The description of the Communication Pathway functional component should describe the passage of information between the functional components, including 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 system. The Applicant should identify the flow of communication (e.g.,

4 See Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices for more information.

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 by wireless transmission, 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.

- Reliable communication between the various device components of the APDS is essential to ensure the correct information is passed to each device component. The Applicant should describe how the system ensures communication with only the devices approved with the system.

V. Indications for Use

The 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."[5] The indications for use statement of different APDS may differ depending on the device design and patient population. Indications should be proposed based upon the design of the control algorithm, clinical study design, and the intended patient population, although we recognize that APDS currently in the research and development phase may not have a final indication until they have been studied in depth.

The following statements are provided as examples of appropriate wording for likely indications for use:

- The APDS device system is intended for patients with type 1 diabetes for the subcutaneous infusion of insulin and the continuous measurement of interstitial glucose to aid in the management of their disease. The APDS automatically adjusts insulin delivery in response to CGM values that have exceeded or are predicted to exceed the bounds of a prespecified blood

5 See 21 CFR 814.20(b)(3)(i).

glucose range. The APDS is intended to assist the patient in achieving metabolic goals.

- The APDS device system is intended for patients with type 1 diabetes mellitus for the subcutaneous infusion of insulin and the continuous measurement of interstitial glucose to aid in the management of their disease. The APDS automatically adjusts insulin delivery in response to CGM values to maintain a prespecified target glucose. The APDS is intended assist the patient in achieving metabolic goals.

FDA recognizes, however, that alternative indication statements may be appropriate depending on the populations and endpoints studied. Sponsors who plan to submit a PMA for an APDS that is specifically intended to improve glycemic control or reduce hypoglycemia will need to provide valid scientific evidence to support those claims as required by 21 CFR 814.20(b)(3)(vi), and should be sure to measure those features as endpoints in the pivotal clinical study designed to support the PMA submission. Sponsors seeking to support different indications for use should discuss appropriate study design and labeling statements with FDA.

VI. APDS Performance

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

A. Software

Software documentation is an important aspect of device validation. The Applicant should provide complete software documentation in the PMA. Some useful guidance documents for software considerations are provided below.

- The Agency considers the APDS and all of the components of the system to be a "Major" level of concern for the purposes of software review in the PMA. 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*.

- Cyber Security - FDA recommends that the concept of information security be addressed when medical devices can store, access, and/or

transfer information externally. Information security is the process of preventing the modification, misuse, and denial of use or the unauthorized use of that information. Specific concepts are confidentiality, integrity, availability and accountability (CIAA) :

- **Confidentiality** assures that no unauthorized users have access to the information.
- **Integrity** is the assurance that the information is correct - that is, it has not been improperly modified.
- **Availability** suggests that the information will be available when needed.
- **Accountability** is the application of identification and authentication to assure that the prescribed access process is being done by an authorized user.

Communication between device components should be secure and prevent communication from other devices that are not part of the system. For additional guidance on cybersecurity, please refer to *Guidance for Industry, Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software*.

B. Report of Prior Investigations (If Applicable)

Data from prior investigations – both clinical and nonclinical -- should be included as part of the PMA to the extent applicable. The Report of Prior Investigations should include a summary of non-clinical information relied upon to address basic device safety, characterize catastrophic failure modes and risk mitigation approaches, and support an expectation that the device will function as intended. The PMA must contain, to the extent applicable, a bibliography of published reports and an identification and discussion of other data and information relevant to the safety and effectiveness of the APDS. 21 CFR 814.20(b)(6) and (8).

C. Biocompatibility

Biocompatibility testing of the APDS should be performed on the final, finished, sterilized device for all device components and accessories. The PMA should include a complete test report of each biocompatibility test performed. Alternatively, if biocompatibility information for a test component has been previously evaluated and found acceptable by FDA (such as during separate premarket review of the component), the Applicant may provide a summary of the testing procedures and study. In this case, the Applicant should reference the FDA document number.

Generally, biocompatibility tests for a PMA device should be performed keeping in mind the duration and level of contact the patient is likely to have with the device. We recommend that Sponsors consider APDS to have prolonged duration of contact with the patient because of the way the device and its accessories will be used.

For additional information and detailed instructions on biocompatibility testing, 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).

D. Sterility

Each of the device components used in the APDS 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 using methods that have been comprehensively validated by the Applicant to provide a sterility assurance level (SAL) of 10^{-6}.

The product labeling should prominently indicate whether each component is supplied in a sterile or non-sterile state. For device components that are not sterile, we recommend that the Applicant provide a scientifically valid rationale for why sterilization is unnecessary.

APDS and accessories intended for prolonged use should include instructions in the labeling for proper cleaning and disinfecting, as appropriate, between uses. Also, where appropriate, "use life" information should be provided in the labeling, with supporting information (see Subsection VI-E, 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). APDS are intended to be used in the home environment. The Applicant should indicate cleaning agents/products in the labeling that are readily available to the average home user along with validated instructions for cleaning the device in a manner that is consistent with the FDA guidance for labeling reusable devices.[6] In addition, 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]

6 See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm252999.htm.

[7] AAMI TIR 12:2010, Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturer

If sterility or the cleaning and disinfection of specific system components has been previously evaluated and found acceptable by FDA (such as during the premarket review of the component), the Applicant should provide a summary of testing procedures, the study results, and the FDA document number where additional information can be found. This approach may be acceptable if the way in which the component is used and the way it is packaged has not changed from the time of the original clearance/approval.

E. Shelf Life

The shelf life of the APDS, 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 also provide data demonstrating that the APDS can maintain the performance specifications throughout the system's shelf life. If accelerated test methods are utilized, the Applicant should demonstrate 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. The packaging 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 the real world (i.e. less-than-ideal shipping and handling conditions), 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. We recommend that confirmatory, real-time package shelf life testing be submitted as part of the PMA. We also recommend that Sponsors use recognized consensus standards for conducting these various simulations and validation tests.[9,10,11]

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[8] AAMI TIR 30:2003, A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices

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

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

If the shelf life (or expiration dating) of a system component has been previously evaluated and found acceptable by FDA (such as during the premarket review of the component), the Applicant may submit a summary of testing procedures and study results along with the FDA document number where additional information can be found. This approach is only acceptable if the way in which the component is used and the way it is packaged has not changed from the time of the original approval.

F. Electrical Safety

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

G. Magnetic Resonance (MR) Imaging Safety

Sponsors should clearly identify on the APDS and its label whether it is MR Safe, MR conditional, or MR unsafe. 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 APDS.

H. Quality of Results from Diagnostic Devices Used During the Clinical Study

Clinical studies often include in vitro diagnostic devices (IVDs) that provide information used as an endpoint of the study, e.g., Hemoglobin A1c (HbA1c), urine or blood ketone results, or blood glucose results from a device other than the BGD used to calibrate the CGM component of the APDS. Therefore, evidence is needed to support the quality of those results.

Applicants should provide the following information:

- Name of the device, and the associated reagent(s);
- An indication of the regulatory status of the device:
  - If it has already been granted marketing approval or clearance, Applicants should provide the FDA document number where additional information can be obtained, if known; or
  - If the device has not been granted marketing approval or clearance, Applicants should provide data supporting the accuracy and reliability of the device[12];

[11] ASTM D4169-09, Standard Practice for Performing Testing of Shipping Containers and Systems.
[12] *See* 21 CFR 809.10(b)(8).

- Any qualifying certifications of the reagent or test system, e.g., National Glycohemoglobin Standardization Program certification;
- Name and concentration levels of the Quality Control (QC) materials run to confirm proper performance of the device during the study;
- The frequency or points in time when QC material(s) were analyzed;
- How it was determined that the devices were functioning properly, e.g., any functional checks performed or criteria applied to QC material results; and
- A statement certifying that a copy of the labeling was provided to each user who is operating a device at home, or that it was available to staff who operated a device in an in-patient setting.

I. Human Factors

The device user interface plays a critical role in the performance of the APDS and should be considered integral to the overall performance of these systems.

Reports of device-related incidents and recalls for diabetes devices have shown that patterns of use errors resulting from deficiencies in the design of the user interface have led to patient harm. Human factors testing can help identify and mitigate these deficiencies. For this reason, FDA recommends that PMAs include comprehensive application of human factors in the design and evaluation of the user interface components of the entire APDS.

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, slide controls)
- Feedback mechanisms (e.g., auditory alarms, visual alarms, status indicators, and other messages to users)
- Graphical user interface, including representations of responses to user actions (including visual feedback related to changes in device operation or status)
- Labeling (including directions for use, user manuals, quick-start guides, package inserts, information on packaging, etc.)

Hazards associated with use of functional components of the APDS are unique in that they exist even if a device operates within its specifications. These hazards often do 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.

Analyses of use-related hazards should consider the following:

- The safety of interactions between the user and all parts of the user interface components of the system:
  - 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 auditory information, including different alarm tones and logic of alarm activation
- Potential use errors or difficulties associated with:
  - Each possible setting or input available to operators
  - Input, selection or modification of critical treatment parameters
  - Non-standard or unusual parameter settings or default values
  - Non-standard, unfamiliar or ambiguous conventions or abbreviations
  - Non-standard, ambiguous, or inadequate alarm condition or informational messages
  - Improper storage conditions (e.g., test strip/reagent storage temperature and humidity, etc.)
  - The user's inability to understand the indications for use of the device and limitations of the device.
- Potential errors associated with use of the CGM component, including:
  - Incorrect data entry during CGM calibration
  - Improper timing of CGM calibration (e.g., when conditions are not optimal)
  - Failure to calibrate the CGM at the recommended frequency
  - Failure to discontinue CGM use at the end of the sensor wear period when CGM results may be compromised (e.g., when there is no hard stop on CGM results generation)
  - Improper anatomical placement of CGM
  - Use of an expired sensor
  - Use of the CGM under inappropriate conditions
- Potential errors associated with use of the BGD used to calibrate the CGM component, including:
  - Improper fingerstick sampling technique (e.g., "milking" the finger)
  - Failure to take a fingerstick sample to confirm questionable CGM readings (e.g., that do not correspond with user's clinical symptoms or user's expectations of what glucose should be at that time)
  - Inadequate volume of blood sample collected
  - Failure to follow recommended quality control procedures
  - Improperly performing quality control procedures
  - Use of expired reagents or test strips
  - Improper storage of BGD reagents or test strips
    - Note: This error is extremely important for Applicants to address. Improper test strip storage (e.g., in car glove compartments) is identified as the most common source of error by manufacturers when consumers report an improperly functioning BGD.

- Improper handling of reagents or test strips, such as leaving the reagent bottle cap off for longer than is recommended
- Inadequate cleaning or maintenance of the BGD
- Patients using a BGD to calibrate the CGM during conditions which are contrary to use of the BGD. For example, measurements from many BGDs are affected by conditions such as ketoacidosis, hypoglycemia or ingestion of large doses of vitamin C.

The APDS development process should include human factors/usability testing to ensure that the device system will be safe and effective in the hands of the intended users. This testing should be conducted with people who are representative of the intended users and under conditions that are comparable to actual conditions of use. The intended users should be defined precisely but they might include health care providers, patients, and lay caregivers (e.g., elderly spouses or parents of children), and the users' ages and functional capabilities could span a wide range. The conditions of use should include provision of labeling, such as instructions for use, and training that is comparable to the training that actual users will receive. The testing should assess not only the user interface components of the devices in the system, but also the adequacy of the labeling and training to support users to use the system safely and effectively.[13]

J. Glucose Monitoring Functional Component

1.CGM Component

Applicants should provide appropriate information regarding the safety and effectiveness of the CGM functional component when used as part of an APDS. Applicants may find it helpful to review the FDA-recognized Clinical Laboratory Standards Institute (CLSI) POCT 05-A guideline[14] and applicable FDA guidance documents.

Applicants should provide protocols and test reports for the following performance characteristics established during the pivotal CGM trial:

- Accuracy of CGM results. Applicants should characterize accuracy by summarizing the point-to-point agreement between blood glucose reference readings and paired CGM results. Applicants should present the total and cumulative percentage (and numbers) of CGM values presented as various differences from the paired blood glucose

[13] FDA has published draft guidance on the use of human factors in optimizing medical device design, *Draft Guidance for Industry and Food and Drug Administration Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design.* Although the recommendations contained in this guidance are not in effect at this time, general information contained in the guidance about human factors considerations in medical device design is relevant to an understanding of this topic.

[14] CLSI POCT 05-A, Performance Metrics for Continuous Interstitial Glucose Monitoring

reference result (e.g., within 10, 20, 30, 40 or >40 mg/dL). FDA recommends that blood glucose reference values be stratified according to glucose concentration (as determined by the blood glucose reference values) in various glucose concentration bins (e.g., <40, 41-50, 51-60, 61-70, 71-80, 81-120, 121-180, 180-250, 250-325, and 326-400 mg/dL).

- Bias across the reportable range of the CGM. Applicants should calculate bias at various glucose concentrations (according to the blood glucose reference values) of 60, 80, 120, 180, 250, 325, and 400 mg/dL and should include 95% confidence intervals.
- Threshold alarm performance (Detection rates and false alarm rates). In addition to point-to-point alarm detection rates, detection rates should also be characterized according to whether the CGM detected the hypoglycemic and hyperglycemic event within 15 and 30 minutes of the event. False alarms should be similarly characterized in a point-to-point analysis and also in an analysis which does not consider an alarm a false alarm if the event actually occurred within plus or minus 15 and 30 minutes of the alarm.
- Prediction alarm performance. Performance of representative prediction alarms that are utilized in the APDS should be summarized. Sponsors should characterize detection rates according to whether the CGM detected the predicted hypoglycemic and hyperglycemic glucose level within the horizon setting(s). A similar analysis should be performed for the false alarm rate.
- Imprecision observed when sensors are inserted into the same anatomical site and when sensors are inserted into different anatomical sites.
- Analytical specificity, including:
    - Cross-reactivity with molecular compounds similar to glucose;
    - Interference (both endogenous and exogenous compounds/conditions, as well as both prescription and over-the-counter medications).
    - Environmental interference (e.g., from temperature or water exposure, such as bathing or swimming, etc.).

Study protocols should minimally include, as applicable: number of patients, number of samples tested, number of replicates of each sample tested, number of devices tested, matrix and concentration of the sample tested, how CGM and blood glucose reference readings were paired and the statistical analysis used.

Applicants should summarize important user functions as characterized during the CGM pivotal clinical trial, including:

- Length of sensor wear period. Applicants should present the distribution of the number of hours that sensors remained functional.

- The number and percentage of CGM results that can be expected to be generated during a wear period. Applicants should present the distribution of the number of CGM results which were generated during each individual wear period for all patients enrolled in the trial. This analysis should include data from all sensors that were calibrated and able to generate data for at least one hour. The percentages of results generated should also be calculated using the total number of values that were possible during each wear period as the denominator, i.e., the sensor had not missed any data in between the calibration and when the wear period ended.

2. BGD Component

Applicants should provide appropriate safety and effectiveness information for the Blood Glucose Device (BGD) component of the CGM. FDA recommends that Applicants refer to recent and applicable study guidelines, such as those published by the *Clinical and Laboratory Standards Institute* (CLSI), and applicable FDA guidance documents to assist with the design of the analytical and clinical evaluation studies and the data analysis.[15,16,17,18] Applicants should identify all applicable standards or FDA guidance documents they followed as they evaluated the device.

- The performance specifications of the BGD and the study protocols and data generated to verify them, including, for example:
  - Bias
  - Imprecision
  - Linearity
  - Measuring range
  - Traceability to reference materials or methods
  - Stability of device components
  - Expected values, as appropriate;
  - Detection limit (e.g., limit of blank, limit of detection, and limit of quantification), as appropriate;
  - Analytical specificity, as appropriate, including:
    - Cross-reactivity with compounds that have similar molecular structures, such as maltose;
    - Interference from endogenous compounds such as ascorbic acid; exogenous compounds such as prescription and over-

[15] CLSI EP5-A2 Protocol (Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition)
[16] CLSI EP7-A2 Protocol (Interference Testing in Clinical Chemistry; Approved Guideline- Second Edition)
[17] CLSI EP6-A document (Evaluation of the Linearity of Quantitative Measurement Procedures, A Statistical Approach; Approved Guideline, 2003)
[18] CLSI EP9-A3 protocol (Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Third Edition)

the-counter medications; or medical conditions such as ketoacidosis or abnormal hematocrit concentrations; and.
        - Environmental interference (e.g., from temperature, humidity and altitude).
    - User studies (where intended users collect (e.g., performing the fingerstick) and analyze the sample, and where results from the BGD are compared to results obtained with a traceable reference method.
    - Matrix comparison, if more than one sample type may be analyzed.
    - Lot release criteria used during the manufacturing of the BGD reagent or test strips.

    Study protocols should minimally include, as applicable: number of patients, number of samples tested, matrix and concentration of the sample tested, number of replicates tested, number of meters, number of test strip lots and the statistical analysis used.

If, as indicated in Section IV, the CGM is an FDA approved device and the device has not been modified in a way which would affect device performance then a copy of the device labeling may be sufficient in lieu of the information in this section.

K. Control Algorithm/Signal Processing Functional Component

The complete description of the control algorithm should be provided as discussed in Section IV-C. In general, Sponsors should submit the control algorithm for an APDS for review as part of the PMA, consistent with FDA practice for other devices that use similarly complex algorithms. In addition to the description, there are critical elements of the control algorithm that should be provided to support its safe use:

- Control Algorithm Verification – prior to clinical use, the sponsor should test the algorithm to assure that it has been properly programmed into software and provide verification. Details surrounding this verification testing can be found in Appendix A-V-C. In addition, we recommend that Applicants describe how they have assured the correct algorithm has been properly coded into their final finished device as part of their PMA applications.

- Parameter Sensitivity Analysis - the control algorithm in an APDS 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), Applicants should provide a comprehensive parameter sensitivity analysis as part of their PMA applications. This analysis should

evaluate the likelihood of an improper/unsafe insulin dose or insulin pump shutoff for all combinations of adjustable parameter values using representative CGM tracings. The CGM tracings should be representative tracings of the selected patient population.

If using theoretical or computer modeling to test the algorithm, the Applicant should provide tracings that demonstrate device behavior when values outside the bounds of expected use are encountered so as to describe device behavior under worst-case scenarios. A summary of the complete test report, 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 the Applicant.

L. Infusion Pump Functional Component

FDA recommends Applicants provide appropriate information regarding the safety of the infusion pump.

- **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 Section VIII, Labeling, 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**
  If the APDS is designed to completely turn off insulin delivery, 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.

- **Dose Accuracy**
  Applicants should provide a complete test report in the PMA submission describing the dose accuracy of the pump. The testing should focus on the ability of the pump to accurately deliver the recommended dose of the control algorithm. The purpose of this testing is to understand how well the infusion pump can deliver the wide range of recommended doses. Details of the Dose Accuracy Bench Testing can be found in Appendix A-V-L.

VII. Clinical Study Progression

The guidelines in this section are intended to facilitate timely progression from an Early Feasibility study to a full pivotal investigation while assuring adequate patient protections. In developing these recommendations, we have considered the least burdensome approach. Each step is designed to test specific aspects of the APDS functionality and performance. Sponsors who believe they already have sufficient, valid scientific evidence to fulfill the purpose of a particular study phase and justify moving to the next study phase are encouraged to discuss the evidence with FDA staff. Such evidence may be clinical or non-clinical and may be obtained from studies performed outside the US that comply with 21 CFR 814.15.

FDA recommends that the APDS be studied in three phases: **Early Feasibility Study, Transitional Study, and Pivotal Study**. The Early Feasibility Study is intended to demonstrate that the APDS functions as expected and has no obvious, unexpected safety concerns. The Transitional Study evaluates the APDS under supervised, real-world conditions while the Pivotal Study is conducted in an outpatient, unsupervised setting.

The size and duration of each study phase is dependent on the design and features of the APDS and its proposed indication. We recognize that each APDS will likely have unique features that affect study design. Therefore, the guidelines below do not set specific requirements for size and duration, but rather build in maximum flexibility for completion of each study phase, while also aiming to take the least burdensome approach. In addition, because some APDS may be composed of parts that have already been approved or cleared by FDA, we encourage Sponsors to leverage what is already known about the safety and effectiveness of the individual components to streamline the clinical testing of such a system.

A. Early Feasibility Study

The Early Feasibility Study (sometimes referred to as the Pilot Study) is intended to demonstrate that the device system functions as expected, does not have any obvious unexpected safety concerns, and can address the hazards associated with errors in the individual system components and the system as a whole. We expect that these studies will be of short duration involving few patients. The precise number of patients required will depend on the device hazards identified and the success of the implemented mitigating factors. Upon completion of the Early Feasibility Study, the APDS should be ready for testing in a real-world setting with close monitoring in a Transitional Study. The clinical protocol for the Early Feasibility Study should be developed with an identifiable goal and pre-specified success criteria.

The objective of the Early Feasibility Study might be to:

- provide proof of a system concept, i.e., the components and an algorithm;
- examine the effects of specific modifications to the algorithm;
- validate performance of the APDS across the operating range of the CGM;
- isolate and examine how an algorithm performs when exposed to conditions known to challenge the system, e.g., meal challenges, exercise, obstruction in IV tubing and errors in the system's components; or
- combine stress conditions in order to more realistically capture home-use conditions.

Information gleaned from each study could be used to make changes to the system or adjust the algorithm. It also might serve to validate the algorithm. When each known or reasonably expected hazard to the system is demonstrated to be adequately mitigated by the APDS, then it may be appropriate for the device to enter the Transitional Phase.

As investigators conduct their Early Fesibility Studies it is not known whether the APDS will adequately mitigate the risks to patients. For this reason we recommend that the Early Feasibility studies be performed in a hospital setting, such as a clinical research center (CRC). The study should be performed under the close supervision of a medical team that can intervene to prevent the occurrence of severe hypoglycemia or hyperglycemia. FDA recommends that Sponsors demonstrate that their APDS can adequately identify and compensate for CGM errors prior to moving to a less supervised outpatient setting.

One condition that will undoubtedly stress the system is significant errors in CGM readings. Currently marketed CGMs experience periods when they generate incorrect data, e.g., indicating that glucose levels are significantly above or below the true blood glucose value, or the CGM indicates that glucose levels are rising when they are actually falling. When incorrect information of this magnitude is fed into the APDS it can be life-threatening to the patient. An additional consideration is that

CGMs may stop providing data, e.g., they may fail to provide data for 2 hours or they might stop functioning altogether. This latter condition might have serious consequences if the patient were sleeping at this time and fails to respond to an alarm.

To provide safety monitoring and for purposes of assessing the accuracy of CGM values during the study, reference blood glucose measurements (i.e., those measured with a traceable laboratory reference method) should be collected and checked frequently. The reference blood glucose measurements will allow the Sponsor to detect when a CGM error may be occurring and anticipate the severity of the error and its effect on the patient.

The Sponsor should design the Early Feasibility Study to verify that the APDS can adequately mitigate CGM errors. The following is a current list of common types of CGM errors. One method by which Sponsors could simulate these errors might be to manually enter false CGM information into the APDS. The effects of these errors should be evaluated at both low and high glucose levels as the effects and potential impacts vary at different glucose levels.

- Erroneously high CGM values;
- Erroneously low CGM values;
- Erroneous CGM trending information:
  - CGM indicates that glucose concentrations are rising when they are actually falling; and
  - CGM indicates that glucose concentrations are falling when they are actually rising;
- The sensor stops functioning:
  - For a short and intermediate length of time;
  - Completely (such as what might occur when the sensor fails or when it reaches the end of the wear period);
  - Any other hazards that occur during the Early Feasibility Study should be recorded as an incident for data analysis;
- The pump stops functioning; and
- The pump does not deliver the appropriate dose.

We recognize that, as CGM technology improves, these factors may change. We encourage Sponsors to discuss with us any other potential errors they wish to measure during a pre-IDE meeting.

B. Transitional Clinical Study

The Transitional Study evaluates the APDS to see if it functions as expected under real-world conditions, while allowing for close medical supervision. In other words, once the hazards associated with the system have been shown to be sufficiently mitigated in the Early Feasibility Study, we recommend that a supervised outpatient study be performed. It is likely that these studies would be conducted at settings such

as a diabetes "camp" or "dormitory", which would allow subjects to undertake more of their day-to-day activities while being closely monitored by on-site personnel.

Transitional studies can provide the opportunity to gain additional feasibility information for the development of the APDS. Specifically, the study should evaluate APDS performance over the life of its disposable components. The study should be conducted for a duration that assures the safe and effective continuous use of system components such as the CGM, catheter, and reservoir. For disposable components, the study should be conducted for a period of time that allows the Sponsor to measure device performance before, during and after the disposable components are changed. Sensors and pump reservoirs should be replaced as recommended.

Ideally, the Sponsor will use the same version of the APDS that will be used in the Pivotal Study to ensure safe and effective continuous use of system components. If modifications to the APDS were made between the Early Feasibility/Transitional and Pivotal study, bridging studies may be appropriate; however, it will depend upon the type and extent of the change(s). We recommend the Applicant/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 system.

The Transitional Study should stress the APDS to identify any potential limitations that should be addressed prior to the Pivotal Study. When appropriate, additional blood glucose results can be obtained.

Sponsors should provide their proposed outcome measures for the Transitional Study in advance. We anticipate that the Transitional Study will be reasonably small and of short duration; however, the Transitional Study will only be considered complete, and the APDS ready for use in a Pivotal Study, when the Sponsor can confirm that the pre-specified clinical outcome measures have been met and the device is safe for use in more patients in an outpatient setting.

In an effort to minimize any delay between Transitional Study completion and Pivotal Study initiation, the Sponsor may choose to submit the Transitional and Pivotal Study plans for review concurrently and predefine the Transitional Study success criteria. FDA may approve the design of the Pivotal Study contingent upon successful completion of the agreed upon Transitional Study plan and submission of the study results.

C. Pivotal Clinical Study

The pivotal study should be performed in the actual use, real-world environment and by the intended use population. It can be conducted with subjects in their homes going about their normal activities of daily living or in children not only at home but also at school and participating in sports. The pivotal study should be conducted with the finished APDS for which approval will be sought and should be designed to demonstrate the safety and effectiveness of the complete device system in the

intended use population. A description of an example of a pivotal study design can be found in Section VII-D.

To demonstrate the safety and effectiveness of the APDS, we recommend comparisons be made between patients using the current standard of care, for example sensor-augmented pump control, and patients using the APDS. The Agency recommends a 6-month minimum study duration to allow for multiple periods of sensor wear, changes in subject needs over time, and repeated HbA1c measurements. We anticipate that, over time, designs of acceptable pivotal trials will evolve as the devices to which a comparison should be made change and as the technologies continue to improve.

A robust trial design to validate an APDS could include a randomized cross-over design or a randomized parallel design for evaluating the safety and effectiveness of the APDS in an outpatient setting. Patients in the control group should manage their diabetes according to the standard of care, e.g, by responding to alarms, performing finger stick blood glucose tests, and determining therapy according to these results. Patients in the test group should monitor their glycemic control by responding to alarms, performing finger stick blood glucose tests, and adjusting their treatment according to these results as directed by the instructions for using the APDS.

The following considerations are important for the Sponsor/Applicant to take into account when designing a pivotal study.

1. Patient Population

The overall goal of an APDS clinical study is to determine the safety and effectiveness of the APDS in maintaining glucose values within range or near target while minimizing adverse events such as hypoglycemia and hyperglycemia. Applicants may choose their study population but should recognize that the population they select to study may influence the study design, sample size, duration of follow-up, and final approved device indications. FDA recommends the following criteria be considered for enrolling patients with DM into initial studies for the APDS:

Initial subject population:

- 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 of:
    - sick days
    - days with exercise

- symptoms of low and high blood glucose episodes

The Agency recommends that initial studies for a novel APDS be performed in subjects age >18 years to ensure adequate ability of patients to respond to device problems. FDA is very interested in promoting the development of a safe and effective APDS for subjects < 18 years. Younger subjects may be enrolled after a sufficient number of adults have demonstrated reasonable safety and prospect of benefit (21 CFR 50 Subpart D).

To improve study efficiency by reducing sample size and study duration, Applicants may wish to enrich the patient population with subjects more likely to reach a study clinical endpoint. Some examples of potential populations are as follows.

1. Patients with a high % HbA1c and frequent hypoglycemia despite aggressive attempts at improved glycemic control;
2. Patients who have purposely maintained a high HbA1c to avoid any hypoglycemia;
3. Patients who have frequent hypoglycemia.

Patients with Sensor-Augmented Pumps

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.[19,20,21,22] Therefore, it is important that any study designed to examine the APDS should specifically test the effects of the APDS function and not simply the effects of newly implemented sensor-augmented pump control.

While the ideal patient population would consist of patients who have already used sensor-augmented pump control for >3-6 months, we recognize it may be difficult to identify and enroll patients who are experienced with sensor-augmented pumps. As an alternative, patients who have successfully used pumps without sensors can undergo a training period with sensors for 4-6 weeks. This learning period will screen out subjects who cannot optimally use sensor-augmented pumps and reduce the likelihood that novel sensor-augmented pump control would confound any effect observed in the study.

[19] Bergenstal RM, et al. (2010) Effectiveness of sensor-augmented insulin-pump therapy in Type 1 Diabetes, NEJM:363:311-320.
[20] 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*)
[21] 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
[22] 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

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

Applicants who desire to develop their APDS for a specific patient population are encouraged to seek the advice of the Agency through a pre-IDE submission to determine how they can most efficiently assess the safety and effectiveness of the device for use in that population.

Broadening Patient Population

Sponsors may want to widen the criteria for the enrollment of subjects (e.g., patients who are younger, who have insulin resistance, or have co-morbidities that may increase their risk during the study) and should consider how the inclusion of different subject groups may affect the study design, endpoints, and analysis of study outcomes. For example, if the Applicant chooses to pursue a pediatric-specific indication[23], the pediatric inclusion and exclusion criteria should be identified, as should any protocol-specific issues (such as exercise or the daily volume allowed for blood draws, etc.).

2. Study Endpoints

Clinical study endpoints should represent objective characteristics or variables that reflect how a patient feels, functions, or survives. Surrogate endpoints should predict meaningful clinical outcomes and be based on valid scientific evidence.

Primary Endpoints

The primary endpoints for the pivotal trial should provide a meaningful assessment of the APDS safety and effectiveness and reflect the anticipated device indications for use. Secondary endpoints can then be used to bolster additional claims or intended uses. We recommend that Sponsors use HbA1c as their primary endpoint.

HbA1c

HbA1c estimates the average glycemic exposure of red blood cells over a 90-day period. It is the primary efficacy measure used in the majority of trials assessing the effectiveness of a treatment or intervention on glycemic control. Additionally, HbA1c has been used

[23] 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.

to inform our understanding of the association of long-term glycemia and the development of complications associated with diabetes.

It is suggested that Sponsors using HbA1c as a primary endpoint design a study to demonstrate a decrease (or, minimally, no increase) in % HbA1c. We recommend a margin of at least 0.4% to demonstrate a detectable difference.[24] We note that Applicants may propose that in certain populations, acceptable increases in %HbA1c may be offset by benefit in another endpoint (such as a reduction in hypoglycemic events).

Co-primary endpoints may be acceptable and could be used by a Sponsor to support a successful PMA. We encourage Sponsors to discuss their choice of primary endpoint and study design with us. Examples of co-primary endpoints may include:

CGM-Based Events

Most endpoints that will be used to evaluate APDS performance require measurement or estimation of blood glucose levels. The characteristics of an APDS necessitate frequent and long-term measurement of blood glucose, and designing a study to achieve this can be challenging. The American Diabetes Association (ADA) Workgroup on Hypoglycemia acknowledged the limitations for obtaining plasma glucose values noting that "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."[25]

FDA proposes the use of a CGM-based correlate in evaluating the APDS. 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,[26] which discussed the clinical expectations of clinical studies for artificial pancreas

[24] 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 and indicate whether it is a NGSP certified method.

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

[26] November 10, 2010, Innovations in Technology for the Treatment of Diabetes: Clinical Development of the Artificial Pancrease (and Autonomous System).

device systems. 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 APDS.

The purpose of this section is to propose a potential method for defining CGM-based events (CGM-BE) so that CGM-based data may be used to evaluate device performance at targets or thresholds within the system. The use of CGM-BE will permit comparison of the rates of these events between treatment groups and further describe the duration and magnitude of the CGM-BE.

Analysis of CGM data should be filtered to avoid erroneous signals. For example, events should not be immediately preceded by a decrease in glucose concentrations of ≥7 mg/dL/min as these rates are not likely to be physiological. In addition, there may be periods when the sensor either fails to report values or has "noise". Filters should be applied in a consistent and pre-specified manner to exclude erroneous signals for the definition of a CGM-BE. Sponsors should use experience gained in the Early Feasibility Study to develop the appropriate signal processing algorithms specific to their systems. Additional filtering can also be provided with a justification.

Sponsors may propose alternate clinically-meaningful methods of defining the CGM-BE beyond those outlined below.

CGM-BE for Hypoglycemia

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

- A CGM-BE correlate for hypoglycemia may be defined as:
  - CGM value < hypoglycemia threshold (e.g., 60, or 70 mg/dL).
  - A CGM value below the hypoglycemic threshold for at least 10 continuous minutes.
  - 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 used/proposed with justification.

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

We believe that a similar endpoint could be developed to detect hyperglycemia. If a Sponsor wishes to develop such an endpoint, we encourage them to discuss it with us during a pre-IDE meeting.

A Note about Time In Range – Time in Range (TIR) is an endpoint that measures how successfully an APDS is able to normalize or improve glycemic control (increased time in range) without increasing hypoglycemia. Although studies have used TIR as a primary endpoint, there is some uncertainty about whether it is a good surrogate for determination of safety and effectiveness. Currently, FDA does not believe that pivotal studies for APDS should be based on a primary endpoint of TIR; however, as more data is developed on this endpoint, we may be willing to accept it in the future. Sponsors who wish to focus on TIR should talk to us during a pre-IDE meeting to determine if it is an appropriate choice for them.

Other effectiveness endpoints may also be considered based on the intended use of the device.

Safety

There are many different endpoints that can be used to determine the safety of an APDS. However, any safety study of an APDS should determine that the APDS does not increase the incidence of severe hypoglycemia (e.g., seizure or need for third party assistance), severe hyperglycemia or DKA. In designing their safety study, the Sponsor should propose specific safety endpoints that address these concerns. Some examples of the types of endpoints Sponsors may consider in developing a safety study include the following metrics, which the APDS should be shown not to increase:

- Severe hyperglycemia blood glucose above 240 mg and elevated ketones;
- DKA;
- Number of CGM-defined hyperglycemic events;
- Mean area under the curve (AUC) above 240 mg/dL as calculated from CGM readings;
- HgbA1C above a predefined accepted increase that may occur as a result of reduction of hypoglycemia;
- Percentage of CGM readings in the higher hyperglycemic ranges;
- Severe hypoglycemia (e,g, seizure or need for third party assistance);
- Number of CGM-defined hypoglycemic events;
- Mean AUC below 60 or 70 mg/dL as calculated from CGM readings; or
- Percentage of CGM readings in the hypoglycemic range (< 60 or 70 mg/dL).

We are open to considering other safety endpoints based on the intended use of the device.

Secondary Endpoints

Additional potential endpoints, as appropriate for the intended use of the device (whether as primary or secondary), include, but are not limited to:

- Incidence of Diabetic Ketoacidosis (DKA) or severe hyperglycemia within each group
- Incidence of catheter blockage within each group
- Capillary blood glucose values < 70 mg/dL and > 240 mg/dL.
- Fasting whole blood ketone concentrations within each group, evaluating elevated beta-hydroxybutyrate concentrations.
- Time spent (hours/week) in hypoglycemic events <70 mg/dL and hyperglycemic events > 240 mg/dL, including both day and night
- Average duration for all hypoglycemic events <70 mg/dL and hyperglycemic events > 240 mg/dL within each group
- Glycemic variability (such as coefficient of variation and standard of deviation within each group)
- Incidence and timing of CGM-BE for hypoglycemia and hyperglycemia (e.g., timing during the day and night)
- Safety and efficacy sub-group analysis, such as pediatric subjects
- Quality of Life

Exploratory Endpoints

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

3. Statistical Analysis

Study Populations

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.

Primary Hypothesis

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

Superiority vs. Non-Inferiority

The statistical plan for the pivotal trial should be defined in advance and may be designed to assess either non-inferiority or superiority between the APDS and control group endpoints. The Agency recognizes that a non-inferiority trial is more likely to be successful. However, the Sponsor may choose to pursue a superiority study to justify specific APDS labeled indications and claims (such as superiority over other DM treatments). We have proposed certain criteria for primary endpoints that Sponsors may apply in the conduct of a superiority study, although the Agency remains open to considering others if sufficiently scientifically justified.

a) HbA1c - Superiority

For Sponsors wishing to demonstrate APDS superiority for the HbA1c endpoint, it is recommended that the study demonstrate a superiority margin of 0.4% (absolute difference). The hypothesis is mathematically expressed as:

$$H_O: \mu_{APDS} \geq \mu_{CONTROL} - 0.4\%$$
$$H_A: \mu_{APDS} < \mu_{CONTROL} - 0.4\%$$

Where μ_{APDS} is the mean of HbA1c (%) of the APDS group, and $\mu_{CONTROL}$ is the mean of HbA1c (%) of the Control group. The Null hypothesis is rejected if the two-sided 95% upper boundary of the difference between the two treatments, $\mu_{APDS} - \mu_{CONTROL}$, is less than -0.4%

A goal for superiority in HbA1c should be 0.4%. However, somewhat lesser improvements may be deemed acceptable based on the effect on the co-primary endpoints and safety profile of the device system.

b) CGM-BE for Hypoglcyemia - Superiority

For sponsors wishing to demonstrate APDS superiority for the primary effectiveness endpoints in terms of reduction of severe hypoglycemia or CGM-based hypoglycemic events, it is recommended that superiority be demonstrated with a margin of 30% (relative difference) for either severe hypoglycemia or CGM-based Event Rate (prevention), or Event AUC (mitigation). The hypothesis is mathematically expressed as:

$$H_O: \mu_{APDS} \geq 70\% \times \mu_{CONTROL}$$
$$H_A: \mu_{APDS} < 70\% \times \mu_{CONTROL}$$

Where μ_{APDS} and $\mu_{CONTROL}$ are the endpoints of the APDS and control groups, 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.

There is limited literature describing the clinical benefit for a reduction in a CGM-BE outcome measure.[27] Based upon this limited information, we recommend a minimum 30% superiority margin be used to ensure that a clinically significant reduction is observed. Smaller success criteria may be appropriate with a justification based upon system design, patient population, and risk profile. Please note, use of smaller success criteria may affect the indication or claims for the APDS.

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 calculate the 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 loss 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

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

imputation, all missing as failures or success, worst case scenario, best case scenario, tipping point, etc.

General Considerations for Data Analysis

FDA recommends that patient demographics, medical history, and other important baseline characteristics (e.g., HbA1c, body mass index, average daily insulin requirements, education levels, etc.) are 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. 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 of all primary endpoints. Appropriate statistical models should be specified to evaluate the impact of covariates. If some covariates are found to confound a primary endpoint, their effects should be adjusted through appropriate models.

Analysis of Secondary Endpoints

For all secondary endpoints, descriptive statistics are recommended. If the Sponsor/Applicant intends to make claims for any of the endpoints in the labeling then the hypotheses, statistical analysis, and success criteria should be clearly specified in advance in the study protocol. An appropriate multiplicity adjustment strategy to control the type I error rate may also needed.

Adaptive Study Design

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 include their proposal in their 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 that lead to patient withdrawal from the trial

- Unanticipated Adverse Device Effects (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; and
- Skin infection.

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 APDS should include:

- a user manual for the patient, written at an 8th grade reading level;
- all training materials;
- professional labeling for the prescribing physician;
- Package inserts for the APDS and all components packaged separately from the system (e.g., BGD reagents or test strips, quality control materials, catheters, inserters, reservoirs, etc.); and
- Box and container labels for the APDS 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 CTR/CTT system.

- *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA* (2001)
- Labeling of Home-Use In Vitro Testing Products; Approved Guideline, CLSI GP-14 (1996)
- Device Advice website titled *Labeling Requirements - In Vitro Diagnostic Devices*
- 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 APDS 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.[28]

The professional labeling for the prescribing physician should describe in sufficient detail the clinical testing performed for APDS approval. The purpose of this information is to allow the physician to make an informed decision on whether to prescribe the APDS 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) and CGM (e.g., analytical specificity, accuracy, etc.) should be described.

IX. Post-Approval Study

As a condition of PMA approval, most APDS will require a post-approval study (PAS) to better assess long-term and real-world performance and/or patient outcomes. It is recommended that the Applicant develop a PAS protocol and submit the protocol with the original PMA. The Agency is willing to consider different PAS study designs, depending on the APDS and its capabilities. We recommend the Applicant develop a PAS and submit this study for review as a pre-IDE submission.

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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 and indicate whether it is a NGSP certified method.

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

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

Appendix A: IDE Content for APDS Studies

This Appendix provides suggested content for IDE submissions for evaluation of an APDS. 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 Early Feasibility, Transitional, or Pivotal (unsupervised outpatient setting) Studies, the section is divided.

I. Background

The Sponsor should provide background information related to the development of the APDS that it intends to 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 US or Outside the US clinical studies performed using this device system (the Sponsor should identify the IDE #).

II. Device Description

This section should include a device description of the APDS.

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 510(k) 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. This would include, for example, whether the run-in time or calibration frequency have been modified. For all components that have been modified, Sponsors should provide a rationale for the change and an analysis of the likely impact it will have on the performance.

If the Sponsor is not using previously approved/cleared devices, FDA recommends the Sponsor include a complete description of all functional components of the system (i.e., BGD, CGM, control algorithm, 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 APDS 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[29] 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 also provide the following information as part of the IDE.

A. Algorithm

The Sponsor should provide information regarding the regulatory status of the algorithm to be used in the IDE study. If the device in question utilizes software that has not been previously reviewed and cleared or approved by the Agency, a description of the algorithm should be provided as part of the IDE submission. If the algorithm is identical to that used in a cleared or approved product, then the IDE submission should contain the name of the product and the FDA document number under which it was cleared or approved (if known).

If the Sponsor does not have access to the algorithm and cannot provide it, a rationale for why it is not being provided should be included as part of the IDE.

[29] *See* 21 CFR 814.20(c). Master files are described on Device Advice. See link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

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.

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.

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. For a PMA, FDA recommends the Sponsor evaluate combinations across the entire range of parameter values and the effects on the system as described in Section VI-K of the guidance. Such an analysis should evaluate combinations of 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. For Early Feasibility studies (Section VII-A of the guidance) where patient safety has been significantly mitigated due to physician monitoring, a limited sensitivity analysis is acceptable.

6. 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 in any IDE for a pivotal study. 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.

B. Software Documentation

Software documentation should be provided for the APDS prior to major clinical studies. Full software documentation is not necessary for Early Feasibility Studies. However, documentation should be provided to demonstrate that the Sponsor can trace the development history of all components of their software and identify any unresolved anomalies (i.e., "bugs") that may affect the safety of their software for the purpose of providing complete software documentation at a later time. For devices that have been modified from their previously approved/cleared form, the Sponsor should highlight any differences between the modified and approved/cleared versions. For assistance in developing the appropriate documentation set, Sponsors should refer to the FDA's 2005 software guidance document.[30] All APDS are identified as a major level of concern for purposes of the guidance. The software documentation set can be included as an Appendix to the IDE.

We encourage all Sponsors whose APDS is comprised of previously approved/cleared devices that they did not manufacture to pursue obtaining an LOA from the manufacturer of such devices to gain access to the software Master File. If the Sponsor is not able to gain access to the software documentation in this way, the Sponsor should provide evidence of his or her attempts to obtain the documentation and an attestation of the manufacturers' refusal to provide it as part of the IDE.

C. Summary of System Communication

If the APDS 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

[30] *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*, http://*www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm.*

previously approved device system, a summary of the system level testing is needed prior to a pivotal study. 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.

D. Safety Measures for Dosing

The Sponsor should identify if there are any hard-limits coded into the software of the APDS that would restrict the minimum and maximum dose recommended by the algorithm. The Sponsor should identify the frequency of dosing recommendations and the time needed to deliver the minimum and maximum dose.

E. 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. If the Sponsor has modified the approved device, it may be possible to reference the 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 documentation is needed as described in Section VI- of the guidance. FDA notes that the biocompatibility testing provided in the IDE may be limited due to the short duration of contact of the APDS in the proposed clinical study design.

F. Electrical Safety

If applicable, the following electrical safety information should be addressed in any IDE submission for major clinical studies. This information may not be necessary for Early Feasibility studies.

- **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 APDS 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, reference should be made to the draft guidance, *Radio-Frequency Wireless Technology in Medical Devices*.[31]

  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. 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.

G. Animal/In-Silico Testing

The Sponsor should provide evidence of safety for the APDS 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. 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

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

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 and time-consuming animal experiments. This tool can be used to justify and support initiation and expansion of human clinical trials. 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 similar 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 APDS in humans. This may be clinical data to support device components of the system (e.g., CGM clinical studies), studies conducted previously in another IDE or studies conducted outside the US. FDA recommends a complete test report be provided.

J. Human Factors/Usability Testing

- **Early Feasibility (Pilot) Study/**
  The Early Feasibility Study will typically involve proof of concept for the technology; thus, user interaction with the device will not be the focus of the study. Human Factors/Usability Testing are generally not expected to be part of the Early Feasibility Study. Use errors should be collected and described in the case report forms.

- **Transitional Study**
  Risks associated with use error are present for any operator of an APDS. FDA recommends the Sponsor evaluate the design of the system, including its labeling

and user training, during the transitional study phase to establish that the design of the system supports safe and effective use by the intended users under conditions of simulated use prior to the initiation of an unsupervised outpatient clinical study. Alternately, Sponsors should design parallel human factors evaluations to assure that human error is controlled and use-related risks are mitigated as much as possible prior to the pivotal study. Sponsors should record all human factors test protocols and results in the Case Report Forms.

- **Pivotal Study/Unsupervised Outpatient Study**
  In an unsupervised outpatient study, data collection is limited. Self-report data (e.g., as recorded in patient diaries) and calls to telephone help lines can provide useful information; however these types of data should be supplemented with essential user performance data, for example collected through a data logger incorporated into the devices used in the study. Depending on the results obtained and consequent design modifications implemented following analysis of results of the evaluation, it might be necessary to perform a simulated-use test to assess the effectiveness of the modifications and overall use safety of the system. Soliciting comments from the participants would provide essential additional information regarding users' perceptions of the system, potential use-related problems, and ways in which the system might be improved.

  An overview of human factors/usability testing processes is described in Section VI-I of this document. FDA recommends the Sponsor conduct, describe, and provide a rationale for the human factors/usability testing they conducted to support the safe use of the system in humans in the outpatient setting.

K. Catheter Occlusion Bench Testing

APDS are in part intended to improve glycemic control by modulating insulin infusion, including, in certain instances, shutting the pump off for finite periods 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 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 system. FDA recommends the Sponsor report the incidence of crystallization and the incidence of catheter blockage due to crystallization.

L. Dose Accuracy Bench Testing

APDS control algorithms currently recommend periodic insulin dosing with frequencies ranging from 1-30 minutes. These frequent bolus doses are extremely small and ask the pump to perform accurately near the lowest doses available in the pump. In order to understand how well the APDS can deliver the recommended insulin or drug, bolus dose accuracy testing should be performed. This testing should evaluate the APDS using the most frequent dosing rate (i.e., the shortest time between dosing adjustments) and accuracy measurements should be tested using the minimum dose, maximum dose and incremental doses between the min and max. The testing of this system should mimic the conditions of the clinical study and the measurement technique should account for evaporation of small doses during the testing. Temperature should be controlled and reflect the use environment.

M. Diagnostic Devices To Be Used During the Clinical Study

In addition to the diagnostic device components of the APDS, other diagnostic devices are commonly used during clinical studies, (e.g., those that measure blood glucose for purposes of evaluating the APDS, or ketones).

To ensure patient safety and the accuracy of these devices Sponsors should provide the following information for each diagnostic device that will be used onsite in the clinical study:

- Name of the device, including model numbers, as applicable.
- Description of the function performed by the device during the study (e.g., monitoring patient glucose or ketone concentrations as a secondary endpoint in the study or calibrating the CGM).
- 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.
- For labeling recommendations of device components that are part of the APDS, please refer to Appendix A-XIII.
- For diagnostic devices used in the clinical study that are not part of the APDS system.
    - Unless a justification can be provided, Sponsors should provide patients who are operating any device all labeling associated with the device.
    - Sponsors should determine whether it is necessary to provide clinical investigators with the labeling of diagnostic devices used at the study site. If Sponsors believe that this is not necessary they should:
        - Describe what functions the investigator will be performing with the device and explain why it is not necessary to provide them with the labeling. (For example, the operator may have extensive experience operating the device.)

        - Certify that labeling will be available at each clinical site should it be needed.
- If the device was previously cleared or approved, Sponsors should describe any physical or labeling modifications that were made to the device for purposes of conducting the study. If modifications were made, Sponsors should:
    - Describe the modification, provide a rationale for the change and description of how the modification might affect device use/performance.
    - Sponsors should also address how they will ensure that the instructions for use properly communicate any changes in how the device is to be operated, if applicable.
- Sponsors should describe how performance of the device will be monitored to ensure accurate results. This information should include, where applicable:
    - Quality Control (QC) materials to be analyzed.
    - Number and concentration of QC materials.
    - Frequency and timing of analysis of the QC materials.
    - Criteria for determining acceptability of QC results.
- Sponsors should describe how individuals using the device during the study will be trained to operate it.

N. Drugs Used During the Study

Please identify the name of the drugs (e.g., insulin, glucagon, etc.) intended to be used in the APDS system and provide the drug labeling. Sponsors should also indicate any drugs, such as acetaminophen, that are given to patients during the study, as they may affect CGM performance.

VI. Bibliography

The Sponsor should provide a bibliography of all relevant 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. The Sponsor should identify 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 plan entire study will take to complete.

E. Inclusion Criteria

The Sponsor should provide a listing of the inclusion criteria.

F. Exclusion Criteria

The Sponsor should provide a listing of the exclusion criteria.

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 APDS 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.

- *Early Feasibility Study (In-hospital):* For studies taking place in CRC settings, Sponsors should use the most accurate method available for measuring subject glucose concentrations, i.e., traceable reference methods. Reliable laboratory tests, such as those utilizing 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. The 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 concentrations. 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 concentration. 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 insulin dosing.

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

- Reuse Risk –The Sponsor should describe if components of the 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, as applicable.

- Hb1Ac risk - Please refer to Section VII-C-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 APDS and all of the functional components during the study. As applicable, this should include training for clinical staff and/or the study subject. 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. 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

The Sponsor should 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.

Early Feasibility & Transitional Studies

In Early Feasibility 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.

L. Statistical Analysis Plan

Early Feasibility & Transitional Studies
These 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
The Sponsor should describe the complete statistical analysis plan to support the study objective(s).

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 as an Appendix. All Informed Consent documents must adhere to the requirements described in 21 CFR Part 50 – Protection of Human Subjects and must contain the information described in 21 CFR 50.25(a). If the Sponsor chooses to pursue a pediatric-specific indication they must be aware that the pediatric population represents a vulnerable subgroup and special measures should be taken to protect the rights, safety, and welfare of pediatric study subjects. The regulations at 21 CFR Part 50 - Subpart D Additional Safeguards for Children in Clinical Investigations further describe specific requirements for pediatric study subjects.

FDA does not recommend that the consent process include only 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.

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.
Financial disclosure of clinical investigators participating in a clinical study is a requirement which applies to any clinical study submitted in a marketing application to the FDA. Financial interests can be a potential source of bias in the outcome of a clinical study; therefore, any financial arrangements must be disclosed. As per 21 CFR Part 54 – Financial Disclosure by Clinical Investigators, Sponsors must certify the absence of certain financial interests of clinical investigators on Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigations FDA Form 3454, or disclose those financial

interests on Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455.

XI. Monitoring Information

The following 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.

Early Feasibility & Transitional Study

Sponsors should provide labeling for the investigational APDS, including the instructions for operating each of its functional components, as necessary. The purpose of product labeling

during an Early Feasibility or Transitional study is to ensure that operators have adequate instructions for safely operating a device during the study. Operators include clinical investigators (when studies or a portion of a study are conducted in a clinical setting) or patients (when a study or portion of the study takes place at home).

The amount of labeling necessary to ensure safe operation of the system or functional components is dependent on the study design. For example, some studies involve having a CGM inserted into patients prior to them reporting to a clinic where the APDS will be evaluated and they are not expected to operate it while they are at home. In this example, it may not be necessary to provide the patient with labeling for the CGM. It may only be necessary to provide patients with instructions on what to do if they experienced an adverse event involving the CGM, such as a reaction at the insertion site. However, a patient might be expected to operate the CGM, BGD, control algorithm, or pump, in which case they should be provided with labeling which provides complete instructions for performing each of the functions they are expected to carry out.

Sponsors should identify each operator involved in the study, and list each of the functions they are expected to carry out.

Sponsors should provide a copy of the draft labeling that includes:

- Adequate instructions that enable each operator to safely perform all of the functions they are expected to carry out during the study.
- A caution statement, "*Caution – Investigational Device. Limited by Federal (or United States) law to investigational use*" on the APDS labeling.
- Unless a justification can be provided, Sponsors should provide patients who are operating the device with all labeling associated with functions they are to perform with the device.
- Sponsors should determine whether it is necessary to provide clinical investigators with the labeling. If Sponsors believe that this is not necessary they should:
  - Describe what functions the investigator will be performing with the device and explain why it is not necessary to provide them with the labeling. (For example, the operator may have extensive experience operating the device.)
  - Certify that labeling will be available at each clinical site should it be needed.

Pivotal Study (unsupervised outpatient study)

The purpose of the product labeling should allow the subject to safely operate the APDS. 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*".

FDA recommends the instructions for use, such as user guides or any written materials that will be provided to individuals during this study should be the same as what will be provided with the system when it is marketed.

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

Early Feasibility Study

This information is not generally needed for Early 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.

Appendix B: Glossary

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 which measures blood glucose concentrations.

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 continually sends information to a receiver, which converts the information to 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.

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

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 a 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)

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)

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