Draft Guidance for Industry and Food and Drug Administration Staff - The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Low GI...

U.S. Food & Drug Administration

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For questions regarding this document, contact Charles Zimliki, Ph.D., 301-796-6297, Charles.Zimliki@fda.hhs.gov [2].

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

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach

satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Pilot Study

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

Pivotal Study

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

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

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

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

the study.

In lieu of CRC studies, Sponsors may be able to provide supporting safety data from previous studies of approved sensor-augmented pump (SAP) systems. Although the data on CGM performance may be used in support of the outpatient study, the analysis of this data may vary from the analysis done to support an indication for ‘tracking and trending’. In addition to the information needed for a pivotal study described in Appendix A [13], the following information should also be provided:

1. A complete device description of all device components used in the study that supported the approval of the SAP system as described Section IV [7].
2. The complete protocol of the study used to generate data on sensor performance. This should include a description of:
    - The study population with inclusion and exclusion criteria.
    - Any interventions performed, such as ‘clamps’ to accrue data pairs (CGM to reference) in the hypoglycemic and hyperglycemic ranges and how these ranges were defined for this study.
    - A reference blood glucose measurement. As this is a reference value there should not be adjustments in the reported value (such as altering the comparison to reflect the error in the reference method).
    - An analysis of data pairs in the lower glucose range should be provided in intervals of 10 mg/dL. For example, 50-60 mg/dL, 60-70 mg/dL, 70-80 mg/dL, and 80-90 mg/dL.
    - An analysis of alarm performance, reactive or predictive, as it relates to the proposed outpatient study. Alarms should be assessed by individual subject experience and not by individual data pairs. Comparisons between CGM and reference BG should be made based on the time it took to detect the threshold of interest (such as 70 mg/dL). For example, the CGM detected 70 mg/dL 10 minutes after (or before) the reference method. False positives and false negatives should also be captured.
    - Individual plots of CGM tracings with reference blood glucose values of the periods analyzed should be provided.

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

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

Appendix C: Glossary

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

Analytical specificity - How well an assay [30] detects only a specific analyte (e.g, glucose) and does not detect closely related substances.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

On-board memory - internal memory for infusion pump.

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

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

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

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

Real time clock (RTC) - a battery-powered clock that is included in a microchip [31] in a computer motherboard [32]. This clock keeps track of the time even when the device is turned off. Real-time clocks run [33] on a special battery that is not connected to the normal power supply [34].

Stability - The capacity of a drug substance and reservoir to remain within established specifications of identity, strength, quality, and purity in a specified period of time. Stability is officially defined as the time lapse during which the drug

product retains the same properties and characteristics that it possessed at the time of manufacture.

Watchdog timer - A computer [35] hardware or software timer [36] that triggers a system reset [37] or other corrective action if the main program [38], due to some fault condition, neglects to regularly service the watchdog. The intention is to bring the system back from the unresponsive state into normal operation.

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

[2] ADA Clinical Guidelines (2011) Diabetes Care, 34 (Suppl 1):S62-69

[3] AACE Guidelines (2011) Endocrine Practice 17 (Suppl 2):1-53

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

[5] Also see the draft Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions *[39]*, issued April 23, 2010.

When final, this guidance will represent the Agency’s opinion regarding elements for consideration for this component.

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

[7] AAMI TIR 12:2010, Designing, testing and labeling reusable medical devices for

reprocessing in health care facilities: A guide for medical device manufacturer

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

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

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

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

[12] CLSI EP5-A2 Protocol (Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition)

[13] CLSI EP17 document (Protocols for Determination of Limits of Detection and Limits of Quantitation)

[14] CLSI EP7-A2 Protocol (Interference Testing in Clinical Chemistry; Approved Guideline- Second Edition)

[15] CLSI EP6-A document (Evaluation of the Linearity of Quantitative Measurement Procedures, A Statistical Approach; Approved Guideline, 2003)

[16] CLSI EP9-A3 protocol (Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Third Edition)

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

[18] Available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM081667.pdf [40]

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

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

[21] November 10, 2010, Innovations in Technology for the Treatment of Diabetes: Clinical Development of the Artificial Pancreas (an Autonomous System). Morning Session [41], Afternoon Session [42].

[22] Bergenstal RM, et al. (2010) Effectiveness of sensor-augmented insulin-pump

therapy in Type 1 Diabetes, NEJM:363:311-320.

[23] Hermanides, J, et al. (2011) Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type 1 Diabetes; a randomized controlled trial. Diabetic Medicine (*Accepted Article*)

[24] Junvenille Diabetes Research Foundation Continuing Glucose Monitoring Study Group (2009) The effect of continuous glucose monitoring in well-controlled Type 1 Diabetes. Diabetes Care 32:1378-1383

[25] Garg, SK et al. (2007) Continuous Home Monitoring of Glucose - Improved glycemic control with real-life use of continuous glucose sensors in adult subjects with Type 1 Diabetes. Diabetes Care 30:3023-3025

[26] The pediatric population is defined as birth to 21 years of age. For details surrounding this definition and recommended pediatric subpopulations, please refer to Guidance for Industry and Staff: Pediatric Expertise for Advisory Panels *[43]*. 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.

[27] CDRH Home Use Website [44]

[28] Master files are described on Device Advice [45].

[29] Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices *[46]*

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

SOURCE [47]

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[26] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/#a14
[27] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/#a15
[28] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/#b
[29] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/#c
[30] http://www.medterms.com/script/main/art.asp?articlekey=8412

[31] http://searchcio-midmarket.techtarget.com/sDefinition/0,,sid183_gci212564,00.html
[32] http://searchcio-midmarket.techtarget.com/sDefinition/0,,sid183_gci212594,00.html
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