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September 20, 2011

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: **Docket No. FDA–2011–D–0464**
Draft Guidance for Industry and Food and Drug Administration Staff: The Content of Investigational Device Exemption and Premarket Approval Applications for Low Glucose Suspend Device Systems; Availability

Dear Sir/Madam:

The American Association of Diabetes Educators (AADE) is pleased to submit comments to the Food and Drug Administration (FDA) regarding the draft guidance document for Low Glucose Suspend systems ("LGS systems") which appeared in the Federal Register on June 22, 2011. LGS systems, a version of an insulin pump which suspends insulin delivery when a monitor indicates a person with diabetes has or is about to have dangerously low glucose levels, are currently being used in over 40 nations around the world and are critically needed for the safety of the millions of Americans living with type 1 diabetes. These systems could help those living with type 1 diabetes to better self-manage their illness. AADE applauds the FDA's efforts and looks forward to continuing to work with the agency to accelerate the research and development in areas that facilitation effective patient management and self-managegment.

Type 1 diabetes is an autoimmune disease that strikes children and adults suddenly, and can be fatal. Until a cure is found, people with type 1 diabetes have to test their blood sugar and give themselves insulin injections or infusions through a pump 24 hours a day every day in order to stay alive. Too much insulin can result in seizures, coma, or death from hypoglycemia, or low glucose levels. Too little insulin over time leads to devastating kidney, heart, nerve, and eye damage from hyperglycemia, or high glucose levels. Even with diligent monitoring, the majority of people with type 1 diabetes still do not achieve recommended target glucose levels – only 30% of their day is spent at a healthy level, and the average patient spends over 90 minutes every day hypoglycemic.[i] People with diabetes desperately need better tools to manage this difficult disease and prevent its life-threatening complications.

ABOUT AADE

Founded in 1973, AADE is a multidisciplinary association of 12,000 healthcare professionals (RNs, RDs, PharmDs) dedicated to integrating self-management as a key outcome in the care of people with diabetes and related chronic conditions. The Association is constantly working towards our vision of optimal health and wellness for all people with diabetes and related chronic conditions. To help us reach this vision, we have created a dynamic organizational structure and a strong mission and values:

Our Mission is to drive practice to promote healthy living through self-management of diabetes and related chronic conditions.

COMMENTS ON FDA'S DRAFT GUIDANCE DOCUMENT

"The Content of Investigational Device Exemption and Premarket Approval Applications for Low Glucose Suspend Device Systems"

AADE believes guidance for low glucose suspend systems is very much needed, and has conducted a thorough evaluation of FDA's draft guidance document. While many aspects of the guidance are on target and we; written, AADE has concerns about some issues of critical importance. AADE believes that as currently written, the low glucose suspend guidance document may delay the availability of lifesaving technology to people with type 1 diabetes who need it; and these issues must be resolved before the draft guidance document is finalized.

CORE ISSUES REQUIRING RESOLUTION

1. **The proposed clinical study pathway in the guidance is excessively burdensome and will require large, multi-year pre-market studies before the technology is available to patients in the United States. AADE recommends that FDA not mandate that in-hospital studies be conducted prior to initiating outpatient studies for LGS systems and that non-inferiority trials be recognized as an acceptable basis for demonstrating effectiveness of LGS systems for the purpose of FDA approval.**

   AADE is concerned because: 1) the current requirement for inpatient studies is very restrictive, and 2) most people with T1 diabetes are seen in an outpatient setting. In considering the risks and benefits of LGS systems, it does not appear that FDA is fully differentiating the intended use of this early design of AP system from the more technologically challenging closed-loop systems that are under development. It is almost a certainty that the probable benefits of a well designed LGS system that suspends the delivery of insulin for a relatively short period of time at pre-specified levels that are at or near hypoglycemia outweigh the probable risks to patients. Evidence demonstrates that

suspension of insulin delivery for two hours poses minimal risk to patients[ii] while the continuation of insulin delivery to someone in low glucose ranges presents significant risks.[iii] In addition, it is AADE's view that pivotal studies of LGS systems that demonstrate that the use of the technology does not lead to a loss of glycemic control should be sufficient for approval of such products. Non-inferiority demonstrated among a significant portion of the target patient population should constitute reasonable assurance of effectiveness. Furthermore, quality of life should be a possible factor that could be considered when determining whether LGS systems are safe and effective and whether they should be made available to patients.

Quality of Life is measurable with an index in an attempt to quantify a nation's livability for its average inhabitant. It is a composite of six sub-indexes, each describing one of the elements which objectively influence the quality of life: health, education, wealth, democracy, peace and environment. Healthy People 2020 posed the question, "Why is HRQOL surveillance important?" To answer this, Healthy People 2020, developed Two overarching goals for Healthy People 2020 are directly related to quality of life: 1) Attain high quality, longer lives free of preventable disease, disability, injury, and premature death and 2) Promote quality of life, healthy development and healthy behaviors across all life stages.

AADE recognizes that the indications for use for LGS systems will be derived from clinical study results. To streamline the approval process, AADE suggests that a "functional" indications for use, i.e., an indication that refers to what the device does and does not specify an indicated patient population or clinical outcome, could present significant advantages. In the cardiovascular area, FDA has used functional indications as a least burdensome method of allowing the clinical community greater freedom to identify the patient populations that would benefit from an implantable cardioverter defibrillator ("ICD").

Without these changes, the LGS guidance will require multiple complex clinical trials (inpatient and then outpatient) of very large size and diversity (to show statistically significant differences in glucose changes in a limited hypoglycemia range) to make available a simple but important feature which shuts off insulin available to an individual pre-hypoglycemic therefore decreasing the probability of severe life threatening hypoglycemia. As a representative of people living with diabetes, I can assure you the effect of hypoglycemia extends beyond the actual period of hypoglycemia adversely impacting the quality of life not only for the patient but to caregivers and/or significant others also. The prevention is simple, the approval overwhelmingly complex. The LGS systems should be approved based on data showing safety and non-inferior effectiveness, with additional clinical effectiveness data among larger populations collected in post-market studies.

In fully considering this core issue, it is critical for FDA to understand that patients and their physicians who face the difficult task of managing type 1 diabetes on a day-to-day basis will understand the potential benefits and risks associated with suspension of insulin delivery for two hours or less and are fully capable of making the decision whether the use of a LGS system is in their best interest.

2. **The proposed guidance does not provide adequate clarity in a key area – use of continuous glucose monitors (CGM) in LGS studies. AADE is pleased the guidance allows use of CGM data in evaluation of LGS systems, but FDA must express a commitment to use of such data or studies could be conducted only later to be found inadequate under a changed standard.**

   AADE finds the statement in the draft guidance that FDA "… may change its guidelines with experience" to be of concern. Although AADE understands that the use of CGM has limitations that could impact study conclusions, the use of CGM represents a reasonable approach to facilitate the development of LGS systems and AP systems. If, after the conduct of a trial, greater precision is judged to be necessary, FDA should consider addressing the issues in the post-market period. A firm commitment to the use of CGM in clinical studies will facilitate the initiation of these studies and the availability of LGS system to U.S. patients.

   Therefore AADE recommends the following changes be made to the guidance: on line 840-841 the sentence "As more information is gathered from the conduct of these studies, FDA may change its guidelines over time," be replaced with one reading "As more information is gathered from the conduct of these studies, FDA may require additional post-market data gathering."

3. **The proposed guidance creates a highly burdensome requirement that substitution of substantially equivalent components in the LGS system would be allowed only if additional separate clinical studies of the system for each component variation are conducted. AADE urges FDA to adopt more efficient means to allow sponsors of clinical investigations and holders of approved premarket approval ("PMA") applications to utilize multiple versions of components or make modifications to their LGS and AP systems.**

   The draft indicates that use of different system components, including "CGMs, BGDs, insulin pumps, and control algorithms" will result in different LGS systems where "… each of these systems would constitute a unique device system that will require individual study for device approval." The draft also states that the agency "…strongly recommends the Sponsor seek FDA input via the pre-IDE process when intending to make modifications to any of the device components included as part of the LGS system."

   Requiring separate individual human clinical trials to enable substitution of equivalent components in an LGS system is an unwarranted proposal that would severely limit choice for patients and create a burdensome pathway that would discourage the development of technologies serving a critical public health need. AADE is very supportive of population management and initiatives that augment public health efforts. The FDA is urged to allow clinical data previously submitted to the agency or bench testing to show equivalence, and require only one clinical trial to evaluate the system.

In addition, the agency should utilize its many regulatory options to allow greater flexibility for sponsors of investigational device exemptions ("IDEs") and holders of approved PMAs to make changes to their systems. In the realm of IDEs, there are 5-day notices that keep FDA apprised of changes in device design without requiring preapproval. With PMAs, FDA can identify changes in device design that it can permit to be made subject to periodic reporting or a 30-day PMA supplement; both of which can facilitate device improvements. AADE is concerned that this guidance does not allow these pathways, long available for other device systems, for LGS systems, potentially deterring the availability of improved systems for people with diabetes. AADE thus recommends the guidance be revised to explicitly allow these regulatory options for LGS systems.

ADDITIONAL COMMENTS

AADE also has additional comments on various aspects of the draft guidance document, from preclinical to post-market issues, which are being offered in support of finalizing the guidance as soon as all comments are carefully considered. To facilitate FDA's consideration of AADE's additional comments, they are presented in three categories: Clinical Considerations, Non-clinical Considerations, and Regulatory Considerations.

Clinical Considerations

4. Once a pivotal clinical study is approved, AADE believes that FDA should only change the protocol if it is judged to be contrary to public health, or a substantial scientific issue essential to determining the safety or effectiveness of the device has been identified, and then, only following an opportunity for the applicant to meet with FDA to discuss the scientific issue involved.

Anything short of a commitment to accept a trial conducted in accordance with FDA's final guidance document represents a business risk to sponsors undertaking the task of conducting pivotal clinical trials in support of PMAs. Use of CGM, as described above in comment #2, is just one example of numerous key study design elements that once agreed to in the study design – need to not be changed once the study has begun. In fact, AADE believes that, with the concurrence of the study sponsor, it is reasonable for FDA to consider approved IDEs that follow FDA's guidance document to represent "binding agreements," subject to the same requirements and limitations that are associated with formal agreement and determination meetings.

5. FDA should provide guidance on outpatient-based pilot studies as a means to progress to outpatient pivotal trials.

The draft guidance document appears to be geared more toward supporting commercial interests (PMA approval) than research interests and quality patient management. This might mean smaller studies sponsored by the National Institutes of Health ("NIH") and AADE. Furthermore, there are areas of the draft guidance that suggest that there is a fundamental misunderstanding of the activities that are ongoing and their relationship to overall AP R&D

efforts. For example, one excerpt from section VII.A.1 of the draft states "… prior to an outpatient (pivotal) study," suggesting that FDA may view "outpatient" as synonymous with "pivotal." But section VII.A differentiates between pilot studies and pivotal studies and asserts that "the pivotal study should be conducted with the finished LGS system for which approval will be sought." Researchers could benefit from more guidance and regulatory flexibility from FDA to get to the outpatient setting so that the basic effectiveness of early prototypes can be meaningfully assessed.

In regard to substantive issues related to study design, there are aspects of the draft guidance that, if applied to outpatient pilot studies, could slow overall progress. For example, requiring an outpatient-based pilot study to have a parallel or cross-over study design with HbA1c as a safety outcome measure would increase the amount of time that each subject would be required to participate in a study. Likewise, requiring a statistical analysis plan for a small pilot study to incorporate a non-inferiority limit for HbA1c, which is highly dependent on sample size, would never be attained. In essence, for researchers not interested in conducting pivotal trials, or not prepared to engage in this level of clinical research, forcing them to do so may not yield results that would justify their effort. High quality research should not be impeded by "hassle factor" that such a requirement would add on.

6. **A study design in which the glucose-suspend function can be either active or inactive, based on a randomization scheme, should be considered as an alternative to a randomized cross-over design or a randomized parallel design.**

   A study design in which the glucose-suspend function can be either active or inactive based on a randomization scheme may be desirable so that the patient will be blinded to the whether they are in the 'intervention' or 'control' arm. The study design proposed in the draft guidance document is possible for overnight studies, but is not really possible for daytime studies.

7. **The following bullets include additional observations that relate to study design and are presented for FDA's consideration:**

   - Section VII.B.2 (Study Endpoints) is written from the strict point of view of a system that alarms first, then takes action if there is no user response. This makes aspects of this section difficult to apply to a more generalized situation where the system takes action without waiting for a user response. AADE encourages FDA to review this section carefully to ensure that investigations will not be more constrained than absolutely required.

   - The guidance is inconsistent in defining hypoglycemia. In some sections a plasma glucose of <=70 mg/dL is used and in other sections a value of <=60 mg/dL is used. AADE recommends that a CGM value <=70 mg/dL be considered as the appropriate correlate for hypoglycemia. A false positive/false negative rate will be more favorable with a threshold of 70 mg/dL compared with 60 mg/dL. This will facilitate patient enrollment and reduce sample size.

- FDA recommends that the initial patient population be subject to specific criteria, including the following:

    - *Disease onset < 40 years old*
    - *T1DM minimum ≥ 2 years*
    - *Stimulated C-peptide negative*

  Without providing greater clarity, it is difficult to understand why these specific restrictions are appropriate.

- AADE understands FDA's interest in enriching trials with patients who are likely to have hypoglycemia to ensure the adequacy of the clinical data; however, imposing criteria such as provided in the example will make it difficult to enroll subjects. Specifically, if patients have a significant history of hypoglycemia with at least <u>one of the following</u> indications of hypoglycemia, recruitment will be limited:

    - *Finger stick confirmed blood glucose (BG) < 70 mg/dL ≥ 3 times per week for the past 3 months on average*
    - *Requirement of assistance from other for the treatment of hypoglycemia at least once in the past six months*
    - *Finger stick confirmed nocturnal hypoglycemia (BG<70 mg/dL) > 1 weekly for the past 3 months on average*

- Event rate is one of two primary effectiveness endpoints. Event rate is operationally defined as follows:

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

  It is unclear why multiple events occurring on one day would not be counted. AADE suggests describing the basis for counting only one event per day. AADE requests additional clarity be added.

<u>Non-Clinical Considerations</u>

8. AADE encourages the agency to take steps to ensure that the guidance document is not misleading to readers or causes unintentional concern among patients.

The illustration in Section II of the draft guidance document does not accurately depict a LGS system that will be the likely output of today's R&D efforts. The guidance presents FDA expectations related to pivotal trials and PMA requirements. In this regard, it may be more appropriate to depict a small external device (e.g. cell phone/PDA) rather than a

computer, or show an external data processing component incorporated into the CGM receiver or pump hardware.

9. FDA should avoid referencing the draft guidance document entitled "Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions" dated April 23, 2010.

Given that the draft guidance document for infusion pumps is being distributed "for comment purposes only", AADE questions whether it is appropriate to refer to this document for insight into the agency's current expectations. Given that the draft infusion pump guidance has been draft for over 15 months, AADE assumes that there are changes in process due to the extensive comments that the agency received. Until these comments are assessed and the guidance document finalized, referring IDE sponsors and PMA applicants to this draft guidance for direction could be misleading.

Regulatory Considerations

10. FDA should explicitly emphasize a commitment to following the least burdensome principles of the Federal Food, Drug, and Cosmetic Act ("FDCA") as well as President Obama's recent Executive Order to all regulatory federal agencies.

A central purpose of the Least Burdensome provision in the FDCA is "to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development.[iv]" Inherent in this goal was a directive to streamline the regulatory process to improve patient access to breakthrough technologies. Lessening regulatory burden, while striving for a reasonable assurance of safety and effectiveness, is a key means to ensuring the timely availability of LGS systems.[v] This concept, among others designed to foster regulatory flexibility, was reinforced in an Executive Order by President Obama on January 18, 2011.

11. FDA should explicitly designate LGS systems as eligible for "expedited review". Furthermore, the agency should consider extending eligibility beyond approval of the first LGS system to facilitate the development of additional systems.

FDA is required by the FDCA to review PMA applications meeting certain conditions on an expedited basis. While FDA will acknowledge that LGS systems meet the statutory eligibility criteria, the draft guidance document does not explicitly state LGS systems will be subject to expedited review procedures. Because of potentially favorable consequences associated with being designated for expedited review; AADE encourages FDA to acknowledge that IDEs and PMAs for LGS system will be reviewed in an expedited basis. Furthermore, because of the public health importance of facilitating the development and availability of additional AP systems, AADE encourages FDA to not withdraw expedited review status with the first PMA approval of a LGS system.

12. FDA and regulated industry should consider approved IDEs that include clinical protocols that are consistent with this guidance to be binding.

Determinations and agreements resulting from meetings conducted in accordance with sections 513(a)(3)(D) and 520(g)(7) of the FDCA are binding. In the case of a Determination Meeting, the determination regarding valid scientific evidence is binding on the agency and cannot be changed unless FDA concludes that adhering to it could be contrary to public health. With an Agreement Meeting, the agreement is binding on the agency and may only be changed when a substantial scientific issue essential to determining the safety or effectiveness of the device has been identified, and only following an opportunity for the applicant to meet with FDA to discuss the scientific issue involved. With a sponsor's concurrence, considering IDEs that include clinical protocols that are in accord with FDA's LGS system guidance and are approved by FDA to constitute a binding determination and agreement may provide a degree of confidence and predictability that will be a significant incentive for companies to invest in LGS system research and development ("R&D") in the U.S.

13. FDA should assume a least burdensome regulatory posture regarding LGS system components. In this regard, AADE suggests continuing to regulate LGS system components in accordance with existing regulatory classifications and avoid subjecting their manufacturers to class III regulatory requirements.

It is important to make every effort to avoid subjecting manufacturers of legally marketed class I and II devices, whose devices may be used as components in LGS systems, to class III regulatory requirements. To do so could prove disruptive and interfere with the development of new and improved class I and II devices. Likewise, every reasonable effort should be made to reduce burden on LGS system manufacturers and to provide them flexibility in updating their systems with new components. The burden for assuring the safety and effectiveness of LGS system lies with the PMA applicant and not component suppliers who may be legally marketing components for use outside of a LGS system.

14. FDA should differentiate early research studies from studies being conducted for marketing purposes and provide greater flexibility for researchers to conduct them.

FDA should explore every means of encouraging the development of AP systems, including LGS systems, and to maintain optimum freedom for investigators in their pursuit of this purpose. In this regard, AADE encourages FDA to consider certain studies to be "non-significant risk" and, therefore, subject to abbreviated requirements (21 CFR 812.2(b)), "exempt" (21 CFR 812.2(c)), and to consider waiving certain requirements (21 CFR812.10), as appropriate. Additionally, there are other regulatory flexibilities that AADE encourages FDA to consider using to a greater extent, including allowing sponsors of studies to report more changes in their annual progress reports and to submit more changes as 5-day notices.

15. In considering the risk to patients, FDA should attempt to differentiate in hospital studies from outpatient studies and rely on local IRBs to oversee the trials without the need for FDA approval.

While AADE firmly believes that inpatient studies should not be necessary for PMA purposes, AADE recognizes that the research community may have interests in conducting inpatients studies. In the draft guidance document, FDA asserts that clinical studies involving LGS systems "… are considered significant risk device systems as defined in 21 CFR 812.3(m)". In the case of in hospital studies, patients are not subjected to significant risk. In this regard, designating in hospital studies "non-significant risk" would shift responsibility from FDA to local institutional review boards ("IRB") without appreciably compromising human subject protection. This in turn would allow the agency an opportunity to use its resources in activities with greater public health impact, including issuing much needed guidance documents and processing significant risk IDEs and reviewing PMAs.

CONCLUSION

AADE appreciates FDA's efforts in developing this draft guidance document and the opportunity to provide input. The issuance of a final FDA guidance for the study and approval of a LGS system is an essential first step facilitating the development and prompt availability of the technology for the treatment of patients with type 1 diabetes the United States.

AADE hopes that this will be of value to the agency and allows for a prompt and efficient process by which a final guidance document can be released for implementation. The release of a final LGS system guidance will be an overt sign of progress that will contribute to ensuring that a draft guidance document pertaining to automated AP systems is available for public comment by CDRH's December 1, 2011 goal.

If you have any questions regarding these comments, please contact Martha Rinker, Chief Advocacy Officer, at 202-624 1510. AADE looks forward to facilitating the research and development efforts to make AP systems available to augment patient self-management of diabetes in the United States.

Sincerely,

Lana Vukovljak
Chief Executive Officer
American Association of Diabetes Educators

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[iii] Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. Diabetes Care. 2008; 31: 2110-2. Epub 2008 Aug 11.

[iv] Food and Drug Administration Modernization Act of 1997. Senate Report No. 105-43 (1997).

[v] Reducing unnecessary burdens associated with the premarket approval process does not require a compromise in the evidence necessary to demonstrate a reasonable assurance of safety and effectiveness.