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STATEMENT

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BEFORE THE

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UNITED STATES SENATE

"TRANSFORMING LIVES THROUGH DIABETES RESEARCH"

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Charles Zimliki,

Chair, Artificial Pancreas Critical Path Initiative, located within the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). I would like to thank the Committee for the opportunity to discuss the artificial pancreas system and what FDA is doing to assist in the development of these critically needed and potentially life-changing devices. As a person living with type 1 diabetes, I am personally, as well as professionally, committed to seeing this important novel medical product come to market.

Diabetes is a lifelong disease for which there is not yet a cure, and which can lead to serious complications such as blindness, kidney disease, and nerve damage. FDA is committed to continuing its work with the Juvenile Diabetes Research Foundation (JDRF), other federal agencies, researchers, academia, and many other interested parties to facilitate the development of these important devices. In particular, FDA applauds the work of the JDRF Artificial Pancreas Project, which brings together JDRF and academic and business partners to speed the development and approval of automated systems for people with type 1 diabetes.

On Monday, June 20, 2011, FDA took an important step toward advancing the development of an artificial pancreas system by issuing a draft guidance that outlines Agency expectations for engineering testing and clinical trials for a first-generation

artificial pancreas system, called a Low Glucose Suspend System. I will discuss the importance of this document later in my testimony.

FDA Regulatory Authorities for Medical Devices

A medical device, as defined by federal law, encompasses several thousand types of health products, from simple articles, such as tongue depressors and heating pads, to cutting-edge and complex devices, such as implantable defibrillators and robotic equipment for minimally invasive surgery.

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) gave FDA specific authority to regulate the safety and effectiveness of medical devices. Medical devices are assigned to one of three regulatory classes based on risk.

Class I, General Controls, is the lowest risk category of devices and includes items such as adhesive bandages. These devices are subject to the General Controls of the Act, which include establishment registration and device listing, compliance with current Good Manufacturing Practice (cGMP), and labeling, recordkeeping, and reporting requirements.

Class II, Special Controls, is a medium-risk category of devices and includes devices such as intravenous catheters and powered wheelchairs. They are subject to the General Controls of the Act as well as Special Controls, which may include special labeling

requirements, mandatory performance standards, and post-market surveillance, in order to ensure device safety and effectiveness.

Class III is the highest risk category of devices and includes devices such as heart valves and coronary stents. These devices are subject to the General Controls of the Act, plus approval prior to marketing of a premarket approval application (PMA) containing scientific evidence of the device's safety and effectiveness.

Background on Diabetes

As you know, Diabetes Mellitus is a chronic, debilitating disease affecting every organ system. Type 1 diabetes usually strikes children and young adults, although disease onset can occur at any age. This form of diabetes is an autoimmune disease in which the pancreas stops functioning effectively.

The pancreas secretes several hormones, including insulin and glucagon, as well as digestive enzymes that help break down food. Insulin helps cells in the body take up glucose (sugar) from the blood to use for energy, which lowers blood glucose levels. Glucagon causes the liver to release stored glucose, which raises blood glucose levels.

Diabetes occurs when the pancreas cannot produce any or enough insulin to regulate blood glucose. People with diabetes can keep blood glucose from getting too high or too low through regular injections of insulin and occasional injections of glucagon. It is critical for diabetes patients to regulate their blood glucose in order to lower the risk of

long-term diabetes complications such as blindness, kidney failure, and cardiovascular disease.

Diabetes is a disease that affects the entire family, especially when a child is diagnosed. When managing type 1 diabetes, patients must vigilantly test blood glucose multiple times per day via finger sticks and a glucose meter. They must calculate insulin doses, administer necessary insulin in the arm, leg, or stomach with a needle or insulin infusion pump to lower blood glucose, and safely dispose of used syringes. Glucagon injection kits should be readily available in any setting to treat severely low blood glucose in an emergency. Some patients benefit from additional monitoring with a continuous glucose monitoring (CGM) system. Diabetes management is constant and pervades all aspects of a person's life, presenting a particularly arduous burden for children and their parents.

Overview of an Artificial Pancreas System

An artificial pancreas system is an innovative device for treatment of type 1 diabetes which, once fully developed, will automatically monitor blood glucose and administer appropriate insulin doses. This life-changing technology will positively impact diabetic patients' health and quality of life and improve long-term health outcomes. As a person with diabetes, I am acutely aware of the benefits an artificial pancreas system will provide. An artificial pancreas system will allow people with diabetes, especially children, to live active lives without the constant need to adjust glucose levels—a constant reminder of the dangers caused by this disease.

While the potential benefits are enormous, an artificial pancreas system is considered a significant-risk device, meaning it presents a potential for serious risk to the health, safety, or welfare of a patient. If not properly designed, use of an artificial pancreas device in an outpatient setting can place patients at significant risk because the device controls the administration of insulin without the oversight of health care professionals. As such, an investigational device exemption (IDE) from FDA and Institutional Review Board (IRB) approval are needed to allow the investigational device to be used in a clinical study. These are necessary in order to protect the rights and safety of human subjects while collecting the data needed to establish the safety and effectiveness of the device in a PMA. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated. FDA has approved 17 IDEs for clinical studies of artificial pancreas systems at various levels of development. To date, FDA has not approved a PMA for an artificial pancreas system indicated for outpatient use.

At the current level of technological development, the artificial pancreas system consists of three devices already familiar to many people with type 1 diabetes: a blood glucose measuring device (such as a glucose meter); a CGM system, which is a sensor placed under the patient's skin that measures the glucose in the fluid around the cells and sends information to a receiver; and an insulin infusion pump, which delivers controlled amounts of insulin into subcutaneous tissue to lower the concentration of glucose in the blood. These three devices are commonly found in sensor-augmented insulin pump systems. What distinguishes an artificial pancreas from a sensor-augmented insulin

pump system is a computer-controlled algorithm (controller) that communicates between the CGM and infusion pump. It communicates by receiving information from the CGM and performing a series of mathematical calculations that result in an automatic and appropriate insulin dose from the infusion pump. It is critical to the health of people with diabetes that these components perform precisely and reliably, individually, and as a unit.

As noted, FDA has approved 17 IDEs for research on three types of artificial pancreas systems, all in various stages of development. These systems differ in how the insulin pump acts on readings from the CGM system and the level of autonomy with which they manage patients' glucose levels. They are the Low Glucose Suspend (LGS) System, the Treat-to-Range System, and the Treat-to-Target System.

Our guidance, released on Monday, June 20, 2011, entitled "Draft Guidance for Industry and the Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Low Glucose Suspend Device Systems," deals specifically with the LGS type of artificial pancreas system and, once finalized, will provide guidance on information that should be submitted to FDA to facilitate marketing of this basic type of artificial pancreas. An LGS system helps eliminate, or reduce the severity of, a dangerous drop in blood glucose levels by temporarily suspending insulin delivery when glucose levels approach a low threshold. This kind of system serves as a potential back up when a patient is unable to respond to a hypoglycemic (low blood sugar) event. Patients using this system will still

need to actively manage their blood glucose levels by periodically checking those levels with a glucose meter and self-correcting their blood glucose levels with insulin.

A treat-to-range system reduces the likelihood of a hypoglycemic event or a hyperglycemic event (when blood glucose is dangerously high) by adjusting insulin dosing if a person's glucose level approaches low or high thresholds. Patients using this system also will still need to check blood glucose levels with a glucose meter and give themselves insulin or eat to maintain control of glucose levels.

A treat-to-target system sets target glucose levels and tries to achieve these levels at all times. This system would be fully automated and require no interaction from the user, except for calibration of the CGM system.

A fully functioning artificial pancreas system, such as the treat-to-target system, will not only monitor glucose levels in the body but will also automatically adjust the delivery of insulin to reduce high blood glucose levels and minimize the incidence of low blood glucose with little or no input from the patient.

The Challenges of a Fully Functioning Artificial Pancreas System

Recreating the precise and dynamic glucose regulation function of a healthy pancreas is a challenging task. This task is further complicated by the numerous behavioral and biological factors that impact diabetes management, and by the current limitations of the devices that are the components of the artificial pancreas.

Current FDA-approved or cleared diabetes management devices have dramatically changed the quality of life for people with type 1 diabetes. While these devices are safe and effective for their individual uses, none is intended to be used alone and all require significant management by the patient. FDA has not yet reviewed their safety and effectiveness as one, closed-loop system designed to perform all functions required for blood glucose management consistently and precisely, with minimal management by the patient. Researchers have made significant progress toward combining these devices into a more dynamic system, and FDA will continue to prioritize this development; however, more research is needed.

Continuous Glucose Monitors

CGMs incorporate sensors that measure glucose levels in the fluid around cells. These glucose levels may differ from the level of glucose circulating in the blood. FDA has not approved CGM values alone as a way to determine insulin dosing. Also, CGM sensors can build up organic matter on their surfaces once they are inserted under the skin. This organic matter can impact the effectiveness of the sensors, leading to inaccurate readings or outright failure of the sensors. More research and advances in sensor technology will help CGM systems more accurately and quickly measure blood glucose and resist build up.

Blood Glucose Monitoring Devices

Blood glucose monitoring devices (such as glucose meters) are used to calibrate CGMs. A more accurate blood glucose monitor provides for a more accurate CGM. Blood glucose monitor readings can be influenced by various factors, such as when a patient is sick, taking other medication, or simply dehydrated. Research to improve the readings of blood glucose monitoring devices can sharpen the accuracy of the overall artificial pancreas system.

*Infusion Pump*s

FDA has identified problems with the mechanical components and software of many insulin infusion pumps. These problems have led to improper insulin dosing and compromised patient safety. These known problems with infusion pump software present challenges to creating the computer programs to connect insulin infusion pumps and CGMs in an artificial pancreas. The Agency is taking steps to bring safer infusion pumps to market, but more research and innovation to improve the overall safety and effectiveness of the pumps would benefit any artificial pancreas system.

Insulin

FDA must also consider the limitations of insulin delivered by artificial pancreas systems. The insulin currently used in artificial pancreas systems can take hours to completely absorb, and the absorption rates can vary, among patients as well as within the same patient throughout the day. Creating a control algorithm that allows the CGM

to take both factors into account is difficult. The development of faster-acting insulin would help artificial pancreas systems better calculate insulin doses.

FDA's Role

FDA is helping advance the development of an artificial pancreas system by prioritizing the review of research protocol studies, fostering discussion, shortening study and review times, and providing clear guidelines and a path to market for industry.

The Critical Path Initiative (CPI) is FDA's national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. In 2007, FDA created the Artificial Pancreas Critical Path Initiative, bringing together a multi-disciplinary group of scientists and clinicians from FDA's three medical product centers (the Artificial Pancreas System Review team) and the National Institutes of Health (NIH). These scientists share knowledge in order to facilitate the transition of devices from research to marketing approval. One of the major goals of this initiative is to identify roadblocks and possible solutions to streamline the regulatory process. Many of FDA's efforts, some of which are described below, are unique to the development of an artificial pancreas system.

Collaboration with Researchers and Other Stakeholders

Many stakeholders play a role in the development of an artificial pancreas system—researchers, clinicians, medical device designers, and manufacturers. FDA has worked to encourage the collaboration of these stakeholders so that an artificial pancreas system can

be brought to patients more quickly. FDA and JDRF have worked together on our shared goal of facilitating the development of artificial pancreas systems. In July 2008, FDA, JDRF, and NIH co-sponsored a public workshop that focused on state-of-the-art research and development of an artificial pancreas. The workshop provided stakeholders with a forum for information sharing to accelerate the development of an artificial pancreas. As a result, JDRF and FDA supported investigators in the creation of a theoretical model of glucose and insulin metabolism allowing quick evaluation of various control algorithms as a substitute for animal testing. Use of this time and money-saving tool expedited the transition from bench-top to bedside testing.

Additionally, in November 2010, FDA co-sponsored a second public meeting with NIH to discuss the clinical development plan for transitioning from clinical trials in the hospital to the outpatient setting. These interactions with stakeholders resulted in the development of the artificial pancreas guidance released on Monday.

FDA continues to share with researchers and other stakeholders what we have learned from pre- and post-market reviews about the performance of artificial pancreas components. For example, FDA has worked to obtain permission from specific manufacturers of component devices to provide certain researchers with confidential information that may help further their research. Enabling a better understanding of the challenges of combining the component devices into a system in which patients can entrust their health and their very lives is critical for product development.

Rapid Response to Preliminary Study Plans

FDA encourages researchers to contact the Agency early to discuss clinical study plans and get informal feedback that can improve their study designs and facilitate the review process. FDA responds within two weeks to investigators seeking preliminary feedback on their artificial pancreas system study plans. This quick, informal feedback can help investigators develop better and more complete study plans for FDA review.

Interactive Review of Investigational Device Exemption (IDE) Study Plans

When investigators submit their final study plans for FDA review, the Artificial Pancreas System Review Team gives these submissions the highest priority and works interactively with investigators to move them quickly and efficiently through the review process. Questions and research challenges are often resolved during the first round of review, helping researchers start their studies sooner.

Guidance and Standards for Researchers and Industry

FDA guidance and industry standards help manufacturers and researchers understand the minimum requirements for making a device that is safe and effective. This helps them make the best use of resources and streamlines the regulatory review process.

As mentioned earlier, on June 20, 2011, FDA issued a "Draft Guidance for Industry and the Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Low Glucose Suspend Device Systems." This guidance outlines the minimum safety and effectiveness

information recommended for product approval, contains an IDE submission template detailing critical information, and provides a clear and predicable regulatory path for manufacturers seeking to market an LGS system. It was developed with considerable input from industry, researchers, and other stakeholders and provides manufacturers with information that could bring a first-generation artificial pancreas system to market.

FDA is asking for public feedback on the LGS guidance. In addition, FDA will be reaching out to the medical communities that work with people with diabetes to obtain feedback regarding the proposed guidance. Based upon the feedback, FDA will update the guidance accordingly.

FDA has continued to pursue all types of artificial pancreas systems and will be proposing another guidance to address the safety and effectiveness testing for the other more advanced autonomous artificial pancreas systems not covered in the first guidance. To expedite the second guidance, FDA has been working with research communities such as JDRF. Their knowledge and understanding of diabetes and diabetes research have significantly accelerated the development of the second guidance. FDA expects to complete this guidance by the end of 2011.

In addition, FDA is working with NIH and other interested parties in developing the next artificial pancreas workshop, which will focus on developing better technology for the creation of a more accurate and reliable artificial pancreas system.

CONCLUSION

FDA is fully committed to the development of an artificial pancreas to meet this critical health need. It is the goal of the Agency to provide a clear pathway for manufacturers to provide people with diabetes with innovative, safe and effective medical devices to treat their disease. Mr. Chairman, this concludes my formal remarks. I will be pleased to answer any questions the Committee may have.