



An Overview of the December 2008 Diabetes Cardiovascular Guidance

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Hylton V. Joffe, M.D., M.M.Sc.
Lead Medical Officer, Diabetes Drug Group I
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

How Did the Guidance Come to Be?

- Diabetes drugs are indicated to improve glycemic control and are approved on the basis of HbA1c
- Safety concerns with some diabetes drugs led to suggestions for more extensive cardiovascular assessment during the approval process

N Engl J Med. 2007; 357:844

N Engl J Med. 2007; 357:1775-7

July 2008 Advisory Committee Meeting

Question: It should be assumed that an anti-diabetic therapy with a concerning CV [cardiovascular] safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?

14 **“Yes”** votes

2 **“No”** votes

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- Final guidance published December 2008
- Reaffirms HbA1c as the primary efficacy endpoint for glucose reduction
- Notes vulnerability of patients with diabetes to cardiovascular disease
- Asks sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk

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- Independent committee should prospectively and blindly adjudicate major cardiovascular events
- Phase 2/3 design should permit a pre-specified meta-analysis of major cardiovascular events
- Trials should include patients at increased risk for cardiovascular disease
- Trial duration(s) should be longer than 6 months to obtain enough events and provide long-term data

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UPPER BOUND OF 95% CI FOR RISK RATIO	CONCLUSION
>1.8	Inadequate to support approval
>1.3 but <1.8*	Postmarketing trial(s) needed to show definitively <1.3
<1.3*	Postmarketing cardiovascular trial(s) generally not necessary
<p>CI=confidence interval *with a reassuring point estimate</p>	

Why 1.8 and 1.3?

- The smaller the excluded risk, the more events needed, and the larger the scope of the development program
- The 1.3 goal-post has been used in other settings for excluding cardiovascular risk (e.g., COX-2 inhibitors)
- The 1.3 goal-post is feasible, but meeting this criterion pre-approval would significantly delay new drug availability
- Willing to tolerate additional uncertainty (capped at 1.8) at approval because glycemic control is necessary for short-term symptomatic relief and reduction in HbA1c lowers risk for long-term microvascular complications

Diabetes Cardiovascular Guidance

- “Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

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Director, Office of Drug Evaluation II