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MEETING PROCEEDINGS

Innovations in Technology for the Treatment of Diabetes: Clinical Development of the Artificial Pancreas (an Autonomous System)

David C. Klonoff, M.D., FACP,[1] Charles L. Zimliki, Ph.D.,[2] LCDR Alan Stevens,[2] Patricia Beaston, M.D., Ph.D.,[2] Arleen Pinkos, M.T.(ASCP),[3] Sally Y. Choe, Ph.D.,[4] Guillermo Arreaza-Rubín, M.D.,[5] and William Heetderks, M.D., Ph.D.[6]

Abstract

The Food and Drug Administration in collaboration with the National Institutes of Health presented a public workshop to facilitate medical device innovation in the development of the artificial pancreas (or autonomous system) for the treatment of diabetes mellitus on November 10, 2010 in Gaithersburg, Maryland.

The purpose of the workshop was to discuss four aspects of artificial pancreas research and development, including: (1) the current state of device systems for autonomous systems for the treatment of diabetes mellitus; (2) challenges in developing this expert device system using existing technology; (3) clinical expectations for these systems; and (4) development plans for the transition of this device system toward an outpatient setting.

The patients discussed how clinical science, system components, and regulatory policies will all need to harmonize in order to achieve the goal of seeing an AP product brought forward to the marketplace for patients to use.

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Introduction

The U.S. Food and Drug Administration (FDA), in collaboration with the National Institutes of Health (NIH), presented a public workshop to facilitate medical device innovation in the development of the artificial pancreas (AP or autonomous system) for the treatment of diabetes mellitus on November 10, 2010, in Gaithersburg, Maryland.

Author Affiliations: [1]Mills-Peninsula Health Services, San Mateo, California; [2]General Hospital Devices Branch, Office of Device Evaluation, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland; [3]Division of Chemistry and Toxicology Devices, Office of *In Vitro* Diagnostic Device Evaluation and Safety, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland; [4]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland; [5]Glucose Sensing and Insulin Delivery Technologies Program, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; and [6]National Institute of Biomedical Imaging and Bioenginerering, National Institutes of Health, Bethesda, Maryland

Abbreviations: (A1C) hemoglobin A1c, (AP) artificial pancreas, (BG) blood glucose, (CDER) Center for Drug Evaluation and Research, (CDRH) Center for Devices and Radiological Health, (CGM) continuous glucose monitor, (DKA) diabetic ketoacidosis, (FDA) Food and Drug Administration, (GPS) global positioning system, (IDE) investigational device exemption, (JDRF) Juvenile Diabetes Research Foundation, (LGS) low glucose suspend, (NIBIB) National Institute of Biomedical Imaging and Bioengineering, (NIDDK) National Institute of Diabetes and Digestive and Kidney Diseases, (NIH) National Institutes of Health, (PD) pharmacodynamics, (PK) pharmacokinetics, (SAP) sensor-augmented pump

Keywords: algorithm, artificial pancreas, closed loop, glucose, insulin, insulin pump, sensor

Corresponding Author: David C. Klonoff, M.D., FACP, Mills-Peninsula Health Services, 100 S. San Mateo Dr., Room 5147, San Mateo, CA 94401; email address *dklonoff@yahoo.com*

An AP is a medical device that links a glucose monitor to an insulin infusion pump where the pump automatically takes action (using a control algorithm) based upon the glucose monitor reading. Because control algorithms can vary significantly, there is a variety of AP systems currently under development. Current research in this area uses existing medical device technology, which has inherent limitations regarding performance and may pose additional obstacles that need to be addressed during the clinical evaluation of these investigational systems. The FDA and the NIH sought feedback on ways to overcome obstacles toward the development of an AP and what might be considered reasonable clinical expectations for systems, considering the existing technology available.

The purpose of the workshop was to discuss four aspects of AP research and development: (1) the current state of device systems for autonomous systems for the treatment of diabetes mellitus, (2) challenges in developing this expert device system using existing technology, (3) clinical expectations for these systems, and (4) development plans for the transition of this device system toward an outpatient setting.

The meeting was divided into six sessions: (1) Welcome and Introductory Remarks, (2) Device Limitations Using Existing Technology for the Artificial Pancreas, (3) Clinical Expectations for Low Glucose Suspend Device Systems, (4) Clinical Expectations for Artificial Pancreas Device Systems, (5) What Safety Information Is Needed from In-Clinic Studies Prior to Adding Outpatient Studies?, and (6) Funding Opportunities for Development of the Artificial Pancreas.

Welcome and Introductory Remarks

In the Welcome and Introductory Remarks session, the first speaker was Jeff Shuren, M.D., J.D., director of the Center for Devices and Radiological Health (CDRH) at the FDA. He discussed the FDA's proactive role in the development of an AP for the treatment of diabetes mellitus, including making presentations at national and international FDA conferences. He pointed out that the FDA has an AP review team that is intended to deliver a rapid, interactive response with investigators of these systems. Dr. Shuren enumerated the FDA's activities in developing guidance and standards documents of components related to AP systems and stated that the FDA is currently updating and creating new guidance and standards for glucose meters and infusion pumps. He described the FDA's commitment to public discourse, as evidenced by the agency having organized or co-organized five meetings in 2010 on topics related to the AP, such as blood glucose (BG) monitors, insulin pump failures, and the AP (this meeting) as well as a session on the AP during a 2010 FDA meeting on a medical device technical innovation partnership for leveraging academic and FDA collaborations to resolve unmet public health needs. Dr. Shuren concluded by pointing out that existing technology has limitations, and he posed three questions for the audience to consider: (1) What are the clinical expectations for an artificial pancreas? (2) How should we study these device systems? (3) Are there specific patient populations that would benefit more than others?

The second speaker in this session was Roderic Pettigrew, Ph.D., M.D., director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Dr. Pettigrew provided welcoming remarks. He presented an oft-repeated saying, that, for many diseases, it is necessary to deliver the right medication at the right time at the right place. He stated that this saying is now a reality for diabetes. Thanks to innovations in technologies, which are the focus of this workshop, patients can receive insulin—which is the right medication—at the right time in the right place. Dr. Pettigrew stated that closed-loop control of insulin based on monitoring and responding to what is monitored is an idea whose time has come. He predicted that, for patients with diabetes, tight glucose control, which can be achieved with an AP, will decrease morbidity and increase longevity.

The third speaker in this session was Gregory Germino, M.D., deputy director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. Germino also provided welcoming remarks. He described the history of the NIDDK's leadership in the field of the AP and its collaboration with the FDA in this area. Dr. Germino stated that the NIH supports cutting-edge research focused on the development of minimally invasive or noninvasive glucose monitors, long-term implantable glucose monitors, new glucose-regulated insulin delivery technologies, technologies to increase the biocompatibility of devices, and algorithms for delivery of insulin that mimic physiologic homeostasis. These items will all eventually be components of an AP system. Dr. Germino stated that the Special Type 1 Diabetes Research and Statutory Funding Program has funded many recent activities related to the AP, and this program is presently set to end in 2011, unless Congress reauthorizes its funding. Dr. Germino stated that the NIDDK participates in the recently chartered Interagency

Council on Medical Device Innovation, which was established by the FDA CDRH. This council's purpose is to identify the most important unmet public health needs, the barriers to innovative medical device development or redesign that could address those needs, and actions that the federal government can take to reduce those barriers. Dr. Germino then linked the purpose of today's workshop with the purpose of the council and stated that development of a working automated closed-loop system for glucose control will contribute to meet a clear public health need—better control of glucose in patients who suffer from diabetes—or prevent costly acute and chronic complications of the disease. Dr. Germino stated that a pressing issue for the regulatory science community is study design. He posed two questions: (1) What clinical study designs are deemed appropriate and acceptable for testing current and future closed-loop systems? (2) What key safeguards and outcomes will be judged acceptable? He stated that the regulatory and scientific communities need clear guidance on these topics to expeditiously assess both the efficacy and the safety of complex systems of regulated devices such as AP systems currently under development. Dr. Germino concluded that the NIDDK is committed to supporting innovation and development of a new generation of glucose-sensing and insulin-delivering technologies as well as preclinical and clinical testing of devices.

Device Limitations Using Existing Technology for the Artificial Pancreas

Charles (Chip) Zimliki, Ph.D., chair of the FDA Artificial Pancreas Critical Path Initiative, gave the first presentation of the second session entitled, *Defining the Artificial Pancreas: An Autonomous System for the Treatment of Diabetes Mellitus*. Dr. Zimliki expressed optimism that existing technology might be sufficient to develop an AP system using a system-based approach. He stated that four elements of a successful initiative would need to be established: (1) system safety requirements, (2) appropriate system mitigations, (3) realistic expectations, and (4) clinical studies. Dr. Zimliki discussed how an AP is regulated and stated that this is a class III device, which requires premarket approval. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Also, class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. These systems are regulated as significant risk devices in accordance with 21CFR 812.3(m), which means they require an investigational device exemption (IDE) to be tested. Dr. Zimliki described the AP points to consider, the AP IDE table of contents, and the AP software documentation set documents, which identify key elements necessary for an IDE review: (1) an adequate system description and an adequate system, (2) documentation of the software and a description of the algorithm, (3) a preclinical assessment and description of prior investigations, (4) a feasibility study design and clinical study design, and (5) administrative assistance and mitigation of risk, including adequate informed consent. Dr. Zimliki discussed the benefits of using an *in silico* model (instead of using animal models) for preclinical testing of an artificial pancreas system. These include the opportunity to explore a large number of theoretical subjects, devices [including insulin pump and continuous glucose monitor (CGM) devices], algorithms, and clinical conditions with no risk of harming a subject. He discussed FDA actions that led to accepting the first *in silico* model, maintaining a device master file for other investigators to use this model with permission from the *in silico* model creators and developing a review process for future *in silico* models. He stated that, if an investigator wishes to develop their own *in silico* model, then the agency has developed a review process to review and vet that model as a viable replacement for substitute for animal models; however, there are pros and cons to developing a new model compared to using one that has already been vetted. Dr. Zimliki then presented four examples of potential features of AP systems: (1) insulin suspension for low glucose levels, (2) treat-to-range, (3) treat-to-target, and (4) bihormonal treat-to-target. He concluded by summarizing the goals for this meeting, which included (1) understanding the challenges of each device component of an AP system, (2) developing realistic expectations for the systems, and (3) identifying appropriate endpoints for clinical study design.

The second speaker in this session was Arleen Pinkos, M.T.(ASCP), a scientific reviewer in the Office of *In Vitro* Diagnostic Device Evaluation and Safety within the CDRH at the FDA. She discussed continuous glucose monitors. Ms. Pinkos began by emphasizing how important it is for product developers to consider both the benefits and the limitations of CGMs as they design closed-loop systems. It is also important for the public to understand the challenges associated with system components so that their expectations for the systems are realistic. Ms. Pinkos stressed the importance of three features of implanted CGM sensors. Ideally, they should be (1) accurate, (2) uninterrupted, and

(3) impervious to physiological conditions and other factors. She pointed out that, while CGMs have evolved and improved significantly since first being introduced more than 10 years ago, there are six factors that continue to affect their performance. Limitations in accuracy, the first of her three ideal features, include (1) periods of unexpected and significant errors, most likely related to biofouling; (2) unstable run-in periods; (3) periods of less accuracy during high physical activity; (4) periods of less accuracy when glucose levels are changing rapidly; (5) calibration errors; and (6) poor accuracy in the hypoglycemic range. Regarding calibration errors, a CGM can only be as accurate as the method used for calibrating it, and sensors are typically calibrated with a single value from a home-use meter. Ms. Pinkos pointed out that home-use meters are not without problems of their own. Typically, manufacturers characterize the performance of BG meters by comparing meter results to results from a reliable reference method during a well-controlled study. Currently, the minimum accuracy requirement for FDA approval, is that 95% of the meter results generated during this idealized study must fall within ±20% of the reference method results at concentrations ≥75 mg/dl and within ±15 mg/dl of the reference method results at concentrations <75 mg/dl. Under real-world conditions, meter performance is likely to be poorer. She described four problems that are often associated with erroneous meter readings: (1) physiologic factors affecting ill patients (e.g., hypoperfusion, shock, anemia, hypoxemia); (2) interfering substances (e.g., maltose, ascorbic acid, acetaminophen); (3) human factors related to reagent strip storage or poor sample collection technique; and (4) strip manufacturing defects. Also contributing to CGM calibration errors is the fact that a single meter value is used to calibrate a nonlinear sensor response curve. Ms. Pinkos noted two limitations related to uninterrupted data in currently marketed sensors, the second of her three ideal features of CGMs. They include (1) early termination (often due to sensor failures or dislodgement) and (2) gaps in data (due to noise, unexplained dropout, or falsely low nocturnal readings). She indicated that the third of her three ideal features of CGMs, being impervious to physiological conditions, could be undermined in today's sensors by alterations in vital signs, exposure to stress, use of medications, or the presence of underlying medical conditions. She pointed out that many factors that may affect CGM results have not yet been fully characterized. A better understanding of conditions that affect CGM performance might be necessary before investigators can completely close the loop. Ms. Pinkos concluded her presentation by giving an overview of the two types of studies that have been used to evaluate CGMs. She believes that the lessons learned from these studies are also relevant to studies that may be used to characterize closed-loop systems. Each study type is necessary, although limited in terms of the information it can provide. In-clinic studies are valuable for assessing the accuracy and safety of a system, as well as the influence of a limited number of variables. It is difficult, however, for these studies to adequately simulate real life, that is, less controlled conditions that often affect performance. Home studies, in contrast, provide information on the ability of users to operate the device. Although they further demonstrate effectiveness and safety of the system, the information has limited value because of a lack of reliable reference readings and deviations in patient adherence with the protocol.

The third speaker in this session was LCDR Alan Stevens, Infusion Pump Team leader, Office of Device Evaluation, CDRH at the FDA, who discussed insulin pumps. LCDR Stevens began by stating that, for insulin pumps, effective performance is synonymous with safety. The FDA Infusion Pump Improvement Initiative recently reported 56,000 infusion pump adverse events from 2005 to 2009, and 45% were related to insulin pumps. Because currently approved insulin pumps were all cleared strictly for continuous subcutaneous infusion of insulin, AP systems, which command intermittent infusion of insulin, were not considered during clearance. Therefore, the FDA is now evaluating whether any safety assurance deficits exist. LCDR Stevens outlined five potential limitations in the performance of currently approved insulin pumps if they were to be used as part of an AP system: (1) accuracy variability at low volumes, (2) the potential for increased rate of occlusion, (3) extended time to detection of occlusion, (4) a potentially prolonged time interval from actuation to delivery, and (5) a lack of validation systems that a bolus has actually been delivered. Currently approved insulin infusion pumps specify basal rates of 0.05–30 U/h, and at 1 U/h the accuracy of delivery is typically within 5% of the programmed dose. These approved pumps also specify bolus doses of 0.05–30 U, and for a bolus of 1 U, the accuracy of delivery (when reported) ranges from ±30% to ±200% of the specified dose. Intermittently infusing insulin pumps can potentially occlude, and it can take as much as 24–60 hours to detect an occlusion. This delay would interfere with safe performance of such a device. The time interval from actuation of a bolus to delivery can be seconds or minutes, depending on the bolus volume and the pump design, which might lead to an unacceptable delay in treatment if an insulin pump was

part of a closed-loop system. Finally, an insulin pump does not validate that a bolus dose actually has been delivered.

The fourth speaker in this session was Sally Choe, Ph.D., team leader in the Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research (CDER) of the FDA. Dr. Choe discussed pharmacokinetic considerations when using insulin and other drugs in the artificial pancreas. Dr. Choe began with a classical definition of pharmacokinetics (PK), which is the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion. She also presented a pair of brief definitions of PK and pharmacodynamics (PD): PK can be thought of as the study of what the body does to a drug, and PD can be thought of as the study of what a drug does to the body. A clinical pharmacologist, who follows PK and PD, can assess the performance of an AP from both a system perspective (which includes both intrinsic and extrinsic factors) as well as a drug perspective (which includes the properties of insulin or any other drug that can be administered as part of the system). System factors are important to identify, because they can alter the PK and PD response to a drug, and it might be possible to compensate for this alteration by changing the dosing regimen. System intrinsic factors, which affect the PK and PD of insulin administered as part of an AP system, include age, race, gender, genetics, renal function, and pregnancy. System extrinsic factors, which also affect the PK and PD of insulin administered as part of an AP system, include smoking, alcohol use, interactions with other medications, and environmental factors. Drug factors are important to identify, because they determine the PK of a drug, which, in turn, determines the PD of the drug, and the PD is what is clinically measured. An example of a clinical effect of a drug is the glucose-lowering property of a bolus of insulin for an AP during a hyperglycemic stimulus. It is necessary to understand all the systemic and drug effects on PK and PD in order to develop an AP and minimize inter- and intrasubject variability in the effects of insulin therapy. Dr. Choe concluded that patient-centered clinical pharmacology specifies the right drug to the right patient from the right device in the right dose at the right time.

The fifth speaker in this session was John Knight, Ph.D., from the University of Virginia, who discussed comprehensive safety analysis applied to medical systems. Dr. Knight first defined safety, explained how to conduct a safety analysis, and finally applied safety principles to an AP. Dr. Knight defined "risk" as an expected loss per unit of time. In providing a definition of safety, he began by stating that there is no such thing as "perfectly safe," but "safety" can be considered as an acceptable level of risk. To develop a safety analysis, it is first necessary to establish safety requirements and then assess or predict safety performance. Standards are a useful tool to determine whether a technology is safe; however, these standards are difficult to tailor, especially for new systems. A safety analysis involves (1) conducting a comprehensive hazard analysis, (2) developing a model environment, (3) developing fault trees for each hazard identified, (4) identifying high probability events, and (5) modifying the system to reduce these probabilities. Eventually, a safety analysis leads to development of a safety case, which is a comprehensive argument that a system is acceptably safe to operate in a particular environment. Dr. Knight provided three examples of potentially serious events that could be associated with use of an AP. First, the insulin pump could fail with no backup insulin supply available. Second, a patient might become hypoglycemic with no food available. Third, a patient might need assistance with no caregiver available. These failures could all be prevented with an enhanced environment information system, which would include patient records, a wireless sensor network, alarms, a support team on call, and a national client center. Dr. Knight concluded by stating that, because an AP is a novel device with significant consequences following failure, prior to deployment, the developers of such a system should consider establishing explicit safety requirements, applying a comprehensive safety analysis, developing a safety case, and undertaking review of the safety case.

Discussion of Device Limitations Using Existing Technology for the Artificial Pancreas

The discussion consisted of comments from the audience and responses from one or two panel members. One topic that was brought up twice during this discussion (by Roman Hovorka, Ph.D., from the University of Cambridge, and Peter Simpson from DexCom) was whether CGMs that are not approved for primary use (and approved only for adjunct use or not approved at all) can be used in clinical trials of an AP system. Dr. Chip Zimliki said twice during this discussion that, from a system perspective, yes, one can use experimental device components within an AP system and it is not necessary to go through an incremental approach for getting a primary indication prior to going out and investigating such a device.

If there is a new experimental sensor, then additional information will be required for the IDE, such as biocompatibility data. Ms. Arleen Pinkos stated that the FDA would also want to see some basic effectiveness or performance data (although not a complete review) before the sensor is used in a larger system, such as an AP, in order to have some confidence in the information it will be providing. She stated that, otherwise, it would not be ethical to use the experimental sensor on volunteer subjects in a study. Another topic that came up twice was whether modified insulin preparations without preservatives should be used in closed-loop clinical trials. Preservatives mixed with insulin might be affecting the PK of the drug (Gerold Grodsky, Ph.D., University of California at San Francisco) or the electrochemical properties in the subcutaneous space where glucose might be measured with an electrochemical sensor in an AP system (Martin Peacock, Ph.D., from Z-Tech Scientific in San Jose, California).

Other topics that were briefly discussed following a comment from the audience were: standards for presenting CGM data for the durations of time lags, which are getting shorter in recent years (Apurv Kamath from DexCom in San Diego, California); variability of insulin action (William Tamborlane, M.D., from Yale University, New Haven, Connecticut), safety analyses for patients with diabetes (Dr. William Tamborlane); methods for calculating the rate of change of blood glucose (Susan Braithwaite from Chicago, Illinois); risk analysis associated with not providing tight glycemic control (Cindy Marling, Ph.D., from Ohio University, Athens, Ohio); the need to clearly state whether insulin pump adverse events are due to mechanical failure or to bad decisions made by patients [Aaron Kowalski, Ph.D., from the Juvenile Diabetes Research Foundation (JDRF), New York, New York]; what the appropriate safety comparisons are to an artificial pancreas (Robert Vigersky, M.D., from Walter Reed Health Care System, Washington DC); benefits of using multiple redundant sensors in a CGM (Jeffrey Joseph, D.O., from Thomas Jefferson University, Philadelphia, Pennsylvania); altered performance of freshly inserted CGM sensors when used for intravascular measurements and not just for subcutaneous measurements (Garry Steil, Ph.D., from Boston Children's Hospital, Boston, Massachusetts); potential barriers or benefits to developing a new alternate model for a safety analysis of an artificial pancreas (Dr. Garry Steil); and an increased frequency of glucose measurements by a CGM does not necessarily improve metabolic control by an artificial pancreas (Lutz Heinemann, Ph.D., from Profil Institute, Neuss, Germany).

Clinical Expectations for the Low Glucose Suspend Device Systems

Dr. Jeffrey Joseph moderated this third session of the workshop. Dr. Joseph introduced the session by presenting a case report of a hospitalized type 1 diabetes patient of his who had a CGM placed because of a hypoglycemic event around surgery. The patient's nurse was blinded to the data. Overnight, the patient had progressive hypoglycemia, and for approximately 5 hours in the middle of the night, she had hypoglycemia below 60 mg/dl. She was found unconscious with a finger stick BG of 18 mg/dl and a plasma glucose of 24 mg/dl. The rapid response team was called, and she received intravenous glucose. The patient awoke with no permanent sequelae. Dr. Joseph stated that this case is an example of an opportunity for a technology, even with its limitations, to be used possibly to prevent this type of event.

Patricia Beaston, M.D., Ph.D., medical officer and endocrine consultant to the FDA Endocrine Consultant Artificial Pancreas Working Group at the CDRH, gave the first presentation of the third session entitled, *Low Glucose Suspend Concepts and Considerations.* Dr. Beaston explained the concept of a reactive low glucose suspend (LGS) feature as a system intended to prevent or mitigate hypoglycemia. As part of an insulin infusion pump, a LGS system will stop delivering insulin at a preset glucose level as detected by a CGM. The pump will then resume insulin delivery after a preset duration of time. Dr. Beaston presented data from the available literature indicating that BG levels have been reported to rise significantly immediately after suspension of continuous subcutaneous insulin infusions. For example, in one study,[1] plasma glucose levels rose by 36–180 mg/dl over a 9 h period in the daytime following discontinuation of continuous subcutaneous insulin infusion in nine insulin-dependent diabetic subjects. In a second study,[2] plasma glucose levels rose by a mean of 72 mg/dl over a 2 h period overnight following discontinuation of continuous subcutaneous insulin infusion in nine insulin-dependent diabetic subjects. In a third study,[3] over a 6 h period overnight following discontinuation of continuous subcutaneous insulin infusion in 15 insulin-treated diabetic subjects classified as hypoglycemic, euglycemic, or hyperglycemic at baseline, BG levels rose by 209, 142, and 148 mg/dl, respectively. Dr. Beaston stated that these studies used fast-acting insulins rather than the more commonly used rapid-acting insulins and suggested that it may be informative to repeat these studies using the insulins proposed for use in the AP systems. Dr. Beaston then showed two slides

detailing the accuracy of a FDA-approved CGM that was not named. She also presented the true and false alert rates of this monitor for identifying low and high alerts. The true alert rate was defined as the percentage of time that the glucose level was as extreme or more extreme than the alert setting and the alert sounded. The false alert rate was the percentage of time that the sensor alarmed but the glucose level was less extreme than the reference level. As the low alert level was set higher than the target, the true alert rate rose and the false alert rate also rose. As the high alert level was set higher than the target, the true alert rate fell and the false alert rate also fell. An alternate approach to suspending insulin delivery when the glucose level falls to a target hypoglycemic level is predictive LGS, which means that insulin delivery is suspended and then restarted later based on an algorithm that meets a specified prediction based on glucose levels detected by the CGM. Dr. Beaston outlined a set of challenges in evaluating a LGS system. These included (1) selecting either a single or a multiple threshold approach, (2) developing a clinically meaningful metric to describe decreased low glucose levels, (3) determining a setting for effectiveness to be demonstrated (in clinic versus outpatient), (4) selecting safety endpoints to be measured, (5) determining a setting for safety to be demonstrated (in clinic versus outpatient), and (6) selecting safety mitigations to be established (in clinic versus outpatient). For example, hypoglycemia is a risk that poses a safety issue, so an investigator needs to state how this safety issue can be addressed in the protocol, such as by providing: a method and frequency of glucose testing; stopping rules for glucose levels of concern; appropriate interventions to have available at the testing site, such as glucagon, intravenous dextrose, a crash cart; and an appropriately trained on-site staff for monitoring and intervention. Dr. Beaston concluded her presentation with a list of lessons learned and points for discussion regarding AP research. These points included the need for (1) individualized thresholds based on patient requirements; (2) agreement on a definition of hypoglycemia; (3) accurately measuring differences in glycemia (area under the curve using continuous glucose and finger stick BG readings are unlikely to be sufficient as the sole measurement); (4) collection of selected data that can be obtained only in a clinical setting, such as laboratory-based glucose levels; and (5) collection of selected data that can be obtained only in the outpatient setting, such as hemoglobin A1c (A1C).

The second speaker in the session on LGS systems was David Klonoff, M.D., FACP, medical director of the Diabetes Research Institute at Mills-Peninsula Health Services in San Mateo, California, and clinical professor of medicine at the University of California at San Francisco. He outlined three potential benefits of using a LGS system: (1) fewer nocturnal hypoglycemic events and therefore fewer acute cardiovascular events, (2) lower A1C, and (3) less glycemic variability, because hypoglycemia can beget severe rebound hyperglycemia. He also outlined four potential risks of using a LGS system: (1) inappropriate suspension, which could lead to rebound hyperglycemia; (2) inappropriate suspension, which could lead to ketonemia, elevated blood beta-hydroxybutyrate levels, or the onset of diabetic ketoacidosis (DKA); (3) inappropriate suspension, which could lead to a rise in A1C levels; and (4) appropriate suspension but failure to protect a patient from a hypoglycemic episode. He acknowledged that a LGS system might result in a tradeoff consisting of fewer hypoglycemic episodes but also higher mean glycemic levels, which would lead to higher A1C levels. Dr. Klonoff described five factors that would affect the balance between benefit and risk and that would need to be studied individually for any specific proposed LGS system: (1) the device itself, including its sensor, predictive algorithms, alarm intensity, shutoff duration, and human factors; (2) the study protocol, including the intended use, LGS threshold, type of insulin used by the pump, time of day, and therapeutic endpoints, which includes quality of life; (3) the subjects who are being tested, including their total daily insulin dosage, their individual risks of acute complications, and their risks of chronic complications; (4) an agreed upon relative impact ratio to compare the benefits of protecting from acute complications compared to protecting from chronic complications; and (5) the availability of alternate treatments (instead of LGS) to prevent hypoglycemia and hyperglycemia. Dr. Klonoff presented unpublished data courtesy of Pratik Choudhary from the X54 Veo UK Multicenter Study of the performance of Veo (Medtronic Diabetes, Northridge, CA), which is a LGS system that is not currently approved by the FDA in the United States. Regarding the four previously listed potential risks of using a LGS system, in this study, Veo was not associated with significant mean rebound hyperglycemia; DKA was not observed, although ketone levels were not measured; A1C or other indices of mean glycemia levels were not measured; and there was not any trend to failing to protect from hypoglycemia, because the mean duration of hypoglycemia was shorter when Veo was used than when it was not used. Dr. Klonoff concluded with a case report of a patient who died of hypoglycemia from excessive insulin therapy in a hospital while wearing a CGM with no LGS feature. Dr. Klonoff speculated that

the patient might have survived had his pump contained a LGS feature.[4] He asked the FDA to consider not only the risks of approving products containing LGS, which are intended to prevent catastrophic acute hypoglycemic events, but also the risks of not approving such products.

The third speaker in the session on LGS systems was Bruce Buckingham, M.D., professor of pediatrics at Stanford University, Stanford, California. Dr. Buckingham spoke on *Evaluating Low Glucose Suspend and Predictive Pump Shut-Off to Prevent Nocturnal Hypoglycemia.* He presented data from the JDRF randomized controlled trial on nocturnal hypoglycemia.[5] This study demonstrated that hypoglycemia occurred during 8.5% of 35,000 nights. The mean duration of hypoglycemia was 81 min. The duration of hypoglycemia was at least 2 h in 23% of episodes and at least 3 h in 11% of episodes. Dr. Buckingham presented data from a study published this year showing that, using algorithms to shut off the insulin pump when hypoglycemia is predicted, it is possible to prevent hypoglycemia on 75% of nights (84% of events) when it would otherwise be predicted to occur.[6] He discussed the need to assess efficacy and safety of hypoglycemia prediction and pump shut-off in the home environment. He raised four questions that should be addressed in assessing the performance of a LGS system: (1) does the system decrease the incidence of hypoglycemia by 50%; (2) is there an increase in nocturnal hyperglycemia, enough to raise the A1C by 0.5%; (3) do multiple nocturnal pump shut-offs result in significant ketosis; and (4) do these systems disrupt sleep or provide less disruptive sleep? Dr. Buckingham stated that it is not feasible to make discrete measurements of BG to assess the outpatient performance of a LGS system to detect nocturnal hypoglycemia for four reasons: (1) most episodes of nocturnal biochemical hypoglycemia do not awaken a patient to do a test; (2) single or multiple measurements will probably miss events; (3) frequent overnight sampling would be needed, and that would disrupt sleep; and (4) it is impractical to house an intravenous line and a laboratory-grade reference glucose analyzer in a home setting. Dr. Buckingham stated that, furthermore, severe nocturnal hypoglycemic events occur infrequently. To support that statement, he pointed out that, in the JDRF study, the incidence of nocturnal hypoglycemia was 13.5 events per 100 patient years, and to demonstrate a 50% reduction in incidence, it would be necessary to follow 10,800 subjects over 3 months. Dr. Buckingham then proposed that CGM data be used as a tool for determining the incidence of hypoglycemia. He pointed out that a CGM is not as accurate as a laboratory-measured glucose level, so use of this tool would require additional study nights. He predicted that there would be 20% more false positive and 20% more false negative events defined using a CGM as compared to a laboratory-reference glucose. He stated that it could be calculated that a treatment effect can still be assessed by increasing the sample size threefold to make up for this inaccuracy.[7] Then, assuming a 15% incidence of nocturnal hypoglycemia in any night, using a CGM would require 2016 study nights to determine if there is a 50% treatment effect as compared to 672 nights using a reference-glucose method. Although it would be valuable to demonstrate that there is no increase in A1C by as much as 0.5% or more, it would be impractical to measure A1C directly. This is because this type of a study is only looking at the effect on glucose levels overnight, and approximately 2/3 of the effects on A1C are from daytime glucose levels. He stated that the best randomization time period should be on an nightly basis rather than in a 3-month block and proposed that elevated mean overnight CGM glucose levels should be used as a surrogate marker for increasing A1C levels. He stated that each 25 mg/dl increase in mean CGM glucose corresponds to an increase in the A1C level by 1%.[8] Dr. Buckingham then stated that LGS should not be evaluated in an inpatient setting for three reasons: (1) LGS is a very basic tool, and no tuning parameters that are part of an inpatient experience need to be tested; (2) the risk of rebound hyperglycemia following suspension of an insulin pump for 2 hours has already been studied in five previous inpatient studies,[3,9–12] and the outcome was mild transient hyperglycemia and minimal ketonemia; and (3) there is a narrow window for evaluating the effectiveness of LGS (between 50 and 70 mg/dl) if this study is activated at 70 mg/dl and terminated at 50 mg/dl. Dr. Buckingham concluded by stating that LGS should be evaluated in a 3-month randomized outpatient study with three endpoints: (1) hypoglycemia that could be assessed by CGM and meter readings, (2) hyperglycemia that could be assessed by A1C and mean BG levels, and (3) ketonemia that could be assessed by morning ketone testing.

The fourth speaker in the session on LGS systems was Dr. William Tamborlane professor of pediatrics at Yale University. Dr. Tamborlane began by defining the major benefit of LGS systems as the rescue of patients who are unconscious and unable to respond to alarms and to shut off their pump for a period of time due to hypoglycemia while asleep during the night. Dr. Tamborlane explained how patients with type 1 diabetes often lack the ability to defend themselves from nocturnal hypoglycemia with the three major responses to hypoglycemia that are used

by patients without diabetes. Type 1 diabetes patients cannot shut off the entry of insulin into the circulation (because it is already present in depot form rather than released only when needed), cannot release a normal amount of glucagon, and, when sleeping, cannot release a normal amount of epinephrine. Next, Dr. Tamborlane showed that prolonged nocturnal hypoglycemia can precede seizures,[13] and there may be an opportunity, if insulin infusion can be suspended, for these glucose levels to rise spontaneously and thus prevent a seizure. Dr. Tamborlane presented data from a study he conducted in 1998 in which he shut off insulin in pump patients. Two hours following suspension of insulin, the rise in BG levels (from approximately 90 to 120 mg/dl) and blood beta-hydroxybutyrate keto acid levels (from 0.2 to 0.3 mmol/liter) was not clinically significant.[10] He then stated that use of a LGS system would be expected to result in (1) an overall lowering of hypoglycemia exposure (both in the daytime and at nighttime) and (2) more consistent sensor use because of added therapeutic benefit to the patient. These two effects of LGS system use would be expected to result in more effective maintenance of target A1C levels in well-controlled type 1 diabetes patients and more effective lowering of A1C in type 1 diabetes patients with A1C levels >7.0%. Dr. Tamborlane then outlined a study design to test the performance of a LGS system. The study would be an outpatient study comparing two groups: sensor-augmented pump (SAP) with LGS versus pump therapy with self-monitoring of blood glucose. Subjects would be eligible if their A1C level was below 7.5%. The primary outcome measure would be the percentage of CGM data points under 60 mg/dl. He stated that he believed that CGM glucose levels could indeed be used as an outcome measure despite their perceived inaccuracy. This is because, if a two-group parallel group study was designed and the same CGM device was used to look at glucose profiles in both the controls using a blinded sensor as well as the intervention group using a SAP plus a LGS, then the errors would even out. The safety endpoints would include a noninferiority comparison compared to controls with a worsening of A1C levels by less than 0.5% in the SAP/LGS group, plus no difference in rates of DKA in the two groups. For safety mitigation, he would compare morning fasting BG and urine ketone measurements following suspension nights compared to nonsuspension nights.

The fifth speaker in the session on LGS systems was Francine Kaufman, M.D., chief medical officer and vice president of Global Clinical, Medical, and Health Affairs, Medtronic Diabetes, Northridge, California. She spoke about Medtronic Diabetes's SAP with LGS: the Paradigm Veo. Dr. Kaufman began by describing the features of Veo, including (1) Veo predictive alerts and event alarms are user programmable; (2) the shutoff glucose range is 40–110 mg/dl; (3) suspension of insulin infusion for a 2 h period; (4) if the CGM sensor glucose remains low 4 h after resuming insulin delivery, then the pump will resuspend insulin delivery; (5) all other sensor functions remain operational during insulin suspension; (6) a patient can interrupt the suspend function at any time or else can shut off the alarm and remain in suspend mode; (7) prevention of bolus delivery when suspended; (8) insulin delivery shut off in patients who are at a glucose level that may be associated with cognitive impairment; (9) not intended to be the method of treatment for hypoglycemia when patients are able to respond to alarms/alerts; and (10) once engaged, LGS will cycle insulin delivery on and off until cancelled or until the pump battery fails. Dr. Kaufman presented data from the European Interpret Study, which is a postmarketing observational study of sensor usage combined with pump therapy in type 1 diabetes, without study-related interventions. Among subjects who were using Veo, A1C levels improved. Among 44 Veo users for at least 3 months, mean A1C fell from 8.4 to 8.2% (p = .3462), and among 27 Veo users for at least 6 months, mean A1C fell from 8.8 to 8.3% (p = .0213). Dr. Kaufman then stated that an analysis of data from the company's CareLink database revealed that 23 million pump days with Veo have been analyzed and over 9 million suspends have occurred, with over 281,000 of them lasting 2–3 h and over 270,000 of them lasting ≥3 h. In the same database, 935 Veo users were studied in the first 7 months of 2010. During 40,734 Veo wearing days, the LGS feature was used 27,216 times by these users. More LGS events occurred in the daytime than at night, with 12:00 PM being the most common time of the day for LGS to occur. More of these suspends were terminated by the patient within the first 5 min than within any other 5 min increment measured. Dr. Kaufman then pointed out that there were 278 patients who used Veo for at least 3 months. Comparing BG levels on days when the system was turned on versus days when the system was not turned on, the BG levels (mean ± standard deviation) were 155.58 ± 67.41 versus 155.06 ± 75.52, respectively. Dr. Kaufman concluded that this data, which had compared using Veo with not using Veo, demonstrated no significant difference in mean BG levels and a suggestion of decreased standard deviation.

Discussion of Clinical Expectations for the Low Glucose Suspend Device Systems

Five members of the audience provided prescheduled comments from the public. The first three speakers were pediatric patients with type 1 diabetes who described their fear of hypoglycemia. They urged the FDA to adopt reasonable standards for LGS devices, to encourage companies to continue developing these devices, and to speed up the approval of the AP. Victor Skladnev, M.Eng., from A1Medics in Sydney, Australia, a speaker with a background in industry, suggested that a closed-loop system should use a failsafe method to trigger a LGS action with a different mechanism of detecting glucose than a traditional glucose sensor. Michael Bédard from CybioCare in Quebec City, Canada, suggested using two different sensors with two different technologies to control the LGS action, and if there was a discrepancy between them, then a capillary BG level could be tested as a tiebreaker. He also suggested that a hypoglycemic alarm should be transmitted from a patient's CGM to another person's cell phone.

A discussion about the how to conduct a trial of a LGS system followed the formal presentations and scheduled comments from the public. The main issues for testing Veo in a clinical trial were (1) how to measure the short- and long-term consequences of appropriate shutoff of insulin infusion in case of true hypoglycemia, (2) how to measure the short- and long-term adverse consequences of inappropriate shutoff in case of false hypoglycemia, and (3) how to balance the benefits of appropriate shutoff and the adverse consequences of inappropriate shutoff for patients using an insulin pump. Regarding the optimal method for measuring short-term glycemic benefits or adverse consequences, there was a wide spectrum of points of view on which methods would be appropriate.

The Veo LGS event-based system was used as the example of a LGS system for almost the entire duration of the discussion. However, an alternate type of LGS system, which is currently in development, was also discussed. This is a predictive algorithm-powered type of system intended to shut off insulin infusion in anticipation of predicted hypoglycemia rather than at the point of a measured event of hypoglycemia (similar to the Veo system). A predictive algorithm-based LGS suspend system is less dependent on point accuracy of a CGM to trigger insulin suspension than on trend accuracy, and CGMs appear to be more accurate in this capability than in determining exact point accuracy. Both FDA officials and the clinical community felt that such a system could offer promise as a future product, because CGM would then be used for its best capabilities, and there is a potential for shutting off insulin infusion in a patient with impending hypoglycemia before the amount of insulin onboard becomes so great that hypoglycemia is inevitable.

For Veo, a widely expressed opinion was that, whichever method is used for measuring glucose immediately following a LGS action, the most meaningful episodes to study are those that do not result in an immediate override of insulin suspension (i.e., does not result in the insulin infusion being resumed within the first 2 h of suspension). Such prolonged suspension of at least 2 h, which generally occurs during sleep but not during the daytime, will best separate the effects of LGS compared to no LGS. This is because most cases of prolonged (and potentially either beneficial or dangerous) suspensions will occur only if a subject fails to awaken from an alarm. A short suspension lasting only a few minutes followed by resumption of insulin dosing accompanied by food intake will likely have little effect on short- or long-term markers of diabetes control. The short-term anticipated period of hypoglycemia, which should be lessened by using this device, may not even appear with rapid correction of hypoglycemia.

The panel members also felt that is impractical to expect a sleeping subject to awaken from most hypoglycemia alarms. During the discussion, several discussants mentioned that most patients with and without diabetes routinely slept through hypoglycemia CGM alarms during the night. If a subject were to awaken because of their alarm (or already be awake in the daytime when the hypoglycemic alarm sounds) and the subject were to subsequently eat to raise the BG level, then it would not be possible to know whether the LGS resulted in less time spent in the hypoglycemic range. This is because the act of eating, and not the LGS activation, would have, in part or in total, aborted the hypoglycemic excursion, and in such a scenario, the magnitude of contribution from LGS insulin shutoff could not be independently assessed. There was consensus that the critical episodes for monitoring outcomes of LGS are nocturnal hypoglycemic episodes resulting in the LGS persisting for a period of time, and in the case of Veo, persisting for at least 2 hours.

There was a limited amount of discussion on whether LGS should be evaluated in an inpatient setting. The majority of a limited number of comments on the topic

were in favor of testing exclusively in the outpatient setting, because LGS is a basic tool, requires minimal patient education, and is especially not the type of education that can take place only in an inpatient setting. Also the subject of some discussion was whether studies in the literature have already demonstrated the safety of a 2-hour period of insulin suspension occurring during euglycemia and also if, in a clinical trial, insulin suspension with the specific LGS device will occur at the protocol-specified levels of glycemia described in the literature or will not occur at these levels because of sensor inaccuracy.

The optimal comparator in an outpatient crossover study or a randomized clinical trial of Veo compared to no use of Veo could use one of two control interventions in outpatients testing daily use of this product. These include either SAP with no LGS or an insulin infusion pump with self-monitored blood glucose. Regarding inpatient studies, there was little sentiment that such a setting was necessary for demonstrating accuracy other than to house subjects who would require reference testing with hospital-based reference blood analyzer technology. There was no sense that inpatient testing would be a useful way to assess effectiveness, since the analyte measures of short- and long-term effectiveness could all be measured in a home setting, except for any necessary blood analyzer tests of glucose. The main benefit of inpatient testing was that this environment would be suitable for comparison studies of the same patients in a hypoglycemic state both with and without Veo. In order to study any patient in a hypoglycemic state, it would be necessary to push exercise, increase the insulin dose, or limit food intake to ensure hypoglycemia. The subject would be at some risk of hypoglycemia, and the best mitigation would be admission for observation. An opposing viewpoint was that it would be sufficient to study response to Veo in populations of subjects either using or not using Veo rather than compare a set of the same subjects both with and without Veo, and in this scenario, subjects would not require manipulation of their morning BG levels. There seemed to be little instruction or observation needed other than for hypoglycemia for patients, which would necessitate inpatient observation.

A wide range of metrics for optimally measuring short-term glycemic responses to the Veo LGS was proposed by discussants. The main short-term responses to LGS were generally perceived to be the percentage of time spent in a hypoglycemic range while using a LGS system and the percentage of time spent in a hyperglycemic range following termination of a 2-hour suspension of insulin delivery by the LGS system, as well as the appearance of significant blood ketonemia or onset of DKA. A beneficial short-term outcome of LGS would be a significant decrease in the time spent in hypoglycemia with no significant increase in time spent in post-suspension hyperglycemia or any significant increase in the incidence of postsuspension ketonemia or onset of DKA. The opposite would indicate adverse short-term consequences of using a LGS system. A significant rise in A1C (i.e., by more than 0.5%) and glucose variability with LGS would indicate excessive suspension of insulin, an overall underdosing of insulin, and attendant higher BG levels with inability to maintain a mean BG level as low as without the LGS system. A fall in A1C levels and glucose variability with LGS could have been attributed to fewer hypoglycemic episodes that would have been accompanied by physiologic rebound spikes in glycemia and attendant higher, more variable BG levels. All of these phenomena would have been prevented by the LGS system.

The preferred methods for measuring severity and duration of hypoglycemia ranged from using the same CGM, which triggered the insulin suspension in the first place, for measuring multiple data points of interstitial fluid glucose to using a handheld glucose monitor for measuring one or more capillary glucose data points to using a laboratory-grade reference method for measuring one or more capillary whole BG or plasma glucose data points. The optimal timing for measuring the onset of a nocturnal LGS activation ranged from awakening a sleeping patient to check a capillary or BG level at the onset of an episode of CGM alarm-diagnosed hypoglycemia to not awakening the subject and instead using the CGM to measure the glucose level at onset of insulin suspension right through the postsuspension period.

For Veo, a variety of candidate technologies were recommended as the best methods for measuring glucose levels following a hypoglycemic event that results in a LGS action and does not result in an immediate override of insulin suspension (i.e., does not result in the insulin infusion being resumed). This topic was the most intensely discussed subject of the daylong workshop. Proponents of using a CGM to monitor duration and severity of hypoglycemia pointed out that only this device can capture multiple data points in a short time period and accurately determine duration spent in hypoglycemia both before and after use of a LGS system as well as the duration of time spent in hyperglycemia following a period of insulin suspension.

Proponents of using a reference method for measuring BG levels at the onset of CGM-diagnosed hypoglycemia pointed out that no CGM is FDA-approved as a primary reference method with traceability to National Institute of Standards and Technology standards in the same way reference laboratory-grade blood analyzers are, and furthermore, it is simply not appropriate to use a system to measure its own efficacy. This point was debated by those who stated that inaccuracy and great variability of CGMs excludes them from being a reference method in any circumstances and those who stated that the absence of bias with currently approved CGMs means that errors will cancel out. This would mean that the mean magnitude and duration of hypoglycemia or hyperglycemia measured by a currently approved CGM for any population will be exactly the same as with a highly accurate method as long as a larger sample size is selected to make up for the greater variability of a CGM compared to a highly accurate sensor. Proponents of using handheld glucose monitors stated that this method combines the advantages of using of a FDA-approved primary method (although less accurate than a reference blood analyzer) with a convenient, simple, and rapid method for self-testing (although less convenient than a CGM). Another advantage of using a CGM that measures glucose automatically compared to BG methods is that a CGM can identify a hypoglycemic episode in the absence of an alarm, and this method is very suitable for monitoring control nights when there will be no alarm to awaken a research subject and LGS will not be activated.

Regarding the comparative benefits of appropriate shutoff and the adverse consequences of inappropriate shutoff for patients using an insulin pump, there was a dichotomy of opinions on this topic. One point of view was presented that (1) the risk of adverse events from insulin shutoff (even when hypoglycemia has not been present) has been demonstrated in the literature as not leading to significant hyperglycemia, increased ketonemia, or DKA in any populations; (2) prolonged hypoglycemia has been associated with preventable acute cardiovascular and neurologic damage; and (3) even with a less than perfectly accurate sensor, in a worst case scenario, inappropriate insulin suspensions by Veo will likely occur within only 10–40% of 70 mg/dl of the usual target of 70 mg/dl, which is still below 100 mg/dl, and these differences in suspension threshold levels will not be clinically significant, so therefore, future trials of Veo would be expected to show net benefit even if the device were to inappropriately suspend insulin occasionally. The other point of view was that (1) the inherent inaccuracy of the Veo sensor will necessarily lead to many inappropriate suspensions in individual subjects; (2) any inappropriate suspensions will lead to higher BG levels and greater glycemic variability that cannot be controlled merely by returning to presuspension insulin infusion rates; and (3) for many individuals using Veo, shutoff may occur at levels as high as 180–200 mg/dl, so therefore, if inappropriate suspensions like this continue to occur in future trials of Veo, then there will likely be a net worsening of glycemic control with little benefit.

Comments were then solicited from the audience. Ken Ward, M.D., from Oregon Health and Science University, expressed frustration that there is no good reference method for benchmarking CGM data. He also stated that, in spite of some anticipated inappropriate suspensions with Veo, if the long-term safety metrics of A1C and urine ketones do not worsen with use of Veo, then we will be in a better place than we are currently. George Cembrowski, from the University of Alberta, recommended the use of medical decision making to determine the net beneficial or adverse tradeoff between accepting appropriate suspensions along with inappropriate suspensions. By this method, one factors in the number of patients who are at high risk from hypoglycemia multiplied by the risk of developing hypoglycemia without a LGS system and compares this to the number of patients who are at low risk from hyperglycemia multiplied by the risk of developing hyperglycemia or acidosis from inappropriate suspension by a LGS system. Low glucose suspend could then be by prescription only, depending on the individual patient's requirements. Ilan Irony, from the FDA, stated that the principle of medical decision-making can be applied to evaluating use of LGS. David Rodbard, from Potomac, Maryland, suggested that a panel convene to establish the accuracy of CGM systems, self-monitoring of blood glucose, and arterial blood analyzers as well as the effects of calibration and time lag. Dr. Lutz Heinemann recommended that circulating insulin levels be measured in LGS-treated subjects to see how long it takes for them to disappear. Dr. Garry Steil cautioned that, even though CGM devices are unbiased at the average calibration point, the linear regression of CGM and reference glucose levels is not necessarily linear throughout the physiologic range because of twists in this line. He stated that CGMs tend to overestimate glucose levels in the hypoglycemia range and underestimate in the hyperglycemia range. He recommended that, in a study of the performance of LGS systems during hypoglycemia, the CGMs be calibrated to be accurate in the hypoglycemic range. Then there will be no bias in the hypoglycemic range where the LGS system is to be tested. Michael Bedard,

from Canada, asked whether failure to respond to an alarm indicates true hypoglycemia. The panel consensus was that euglycemic patients can also fail to respond to alarms. Nate Paul, from Oak Ridge National Laboratory, suggested development of a multimodal alarm system for hypoglycemia to include turning on lights and the television, setting off a vibrating pillow, and summoning one's dog. Dr. Patricia Beaston then cautioned the audience about the risks of linking multiple medical devices, because this device interoperability requires constant software compatibility, a lack of which can lead to linked systems causing each other to fail because of clashes in the software.

Clinical Expectations for Artificial Pancreas Device Systems

Dr. David Klonoff moderated this fourth session of the workshop. Patricia Bernhardt, M.T.(ASCP), from the CDRH at the FDA, gave the first presentation of the session, entitled, *Clinical Expectations for the Artificial Pancreas*. She posed seven questions about protocols for developing an AP to facilitate regulatory review of this technology (see **Table 1**): (1) What is the acceptable target range for closed-loop control? (2) What are the appropriate effectiveness endpoints to be used (effectiveness endpoint)? (3) How can this effectiveness be demonstrated in clinical studies (in clinic versus outpatient)? (4) What safety issues would be appropriate for this system (safety endpoint)? (5) How can this safety be demonstrated in clinical studies (in clinic versus outpatient)? (6) What safety mitigations should be established for these studies (in clinic versus outpatient)? (7) What is the acceptable balance for effectiveness and safety for success?

Table 1.
Clinical Expectations for the Artificial Pancreas: Seven Questions

1	What is the acceptable target range for closed-loop control?
2	What are the appropriate effectiveness endpoints to be used (effectiveness endpoint)?
3	How can this effectiveness be demonstrated in clinical studies (in-clinic vs. outpatient)?
4	What safety issues would be appropriate for this system (safety endpoint)?
5	How can this safety be demonstrated in clinical studies (in-clinic vs. outpatient)?
6	What safety mitigations should be established for these studies (in-clinic vs. outpatient)?
7	What is the acceptable balance for effectiveness and safety for success?

The second speaker in this session was Dr. Klonoff. Dr. Klonoff covered the AP from the perspective of where we are now, where we are going, and how we will get there. The current three basic components of an AP system include a continuous glucose sensor, an insulin delivery system, and a local controller, and all three components can communicate by way of a radio. Emerging systems will also contain a daily insulin sensitivity detector, a glucagon delivery system, and a remote controller. Future AP systems will also contain software for integration of electronic medical record data, telemedicine management capabilities, exercise and food sensors, and global positioning system (GPS) to provide capabilities for emergency services. Data inputs into an AP include both glucose data and nonglucose data. Dr. Klonoff stated that the future AP will provide telemedicine care. He proposed a future such system known as Knowledge of Loop Operations Necessary System to Accomplish Repairs or KLONSTAR. This system would be alerted in the event of hypoglycemia, and a representative would call to check on the patient's condition. If the patient cannot respond, then help would be dispatched to the location determined by the system's GPS. KLONSTAR would relay critical diabetes information to emergency responders. He showed a reference by a team from the University of California, Santa Barbara, of a CGM system enabled with GPS and texting capabilities, which can be linked to an insulin pump.[14] Dr. Klonoff stated that the FDA is concerned about whether currently envisioned closed-loop systems are safe and effective and if the FDA wants to see robust studies of these new technologies. He then described the recent JDRF Clinical Recommendations Panel on Closed-Loop Systems, which comprised nine scientists and clinicians who are interested in closed-loop control. He then introduced three of these members to provide comments during this session of the workshop. These JDRF panel members and their topics for the FDA meeting were Dr. Richard Bergenstal (inpatient studies), Dr. Robert Vigersky (outpatient studies), and Dr. David Nathan (safety, risks, and benefits). Dr. Klonoff concluded that, for appropriate FDA regulation of closed-loop systems, (1) these systems must be safe and effective; (2) to define safety, patient populations, device features, intended use, and alternative therapies must be defined; (3) to define effectiveness, intervention and study endpoints must be defined; and (4) FDA standards must evolve to keep pace with new AP technologies.

The third speaker in this session was Richard Bergenstal, M.D., executive director of the International Diabetes

Center at Park Nicollet Clinic in Minneapolis, Minnesota. Dr. Bergenstal first reviewed how safety with use of diabetes technologies has been progressively evolving. During the Diabetes Control and Complications Trial study in 1984, there were 62 severe hypoglycemic events per 100 patient years, with a mean A1C of 7%, and in 2009, in the JDRF SAP study, there were only 13 severe hypoglycemic episodes per 100 patient years, with a mean A1C of 7.5%. He stated that, to reach the next set of milestones, which would be A1Cs under 7% and elimination of hypoglycemia, new technology, such as an AP, will be necessary. Dr. Bergenstal stated that AP research should begin in the hospital with an emphasis on safety and identifying ideal candidates, and then it would be appropriate to gradually explore more advanced studies, more advanced circumstances, and more effective algorithms. This approach would be different than the ideal approach for a LGS system. Dr. Bergenstal stated that an inpatient study should challenge the algorithms and technology with variations in exercise, meals, and other types of challenges, and these types of studies can never be replaced by *in silico* studies. Dr. Bergenstal reviewed elements of inpatient studies from the perspectives of the hospital environment, patient selection, protocol design, technology, and transition to outpatient studies. The environment should be a diabetes research center with experience in continuous subject monitoring, with some elements resembling the outpatient environment, such as nonhospital types of food or places to walk around. The patients should be experienced with using an insulin pump and a CGM to lessen the need for training. They should be adherent and regimented adults initially. The protocol does not require control groups at the outset but must include safety parameters and performance parameters. Eventually, there could be cross-over from SAP therapy to AP therapy. Study durations might range from 1–2 days if the focus is on technology, up to 2 weeks if the focus is on transitioning to the outpatient setting. All currently available rapid-acting analog insulins could be treated interchangeably without requiring separate studies, but newer potentially even faster acting insulins are under development, and these products will need to be tested independently. The protocol would contain safety mitigations for underdelivery or overdelivery of insulin. Relevant technologies would need to be constantly reviewed, such as new pumps, new alarms, or new dual glucose sensors. The emphasis will be on inpatient studies that can transition patients from the inpatient setting to the outpatient setting through such stages as studies where the subjects are making their own adjustments and the investigators are observing closely. Later, studies will be needed where the subjects will be in charge of their devices and will go into the outpatient setting. Eventually, the inpatient staff will be merely monitoring these subjects at a distance.

The fourth speaker in this session was Dr. Robert Vigersky, M.D., COL MC, director of the Diabetes Institute at the Walter Reed Health Care System. Dr. Vigersky focused on six elements of outpatient studies of an artificial pancreas: (1) subject selection, (2) indications for use, (3) therapeutic goals, (4) study duration, (5) safety and efficacy, and (6) standards of care. He stated that, initially, the ideal volunteer with type 1 diabetes would be an adult experienced with using an insulin pump and a CGM. The subject would need to have a history of good control defined as no A1C below 7.5% in the past year, no severe hypoglycemia over the past 6–12 months, and no behavioral issues. In later studies, the profile could be expanded to include adolescents and then adults. Also, later studies could include patients with unstable control, such as brittle diabetes, gastroparesis, frequent hypoglycemia, blindness, or a corticosteroid-requiring illness. Dr. Vigersky stated that the main two indications for use in these studies should be severe recurrent hypoglycemia and failure to achieve adequate metabolic control without hypoglycemia. Treatment goals for these two sets of subjects would be different. For recurrent hypoglycemia subjects, the primary outcome would be superiority of the test method for avoiding hypoglycemia both during the night (the most important goal) and the day (the second most important goal) in crossover studies compared with open-loop control. The secondary goals would be to maintain the A1C level (a noninferiority goal) as well as to improve the counter-regulatory profile and the quality of life as assessed by validated tests. For failure to achieve metabolic goals subjects, the primary outcome would be improvement in A1C in parallel studies compared with open-loop control. Secondary goals for these subjects would be noninferiority-based frequency of hypoglycemia or measures of glycemic variability. He stated that study durations should be at least 2–3 months, but the studies should include telemetry monitoring or daily phone calls initially and less contact eventually, as infrequently as every 2 weeks. Regarding safety, Dr. Vigersky stated that there should be no increase in DKA, symptomatic hypoglycemia, or any other adverse event associated with the use of this specific technology, such as hospitalizations or catheter complications. Regarding effectiveness, Dr. Vigersky stated that the primary outcome would be achieving metabolic control as measured by A1C but that other measures of metabolic control might be the percentage of time spent in the euglycemic range and less glycemic variability. Increased

quality of life would be another measure of effectiveness of this type of system. Dr. Vigersky stated that there is currently no consensus standard of care for using an AP. The Endocrine Society will be publishing guidelines for use of CGMs in 2011. He concluded that the standard of care for using this technology should be to provide better care than what is currently being delivered.

The fifth speaker in this session was David Nathan, M.D., professor of medicine at Harvard Medical School in Boston. Dr. Nathan began his presentation by recounting the benefits of intensive control as well as the hazards of hypoglycemia, which is the main safety concern associated with that approach. He began his summary of discussion from the JDRF panel by stating that, for safety and benefits, one size does not fit all, meaning that multiple types of patients will each have their own priorities for safety and benefits if they will be using an AP system. The only common goal for all types of patients is that AP therapy should never result in an increase in the incidence of DKA. Dr. Nathan then discussed safety and effectiveness priorities for three subsets of type 1 diabetes patients. First, patients with severe recurrent hypoglycemia have the greatest need for an AP, and their major goal is a safety goal: a decrease in their incidence of hypoglycemia. Although it is hoped that intensive control with an AP might result in A1C not worsening or even improving, the risk of hypoglycemia is so severe that an increase in A1C might be acceptable if the primary safety goal of less hypoglycemia could be achieved. Second, patients with acceptable A1C levels and infrequent severe hypoglycemia by definition have too few hypoglycemic episodes for a decrease in the incidence of this complication to be used as an endpoint. For these patients, the potential benefits would be improvements in glycemic variability, less time spent in hypoglycemia, and improved quality of life, all accompanied by no rise in A1C levels. Third, patients with above-target glycemic control are at increased risk of microvascular disease. For these patients, the priority therapeutic goal would be a decrease in A1C without an increase in their incidence of hypoglycemia. Additional possible goals might be a decrease in the duration or severity of hypoglycemic periods as well as an increase in quality of life. Dr. Nathan concluded by stating that, for any subset of patients, the goal of therapy with an AP is to provide benefit and reduce risk.

The sixth speaker in this session was John Mastrototaro, Ph.D., vice president of global research and development for Medtronic Diabetes in Northridge, California, who began his presentation with a description of two feasibility trials of closed-loop control conducted by Dr. Stuart Weinzimer from Yale University. In the first of these closed-loop trials, ePID-01, the Medtronic MiniMed external physiological insulin delivery system, which combines an external pump and sensor with a variable insulin infusion rate algorithm designed to emulate the physiological characteristics of the beta-cell, was used in two experiments to achieve closed-loop control.[15] In one experiment, using this system, subjects increased the percentage of time they spent in a euglycemic range and decreased the percentages of time they spent in hypoglycemic and hyperglycemic ranges. In a second experiment, using this system, mealtime bolus dosing was compared with no mealtime bolus dosing. The rationale for providing a small mealtime bolus dose of mealtime insulin was to take the edge off the meal-induced rise in glucose levels by getting some insulin on board to reduce the magnitude of the postmeal glycemic excursion. The addition of manually triggered mealtime bolus insulin resulted in lower mean glucose levels compared to complete closed-loop controlled insulin delivery. In a third experiment, which is not published, closed-loop control, compared to open-loop control, resulted in lower mean BG levels both prior to and following exercise. Dr. Mastrototaro then stated that he believes that we should not let perfection be the enemy of improved glycemia control. Next, he introduced the concept of CGM guided, protected, and directed therapies as progressively more complex steps in a continuum toward an AP. Continuous-glucose-monitor-guided therapy is a system with no closed-loop control at all. The CGM provides recommendations on how much insulin to deliver and when to check BG levels, but the CGM has no direct effect on insulin delivery with the system. Continuous-glucose-monitor-protected therapy is a system that will automatically respond to a severe perturbation to stabilize the situation if the patient is not addressing this fault. Otherwise, if the situation is not severely out of control, then the system will allow the patient to make all the management decisions. Dr. Mastrototaro referred to the process of bringing the glucose level from being out of range to being within range as "treat-to-range." A treat-to-range protocol does not seek to bring the glucose level to a target level, but instead to a target zone. Given the inaccuracy of current glucose sensors, it is more practical to aim for CGM-controlled treat-to-range therapy than treat-to-target therapy. A LGS system or a high-glucose bolus infusion system would both be examples of treat-to-range systems. Continuous-glucose-monitor-controlled therapy means that a CGM is controlling the amount of insulin delivery for an extended period of time, such as overnight. Dr. Mastrototaro then addressed the seven questions posed by the FDA about AP clinical trials.

First, the acceptable target range for closed-loop control depends on sensor performance at both the high and low ends, sensor outlier performance, and a system's ability to self-diagnose sensor/system errors. There is a role for data mining, simulation, and modeling. Second, the appropriate effectiveness endpoints to be used include A1C, the duration of time within a predefined range of adequate control, a "goodness" score (which penalizes minor deviations from target glycemia with low scores and extreme deviations with high scores), and the areas under the hypoglycemia and hyperglycemia curves. Third, effectiveness can be demonstrated in-clinic with forced hypoglycemia and hyperglycemic events, but he felt these artifactual maneuvers expose subjects to unnecessary discomfort. Effectiveness can also be demonstrated in outpatient randomized controlled trials of closed-loop control compared to open-loop control, which resemble the real world. Fourth, safety issues would include severe adverse events, including severe hypoglycemia and DKA. Fifth, safety can be best demonstrated in an outpatient setting by randomized controlled trials of closed-loop control compared to open-loop control, which resemble the real world, but not in an inpatient setting because of subject risk and small sample sizes. Sixth, the appropriate safety mitigations for inpatient studies (or in lieu of inpatient studies) are simulation, modeling, and data mining. Seventh, the acceptable balance for effectiveness and safety for success would be superior outcomes compared to what can be achieved with open-loop control in terms of serious adverse event rates, such as severe hypoglycemia and DKA. Dr. Mastrototaro concluded his presentation by reiterating that an evaluation of a CGM-protected system in clinic is very problematic. To evaluate in-clinic effectiveness for this type of system, the insulin effect is already known. Regarding in-clinic safety, the sample size would be too small, and in such an artificial environment, it would be difficult to force failure modes because of the safety risk associated with induced hypoglycemia. Finally, Dr. Mastrototaro acknowledged that, for a fully closed-loop system, an in-clinic assessment would be necessary.

The seventh speaker in this session was Henry Anhalt, D.O., medical director of the Artificial Pancreas for Animas Corporation, West Chester, Pennsylvania. Dr. Anhalt described the tension in managing diabetes as a balance between glucose levels that are too low and too high, and each extreme causes problems. He stated that his company is working on a combination device that will include a LGS system and a high-glucose insulin infusion system. Both the hypoglycemic and the hyperglycemic minimizers, which will be for glucose levels out of the 60–180 mg/dl range, will operate on a predictive algorithm that will include alarms rather than a threshold point. He stated that development of this product will require an iterative process that will involve testing it in the clinic, modifying the algorithm, and then retesting. The system will use model predictive control algorithms and will be set up to deliver multiple microboluses. Dr. Anhalt is closely following several insulin delivery products that would be more useful if new super-rapid-acting insulin would be approved by the FDA. Novel compounds include transdermal insulin, intraperitoneal insulin, and rapidly absorbed subcutaneous insulin. He concluded his presentation with a list of four engineering and four additional factors that are beyond engineering, which will be needed for an AP. The engineering factors are (1) precise insulin delivery, (2) enhanced CGMs, (3) wireless communication, and (4) control algorithms. Factors beyond engineering are (1) human factors, (2) usability and safety, (3) clinical research, and (4) training plus education.

Discussion of Clinical Expectations for Artificial Pancreas Device Systems

Seven members of the audience provided prescheduled comments from the public. Two patients with type 1 diabetes and the mother of a patient all urged the FDA to move quickly to approve new technology that could help people with diabetes. Dr. Ken Ward pointed out potential benefits of using multiple redundant sensors as part of an AP. Dr. Jeffrey Joseph in the audience concurred with this idea. Boris Kovatchev, Ph.D., from the University of Virginia, suggested that a robust LGS system algorithm be based not only on CGM point data, but on a system approach, which means using other sources of information, as well, such as CGM trend data, insulin pump data, and other data. Richard Mauseth, M.D., a pediatric endocrinologist from Woodinville, Washington, recommended that adolescents and children be considered for trials of AP systems. Dr. William Tamborlane in the audience concurred with this idea. Dr. Aaron Kowalski urged the FDA to define a clear and reasonable regulatory pathway to allow studies of closed-loop technologies to move forward. He also expressed support for conducting clinical studies on LGS systems and suggested that treat-to-range technologies using predictive algorithms could be useful tools for patients with type 1 diabetes. Frank Schwartz, M.D., from Ohio University, recommended case-based reasoning to look at patient-specific responses to exercise and other known perturbations of glucose levels and to incorporate this individual data into AP algorithms to best determine insulin dosing.

The panel discussed multiple topics related to seven questions about optimal research studies for an artificial pancreas. These questions had been presented by Ms. Patricia Bernhardt to the panel at the beginning of the session.

1. What is the acceptable target range for closed-loop control? For many patients, a goal would be A1C in the range of 7%, which corresponds to a mean glucose level of 150 mg/dl. If this level of mean glycemic control can be achieved, then the target can be slowly ratcheted downward in the future. For patients with severe recurrent hypoglycemia, their major goal is a safety goal (a decrease in their incidence of hypoglycemia), and the A1C goal is to be noninferior to the baseline level. For patients with acceptable A1C levels and infrequent severe hypoglycemia, the goals would be improvements in glycemic variability, less time spent in hypoglycemia, and improved quality of life, but these goals would be accompanied simply by no rise in A1C levels. For patients with above-target glycemic control, the therapeutic goal would be a decrease in A1C to the 7% range, provided that there would be no increase in the incidence of hypoglycemia. For an adolescent or child with usually poor control and A1C of 10–11%, if this pediatric patient with probably poor adherence to therapy was in a study of an AP system (this person would not be one of the first people to be recruited as a research subject), then a more modest goal of A1C around 8% would be reasonable.

2. What are the appropriate effectiveness endpoints to be used (effectiveness endpoint)? The effectiveness endpoints include the acceptable target ranges discussed in response to question 1. An additional metric for assessing effectiveness of control is the percentage of time spent in the target range. In addition, a "goodness" score, which penalizes minor deviations from target glycemia with low scores and extreme deviations with high scores, would be helpful. The areas under the hypoglycemia and hyperglycemia curves are a traditional way to assess the magnitude of deviations from normal and might be used, but unlike a goodness score, these measures do not penalize deviations proportionate to their magnitude. Glycemic cut points for the lower limit of the target range would be both 70 mg/dl, which is where counter-regulatory hormone release occurs, as well as 50 mg/dl, which is where symptoms often occur.

3. How can this effectiveness be demonstrated in clinical studies (in clinic versus outpatient)? As described by the panel members who also served on the JDRF panel, a process is developed for a subject to begin a study in the hospital or clinic and then eventually transition to the home setting. The inpatient setting should be a diabetes research center with experience in continuous subject monitoring. This type of facility is most needed for teaching subjects how to use AP technology. Next, the subject could be transitioned into some type of a semiautonomous situation such as an apartment on the hospital campus grounds. Here the emphasis should be on resuming a lifestyle similar to the home environment with nonhospital types of food and places to walk around both being available. From such a setting, the subject would be able to return to the metabolic research unit and be checked regularly, or a nurse can walk over and see how the subject is doing. Not every hospital has a semiautonomous living quarter arrangement exactly like that, but they can usually arrange something that will be a step down from hospitalization. There are usually some rooms on the hospital complex where a person can stay. Next, a subject would transition to the outpatient setting, where they are on their own, but the subject will still need to be observed. The subject must have a loved one staying with them, and they must have frequent and scheduled consultation at least every 1–2 weeks with a diabetes nurse or educator. A LGS system can be tested either in clinic with forced hypoglycemia and hyperglycemic events or in outpatient randomized controlled trials.

4. What safety issues would be appropriate for this system (safety endpoint)? The safety endpoints are discussed along with the effectiveness endpoints in the response to question 1. Furthermore, no system should be associated with an increased incidence of DKA.

5. How can this safety be demonstrated in clinical studies (in clinic versus outpatient)? The safety endpoints are discussed along with the effectiveness endpoints in the response to question 1. A pair of related tools for assessing safety associated with outlier glucose data points will be a hypoglycemic index and a hyperglycemic index, which resemble the aforementioned "goodness index," which was described in the answer to question 2. These formulas will assess the glycemic pattern and will assign a progressively greater penalty to data points that are progressively more extreme outliers from the target range. For example, with this metric, a prolonged

period of mild hypoglycemia might possibly be scored as less dangerous than a brief period of severe hypoglycemia. The score for outliers in the hyperglycemic range and the hypoglycemic range can be normalized to be quantified with the same units. This weighting of outlier data will result in a new paradigm for calculating area under a hypoglycemia curve, because different hypoglycemic zones will be hierarchically weighted differently, and therefore not all calculated areas (without factoring in the penalty weighting) will be considered to have the same significance.

6. What safety mitigations should be established for these studies (in clinic versus outpatient)? Examples of safety mitigations of an AP system include (1) the use of predictive algorithms for decision making, rather than threshold-based algorithms; (2) case-based pattern analysis to modify an algorithm that has been custom crafted for an individual patient, according to the individual's current insulin sensitivity, which can vary from day to day; (3) multiple implanted sensors to improve accuracy of the glucose readings; (4) dual hormone therapy with the addition of glucagon to insulin therapy; (5) triple hormone therapy with the use of pramlintide added to insulin and glucagon; (6) telemetry by way of a GPS-based monitoring system with a central station to summon assistance in case of a medical emergency; (7) simulation and modeling to avoid exposing subjects to dangerous situations; and (8) data mining to suggest hypotheses. It should be noted that prolonged glucagon infusion might require use of a new formulation or analog molecule to avoid fibrillation.[16] The use of such a drug in a clinical trial would have to be cleared by a joint process involving two FDA centers, the CDRH and the CDER. Although the panel endorsed the idea of "one size will not fit all," which means that various patients will require various protocols and outcomes, this diversity of outcomes might be achievable with a limited number of products or tools that can be calibrated to the needs of the individual patient.

7. What is the acceptable balance for effectiveness and safety for success? The answer depends on who the patient is. There are three main types of patients where the benefits of a well-designed trial would likely outweigh the risks, and these types of patients are discussed in the answer to question 5. In general, the objective should be to mitigate the subject's greatest problem, whether it is severe hypoglycemia, elevated A1C, or increased glycemic variability. Any increase in DKA is not acceptable. Any worsening of quality of life is probably also unacceptable. It is hoped that this metric will actually improve with many future systems, even if it turns out that the glycemic outcomes do not improve by much. If an AP system were to improve quality of life, even in the absence of documented glycemic benefit, then this would still be a sufficiently beneficial outcome. Finally, if a decrease in the short-term complication of hypoglycemia is accompanied by a small increase in A1C, then this might still be an acceptable balance.

What Safety Information Is Needed from In-Clinic Studies Prior to Adding Outpatient Studies?

Dr. Robert Vigersky moderated this fifth session of the workshop. Edward Damiano, Ph.D., from Boston University in Boston, Massachusetts, gave the first presentation of the session, entitled, *Clinical Testing of a Prosthetic Endocrine Pancreas: A Staged Approach for Moving from Clinical Research Center to Outpatient Studies.* Dr. Damiano described his past, present, and planned future closed-loop research. He presented human data from his first-phase Inpatient Feasibility Study at the Massachusetts General Hospital Clinical Research Center from 2008–2009. He studied type 1 subjects who were negative for stimulated C-peptide. He administered three large meals over 27 hours and no rescue snacks. Venous BG levels were sampled every 5 minutes. Subcutaneous insulin and glucagon were administered according to results from his blood-glucose-controlled algorithm, and no premeal priming boluses were administered. No exercise was performed. The only clinical interventions in the protocol were for hypoglycemia or extended hyperglycemia. Each subject's outcomes were eventually reported and not just mean responses for the entire cohort. A comparative study of three commercially available CGMs was performed to select a product for the second phase of the study. The Navigator had the lowest mean average relative difference compared to the DexCom 7 and Guardian RT. Dr. Damiano then presented his second-phase Inpatient Feasibility Study, which is in progress during 2010–2011. This 2-day, six-meal study utilizes a partial premeal insulin priming bolus dose to assist with control. Venous BG is tested every 15 minutes to measure the performance of each system, so the CGM is not used to measure its own performance. Subcutaneous insulin and glucagon is administered according to results from his CGM-controlled algorithm, and no rescue snacks

are administered. The setup is portable, which allows the subject to walk in the hallway and ride an exercise bicycle. Dr. Damiano then described his planned third-phase Inpatient Feasibility Study of a CGM-driven closed-loop system, planned from 2011–2012. The plan is to use a fully portable system worn in a waist pouch with the control algorithm residing on personal digital assistant or palmtop computer, but not a laptop computer. Each study will be 5 days. One-on-one nursing care will be provided. Both bihormonal and insulin-only configurations will be tested. There will be no intravenous phlebotomy, but the subject will have a saline lock for safety in case intravenous dextrose is needed. Capillary BG samples will be tested on a Hemocue system hourly from 7:00 AM to 11:00 PM, and as needed overnight. Subjects will be free to move about the hospital campus and will have access to unrestricted meals (including snacks) and physical activity (with a minimum amount of physical activity). Endpoints will be mean capillary glycemia and the frequency of hypoglycemia based on capillary glucose levels during symptoms or around CGM low and projected low alarms. Mean glycemia will be reported as the mean of the daytime glucose levels. Dr. Damiano then described his plan for an in-home outpatient feasibility study that could begin in 2012. This study will be exactly the same as the planned third-phase inpatient study except that it will take place in the home. A nurse would accompany the subject to the home and measure Hemocue glucose readings in the home and would bring bags of dextrose and an exercise bicycle. The next step would be an outpatient pilot study of the final embodiment of the CGM-driven closed-loop device, to begin in 2013. This study would not have a nurse in the home. There would be extra finger stick calibrations of the CGM. It would be a 12-week trial, 6 weeks under open-loop control and 6 weeks under closed-loop control, either as a parallel study or a crossover study. Endpoints would be A1C levels, fructosamine levels, and the frequency of hypoglycemia (based on either symptoms or capillary glucose levels measured for CGM low readings or low projected alarms). Finally, Dr. Damiano described a pilot study of a CGM-controlled closed-loop system that could begin in 2013. This study would resemble the pilot study, and it would not depend on CGM measurements to confirm that the CGM-powered algorithm was effective. It would use frequent A1C and fructosamine levels to assess mean glycemia as well as finger stick glucose levels (checked in the event of hypoglycemic readings on the CGM) or to document asymptomatic hypoglycemic episodes. He stated that an outpatient pivotal trial of this system could begin in 2014.

Dr. Roman Hovorka, from the Institute of Metabolic Science and Department of Pediatrics at the University of Cambridge in the United Kingdom, gave the second presentation of this session: *How to Get to the Outpatient Setting as Quickly as Possible.* Dr. Hovorka described three types of clinical studies: (1) inpatient studies in a supervised environment with frequent BG sampling and a rudimentary AP prototype operated by staff; (2) transition studies in a supervised environment that can be in an inpatient setting, a hotel-like setting, or an outpatient setting with infrequent BG sampling and an AP operated by the subject; and (3) outpatient or home studies in an unsupervised environment with infrequent BG sampling and an AP operated by the subject. Dr. Hovorka pointed out that, in addition to the risks of hypoglycemia and hyperglycemia, the use of an AP system confers multiple risks on the system level that must be considered. He provided 15 examples of hazard situations (in parentheses is an example of the hazard situation): (1) hardware failure (display failure), (2) software failure (driver failure), (3) communication failure (wireless communication lost), (4) power management hazards (battery drained), (5) data corruption (data corrupted), (6) unintentional subject actions (infusion cannula withdrawn), (7) system configuration (time not synchro nized), (8) environmental (radio frequency emission interference), (9) subjects related hazards (calibration error), (10) system tampering (third-party system operation), (11) wrong subject characteristics (untrained user), (12) unreported insulin delivery (manual injection), (13) accidental damage (water ingress), (14) electrical safety (electrocution), and (15) control algorithm computation (insufficient CGM data). Dr. Hovorka stated that he uses a simulation environment designed to support the development and testing of closed-loop insulin delivery systems.[17] He stated that simulation studies are particularly useful for assessing "edge of the envelope" scenarios that might be or are expected to occur rarely in the real world. Simulations are useful for predicating the system's response to data dropout, unannounced meals, errors in CGM calibration, or errors in meal carbohydrate estimation. Dr. Hovorka stated that he uses inpatient studies to study perturbations where a system could fail, such as exercise or large meals. He uses transition studies, which are between inpatient and outpatient settings, to assess his subjects' competence to work with the system. Dr. Hovorka showed that when he used both a YSI analyzer and a CGM to simultaneously calculate the time in target in a 45-night overnight closed-loop study, the YSI device provided a slightly more favorable assessment compared to the CGM. Dr. Hovorka explained that he is planning to launch an outpatient overnight closed-loop

study in 2011. Following a training period, a transition study will take place at the homes of subjects with a nurse present overnight for the first four nights. The first two nights, the nurse will turn the system on and off, and the next two nights, the nurse will only observe the subject. Dr. Hovorka concluded his presentation by summarizing his approach to safety by listing the necessary steps for proceeding to an outpatient study by establishing safety through: (1) inpatient studies, (2) simulations, (3) transition studies, and (4) validation and verification of the entire system.

Discussion of What Safety Information Is Needed from In-Clinic Studies Prior to Adding Outpatient Studies?

The discussion period focused primarily on three topics in which there were exchanges between panelists and audience members: (1) how to select subjects for outpatient trials of closed-loop control, (2) how to assess overnight glycemic control in home studies, and (3) how to reconcile mealtime priming boluses with automatic closed-loop control systems.

Regarding selection of subjects for outpatient studies, Dr. Edward Damiano stated that, although he gradually expanded his inclusion criteria when he performed a series of inpatient studies, he expects to contract the entry criteria for his planned outpatient study. He is now planning to focus on including subjects with lower A1C levels and less hypoglycemia. Dr. Damiano stated that, for his upcoming outpatient study, he was planning to recruit subjects with A1C below 10%, pump experience of at least 6 months, as well as good hearing and good vision so that they can hear and respond to alarms. He was planning to exclude subjects with severe hypoglycemia. Dr. Markham Luke from the FDA, who was in the audience, stated that he agreed with the previously expressed idea that early research subjects should already be adherent to therapy, because these are the types of patients who will be advised by their physicians to use this technology when it first becomes available.

Regarding how to assess overnight glycemic control in home studies, Dr. Bruce Buckingham in the audience led off this discussion by asking the panelists to clarify their methods for monitoring closed-loop overnight. Dr. Damiano stated that he is currently not planning to use CGM measurements of glucose to assess overnight control, but he will be using finger stick readings to monitor daytime control. He will also be using A1C and fructosamine levels to assess overall control, but these tests will not provide specific information about overnight control or overnight hypoglycemia. Dr. Damiano stated that the CGM that is controlling insulin infusion cannot be used to evaluate the outcome of the closed-loop system overnight, because it is a circular argument to use a CGM to monitor itself. He suggested that a separate CGM, which is not controlling the sensor, might be useful for monitoring overnight control. Dr. Hovorka stated that, for his home study, the primary outcome is time and target glucose levels as measured by a CGM.

Regarding how to reconcile mealtime priming boluses with automatic closed-loop control systems, Dr. Frank Doyle, from the University of California, Santa Barbara, in the audience questioned whether this practice is compatible with the concept of a closed-loop system to control glycemia. There was a consensus among panel members that a premeal priming insulin bolus dose can and must be accounted for by the algorithm. Dr. William Tamborlane in the audience stated that patients already have a lot of responsibilities to maintain their equipment, and an additional task of actuating a priming dose of insulin for a closed-loop system does not change the overall idea that most of the work is done automatically, particularly during the night. He stated that he was more concerned about the risk of a system error that could result in accidental overdelivery of a bolus of insulin, and more work is needed to mitigate this risk, whereas he felt that a brief suspension of insulin based on a LGS algorithm would be safe. He also pointed out that more work will be needed to prevent erroneous calibrations and other potential errors that could be made by patients.

Three additional topics, which were related to clinical research on AP systems, were briefly addressed during the discussion session: (1) data handling, (2) calibration technology, and (3) telemedicine. First, Dr. Markham Luke called on investigators to submit not only composite summaries of patient data, but also actual data points and specific subject-level data. He also called for research data to be shared by investigators. Second, Dr. Patricia Beaston pointed out that, if the BG monitors, which are being used for calibrating CGMs, can become more accurate, then the performance of CGMs in clinical trials of algorithms will improve. She mentioned that some inpatient studies have used highly accurate reference devices to calibrate CGMs, and in these studies, the CGM readings have been quite accurate. Third, Dr. John Knight called for AP systems to be in constant communication with a central station to upload data about the patient and the system. The station staff could monitor the system using this telemetry data and alert a patient if the system is beginning to fail.

Funding Opportunities for Development of the Artificial Pancreas

Dr. Robert Vigersky moderated this concluding session. First, Guillermo Arreaza-Rubín, M.D., from NIDDK, and, second, William Heetderks, M.D., Ph.D., from NIBIB, spoke sequentially on the first topic of the session: *Funding Opportunities for New Technology*.

Dr. Guillermo Arreaza-Rubín focused on the NIDDK program. He stated that the NIDDK strategic plan, which was elaborated in 2010, selected the AP and bioengineering approaches for the development of an AP to improve management of glycemia as one of the focused topics. This theme included research in glucose sensors, algorithm development, insulin delivery and formulation, telemedicine, and tissue engineering for the replacement of pancreatic islets. He described recent SBIR, R01, and R21 announcements as well as two upcoming initiatives. The first of these initiatives is to promote technical innovation and clinical testing of single or combined components of a closed-loop system. The second of these initiatives is the diabetes impact award, or DP3, which is focused on major issues or areas in type 1 diabetes research that have been identified by the strategic diabetes plan. Those areas are imaging, biomarker development, autoimmunity diabetic complications, and the engineering of the AP. This program is encouraging the use of interdisciplinary approaches for big projects to develop emerging technologies. Applications for these two programs would be due in November 2010 and March 2011, respectively. An additional funding vehicle is a collaborative interdisciplinary team science project. This program funds seeding projects and also provides full awards. The seeding projects are to establish a collaborative team. Full award projects can be funded once the collaborative team has been established and some preliminary data have been generated. Dr. Arreaza-Rubín stated that the NIDDK would continue to work with other government agencies and nongovernment entities to promote new projects, and he mentioned future collaborations with the Artificial Pancreas Working Group, National Science Foundation, and National Institute of Standards and Technology.

Dr. William Heetderks focused on the NIBIB program. He presented information on a recent announcement by his institute about two funding opportunities related to an AP. Both types of awards fall within the overall topic, "Design and Development of Novel Technologies for Healthy Independent Living." This program is seeking applications to develop technologies to monitor health or deliver care in a real-time, accessible, effective, and minimally obtrusive way. An R21 program is focused on novel sensor or monitoring systems, home-use point-of-care monitoring devices, home or mobile therapy or rehabilitation tools, or information systems and should have the goal of fostering healthy and independent living. An R01 program is focused on technology to integrate, process, analyze, communicate, and present data so that individuals are engaged and empowered in their own health care with reduced burden to care providers. Dr. Heetderks stated that these two programs relate to the technologies used in an AP system and complement the work of the NIDDK.

Dr. Chip Zimliki provided closing remarks. He stated that a webcast, a transcript, and a summary of the meeting would all be available. Dr. Zimliki stated that a statistical workshop about developing clinical study design is needed and that industry, academia, the FDA, and the NIH should work together to develop the right clinical trial designs. He pointed out that the purpose of the Artificial Pancreas Workshop had been achieved, which was to garner perspectives about AP systems. Dr. Zimliki also thanked the children with diabetes for coming forward. He concluded by stating that it is definitely possible for an AP system to be approved within the predicted time frame of 4–5 years.

Summary of Major Themes of the Workshop

This workshop focused on 10 major themes. They are summarized in **Table 2**.

The first theme of the workshop was that current AP systems are limited by suboptimal performance of system components, including sensors, insulin products, insulin delivery systems, algorithms, and failsafe integration of components. As technology improves for each component, it is likely that the performance of multicomponent systems will improve when they contain more accurate sensors, faster-acting insulin, more responsive insulin pumps, more complex and sensitive-to-nonglucose-data algorithms, and safer system analyses.

The second theme was that development of an AP will go through a stepwise evolution of complexity. These products will evolve from being CGM guided to CGM protected to CGM directed, which will be the ultimate goal of research in this field.

The third theme was that the current best level of control in the United States is GGM guided, and it is inadequate. This means that the patient uses CGM data to assist with management of insulin dosing, provided that this data leads to self-monitoring of blood glucose and that actions are based on BG results. The glycemic control and protection from hypoglycemia afforded by this level of therapy, which is CGM guided, is not felt by the clinical or patient communities to be sufficiently automatic and effective, especially for protecting from nocturnal hypoglycemia.

The fourth theme was that, currently, the next necessary step in the development of a closed-loop system will be to develop a CGM-protected system that will automatically manage the patient away from hypoglycemic and/or hyperglycemic events. Such a system could be activated if either the glucose level reaches a CGM-measured threshold level or if a predictive algorithm incorporating both CGM point and trend data triggers an action. The action might be to suspend insulin to mitigate hypoglycemia or to deliver insulin to mitigate hyperglycemia.

The fifth theme was that a current product, Veo, which is being marketed outside the United States, has some attractive features that might eventually make it the first FDA-approved CGM-protected product in the United States; however, appropriate clinical trials must first be designed. The product must then demonstrate sufficient safety and effectiveness in those trials. There is no clear consensus at this time about the most accurate and practical way to monitor performance of a LGS device that is triggered by data from a CGM to prevent nocturnal hypoglycemia.

Table 2.
Ten major themes of the Artifical Pancreas Workshop

1	System performance is limited by component performance
2	An artificial pancreas will evolve through: CGM guided, CGM protected, CGM controlled
3	The current best level of control in the US is CGM guided
4	The next step in closed loop control will be a CGM protected system
5	Veo must undergo clinical trials to assess safety and effectiveness
6	Various patients will have various indications and goals for using an artificial pancreas,
7	Trials of an artificial pancreas must include inpatient, transition, and outpatient settings
8	Safety mitigation systems will be required in an artificial pancreas system
9	Approval of an artificial pancreas involves an analysis of features and tradeoffs
10	Study design requires proper documentation of safety and effectiveness

The sixth theme was that a limited number of AP products will be used for many types of patients and, in terms of protocols, one size will not fit all for various indications for use. Individualized goals will need to be established for each subject depending on whether the problem is mostly hypoglycemic episodes, excessive mean glycemia, or increased variability.

The seventh theme was that clinical trials of AP components will need to include three phases, which are the inpatient unit, transitional care unit, and free-living scenarios. The inpatient phase of these studies will emphasize safety, the transition phase will emphasize education for the subject to be able to operate the system without assistance, and the outpatient phase of the studies will emphasize effectiveness; however, both safety and effectiveness will be part of all three phases.

The eighth theme was that safety mitigation measures will be critical for trials of AP systems. These systems will need to incorporate many complex stabilizing tools that have a parallel in the control engineering world. Not only will methods be needed to avoid excessive insulin administration or malfunctioning sensors, either of which could lead to hypoglycemia, but also system-wide integrated software and hardware safety measures to detect and prevent problems before they can affect the system's user.

The ninth theme was that regulatory approval of an AP component or system involves an analysis of features unique to that product and of tradeoffs between potential benefits and potential hazards. These features and tradeoffs for each product include (1) specific hardware and software features of the device or system, (2) specific features of study protocol related to how the product is intended to be used, (3) specific features of study subjects related to the product's intended user, (4) tradeoffs of comparative impact and frequency of the device's beneficial and harmful outcomes compared to outcomes from current therapy, and (5) tradeoffs of safety and effectiveness of existing alternative therapies compared to those properties of the study system.

The 10th theme was that study design is a critical priority of regulatory science. Multiple issues were raised at the workshop related to proper documentation of the safety and effectiveness of components and entire systems for partial and complete closed-loop control. Because of a lack of consensus on some specific aspects of study design, it would be very useful for a meeting to be convened to focus on study design for trials of an AP and its components. The JDRF convened a panel in late 2010 to develop a report on trial design for AP studies, and their set of recommendations could be incorporated into this trial design meeting.

Conclusion

At the FDA/NIH Artificial Pancreas Workshop conducted on November 10, 2010, the participants agreed on a concept that was discussed during every session of the workshop. The concept was that clinical science, system components, and regulatory policies will all need to harmonize in order to achieve the goal of seeing an AP product brought forward to the marketplace for patients to use. At this workshop, scientists and clinicians from academia, industry, the NIH, and the FDA demonstrated to each other and to the world that they are making steady and exciting progress toward realization of this goal.

Disclosures:

Dr. Klonoff is a consultant for C8 Medisensors, Inc.; Insuline Medical Ltd.; LifeScan, Inc.; Medtronic Diabetes; Merck; and Roche Diagnostics.

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