March 5, 2012

The Honorable Margaret A. Hamburg, M.D.  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

RE: Draft Guidance for Industry and Food and Drug Administration Staff: The Content of Investigational Device Exemption and Premarket Approval Applications for Artificial Pancreas Device Systems

Dear Dr. Hamburg:

On behalf of The Endocrine Society, I would like to thank you for the Food and Drug Administration’s commitment to advancing the artificial pancreas through the December 6, 2011 “Draft Guidance for Industry and Food and Drug Administration Staff - The Content of Investigational Device Exemption (IDE) and Premarket Applications for Artificial Pancreas Device Systems.” The Society represents more than 15,000 physicians and scientists engaged in the treatment and research of endocrine disorders, such as diabetes, osteoporosis, hypertension, infertility, obesity, and thyroid disease. Our members strongly believe that the FDA should adopt the proposed guidance to enable researchers to study the effectiveness of the artificial pancreas on the treatment of type 1 diabetes in an outpatient setting.

The Society believes that the current draft contains many positive provisions that will ensure that the artificial pancreas is developed in a safe and expeditious manner. However, we would like to offer the following comments in order to strengthen the guidance.

Time in Range (TIR)
The draft guidance states, “Although studies have used TIR as a primary endpoint, there is some uncertainty about whether it is a good surrogate for determination of safety and effectiveness.” There is interest among researchers to be able to use TIR as a primary endpoint in studies, and the Society would like to encourage the FDA to be more prescriptive about what more is needed to be able to use TIR without A1C as a primary endpoint. A1C does not measure variability, and variability reduction (particularly hypoglycemia reduction) is one of the major goals of an artificial pancreas. The Society would be happy to work with the FDA to determine a plan for how TIR could be accepted as a primary endpoint.

Superiority Margins
In the draft guidance, the FDA recommends that there be a 30 percent superiority margin for hypoglycemia events measured by CGM, and a 0.4 percent superiority margin for HbA1C. The Endocrine Society believes that these superiority margins are too high and recommends that a simple superiority margin would represent a clinically meaningful difference. A simple superiority margin would also be consistent with statistical standards for clinical trials. Furthermore, based on patient population, different superiority margins may be justified.

The Society is also concerned about the precedent being set by including a specific superiority or non-inferiority margin for AP trials. No previous guidance documents developed by the FDA have included a specific superiority or non-inferiority margin, and have allowed the study sponsor to determine the appropriate margin that they believe can be justified. The Society recommends that the FDA continue to allow study sponsors to determine the appropriate margins for studies based on patient populations and other relevant factors, and require that the sponsor provide the justification for that margin.
Study Progression
The Society appreciates the inclusion of a reasonable study progression to ensure the safety and effectiveness of artificial pancreas systems. As each of these stages is designed to test specific aspects of the functionality and performance of the artificial pancreas device systems, the Society believes that it is important to further refine the manner in which these stages are defined to ensure that additional research pathways are included. For example, the guidance specifies that pivotal studies should be conducted in an outpatient, unsupervised setting. However, not every outpatient study is a pivotal study and the Society believes that it is important to make this distinction. Furthermore, it is important that early feasibility studies are not omitted and that outpatient transitional studies are included before pivotal studies to ensure that the safety of the artificial pancreas technology is tested in multiple settings before its approval for use in real-world clinical situations.

The Society believes that the release of the guidance on the artificial pancreas is a significant step forward in continuing research on these important systems. If the Society can be of any assistance during this process, please do not hesitate to contact Stephanie Kutler, Director of Government Affairs, at skutler@endo-society.org.

Sincerely,

Jason A. Wexler, M.D.
Chair, Clinical Affairs Core Committee
The Endocrine Society