

Testimony of Robert Vigersky, MD, Colonel, Medical Corps
President-Elect, The Endocrine Society
To the
Food and Drug Administration Center for Drug Evaluation and Research
Endocrinologic and Metabolic Drugs Advisory Committee
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Mr. Chairman and members of the Advisory Committee, thank you for the opportunity to testify today. My name is Robert Vigersky. I am the Director of the Diabetes Institute at the Walter Reed Health Care System and Professor of Medicine at the Uniformed Services University of the Health Sciences.

But I am here today as President-Elect of The Endocrine Society, the world's largest professional organization of endocrinologists, representing over 14,000 members. The Society would like to commend the Agency for its excellent analysis of the problem in the "Background Introductory Memorandum." In many respects, the issues raised in the Memorandum encapsulate the conundrum of drug development in the 21st century - How does our society encourage the development of safe and effective drugs by pharmaceutical companies without imposing Draconian requirements that stymie these activities? Such inhibition would likely occur if the large, costly, and long-term studies required to assess clinical endpoints were required in the pre-marketing phase before FDA approval of diabetes drugs. On the other hand, the FDA, our patients, and their physicians should have as much information as possible in order to make an informed decision about whether or not the benefits outweigh the risks of taking any medication at a given point in time. It is the timing of this available information on which we would like to focus.

Historically, pre-approval studies of diabetes drugs have been designed to show glycemic effectiveness because it is the *sine qua non* of approval. These studies have used hemoglobin

A1C measurements for over 20 years as the surrogate end-point because it most directly correlates with the microvascular clinical complications of retinopathy, nephropathy, and neuropathy. While this relationship continues to be a well-accepted fact what is not yet clear is whether there is a similar relationship of glycemic control to macrovascular disease and cardiovascular events and/or whether there are drug effects independent of glycemic control that influence clinical cardiovascular outcomes. Since cardiovascular disease is the principal cause of hospitalization of patients with diabetes, and cardiovascular morbidity and mortality is the largest cost driver in the care of patients with diabetes, these are questions that must be answered, yet the path to do so is not obvious.

The Endocrine Society believes that a two-stage approach should be considered in the approval process for all new diabetes medications. Studies should be designed and powered to capture both surrogate glycemic, such as A1C, and cardiovascular end-points, like lipids, highly sensitive C-reactive protein, and carotid intima medial thickness, as well as both adverse clinical endpoints, including all-cause mortality, fatal and non-fatal MI, and stroke and beneficial clinical outcomes such as delay in onset of renal failure, retinopathy, or neurologic damage.

Having an appropriate control group for the entire study duration is essential to this approach. A drug showing appropriate glycemic effects without an adverse short-term cardiovascular outcome would achieve “conditional” approval and labeling would reflect the interim nature of the results *vis a vis* clinical cardiovascular end-points. At some agreed-upon future time, the clinical macrovascular results would be evaluated and final approval granted with those results included in the new label. Improvement in macrovascular outcomes should not be a requirement for approval since the benefit of the drug on microvascular disease would need to be balanced against the overall adverse effects. However, worse macrovascular outcomes would be grounds to rescind approval or substantially alter the label such as having a Black Box warning. Because of the substantial additional expense that such studies would engender, additional years of market exclusivity for the drug might be a reasonable offset to the costs.

Finally, The Endocrine Society suggests that the FDA commission a study by an independent third party such as the Institute of Medicine of the National Academy of Sciences to evaluate and

make recommendations about the critical issues raised in the “Background Introductory Memorandum” since they are pivotal for the future of drug development in the United States.

Thank you, again, Mr. Chairman, for the opportunity to address the panel.