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# **Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry**

## ***DRAFT GUIDANCE***

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For questions regarding this draft document, contact Silvana Borges at 301-796-0963.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**March 2020  
Clinical/Medical**

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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## **Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry<sup>1</sup>**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

### **I. INTRODUCTION**

The purpose of this guidance is to provide the Food and Drug Administration's (FDA's) current recommendations regarding the overall evaluation of safety for the development of drugs and biologics<sup>2</sup> indicated for improvement of glycemic control in patients with type 2 diabetes mellitus. The recommendations in this guidance reflect discussions at the Endocrinologic and Metabolic Drugs Advisory Committee meeting held October 24–25, 2018,<sup>3</sup> that considered FDA's review of cardiovascular (CV) outcome trials (CVOTs).

The CVOTs reviewed by the Endocrinologic and Metabolic Drugs Advisory Committee were recommended in the guidance for industry *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008) (Diabetes Mellitus December 2008 guidance). We are withdrawing the Diabetes Mellitus December 2008 guidance and replacing it with this draft guidance. We are also withdrawing the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (February 2008) and replacing it with this draft guidance.

This guidance provides recommendations on the size and nature of the safety databases needed to support drugs for chronic use to improve glycemic control in patients with type 2 diabetes.

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<sup>1</sup> This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

<sup>3</sup> See the Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting October 24–25, 2018, available at <https://www.fda.gov/media/121265/download>.

## ***Contains Nonbinding Recommendations***

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36 This guidance is intended to serve as a focus for continued discussions among the Division of  
37 Metabolism and Endocrinology Products, pharmaceutical sponsors, the academic community,  
38 and the public.<sup>4</sup>  
39

40 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
41 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
42 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
43 the word *should* in Agency guidances means that something is suggested or recommended, but  
44 not required.  
45

## **II. BACKGROUND**

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49 The withdrawn Diabetes Mellitus December 2008 guidance stated that sponsors should  
50 demonstrate that new drugs intended to improve glycemic control in patients with type 2 diabetes  
51 do not result in an unacceptable increase in CV risk. In response to the 2008 guidance, many  
52 CVOTs have been completed. In reviewing those final reports, the Agency has found that  
53 inclusion of meaningful numbers of patients with diabetes-associated complications and  
54 comorbid conditions in clinical trials is feasible and valuable in assessing the safety profile of  
55 new antidiabetic drugs, allowing valid assessment of CV risk. However, none of the CVOTs to  
56 date have identified an increased risk of ischemic CV events. Some of the CVOTs have instead  
57 demonstrated a reduced risk for CV events.  
58

59 In light of these CVOT results, the Agency convened an advisory committee meeting on October  
60 24–25, 2018, to discuss the recommendations in the Diabetes Mellitus December 2008 guidance.  
61 Committee members were asked to consider the robustness of development program safety  
62 databases before 2008, the new information learned since 2008, and whether the  
63 recommendations in the Diabetes Mellitus December 2008 guidance were still appropriate.  
64 Committee members stressed the need for sufficient safety data submitted before approval to  
65 inform decision-making, the continued importance of CV safety data not limited to  
66 atherosclerotic events, and the need to base postmarketing requirements on consideration of  
67 signals of risk identified in the development program rather than a one-size-fits-all approach.  
68

69 Based on these considerations, the Agency recommends a new approach in the evaluation of the  
70 safety profile of new drugs to improve glycemic control in patients with type 2 diabetes mellitus  
71 detailed in this guidance.  
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<sup>4</sup> In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during development.

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74 **III. EVALUATING SAFETY OF NEW DRUGS TO IMPROVE GLYCEMIC**  
75 **CONTROL FOR PATIENTS WITH TYPE 2 DIABETES MELLITUS**

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77 **A. Size of the Safety Database**

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79 Patients with type 2 diabetes mellitus require chronic therapy, generally for many years. Given  
80 the prevalence of diabetes, substantial patient exposure can be expected. Therefore, drugs  
81 approved to improve glycemic control in these patients should have well-characterized safety  
82 profiles based on shorter term studies, but some safety concerns may only be identified in longer  
83 term studies. For these reasons, the safety database of a new antidiabetic drug for type 2 diabetes  
84 mellitus should also include a substantial number of patients exposed to the drug for longer  
85 periods to allow for a thorough assessment of the drug's longer term safety profile. Therefore,  
86 the safety database for a marketing application for a new drug for glycemic control should  
87 include data from controlled clinical trials and controlled clinical trial extensions with the  
88 following exposures:

- 89
- 90 1) At least 4,000 patient-years of exposure to the new drug in phase 3 clinical trials. (This  
91 exposure includes all dosage strengths studied in the phase 3 clinical trials.)
  - 92
  - 93 2) At least 1,500 patients exposed to the new drug for at least 1 year.
  - 94
  - 95 3) At least 500 patients exposed to the new drug for at least 2 years.
  - 96

97 **B. Patient Characteristics in the Development Program**

98  
99 Patients with type 2 diabetes mellitus often have comorbid conditions and/or diabetes-associated  
100 complications (e.g., chronic kidney disease, CV disease). Therefore, it is important to evaluate  
101 the safety of new drugs to improve glycemic control in the population of patients who will be  
102 using the drugs, including a meaningful number of patients with underlying CV disease, chronic  
103 kidney disease, and older patients. When a sponsor submits a marketing application for a new  
104 drug for glycemic control, the safety database should include data from patients with relevant  
105 age, comorbid conditions, and/or complications in the phase 3 trials as follows:

- 106
- 107 1) At least 500 patients with stage 3/4 chronic kidney disease exposed to the new drug.
  - 108
  - 109 2) At least 600 patients with established CV disease (e.g., previous myocardial infarction,  
110 documented coronary artery disease, previous stroke, peripheral vascular disease)  
111 exposed to the new drug.
  - 112
  - 113 3) At least 600 patients older than 65 years of age exposed to the new drug.
  - 114

115 Recognizing that a given patient could fall into more than one of these three categories, sponsors  
116 should aim for at least 1,200 patients with at least one of these conditions.

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**C. Other Considerations**

Sponsors should also consider the following concerning the collection of safety data:

- Adverse CV outcomes remain an important source of morbidity and mortality for patients with type 2 diabetes mellitus. Therefore, sponsors should use rigorous methods for the collection of adverse CV events and assess them by adjudication.
- In some cases, the evaluation of a premarket safety concern may require that a drug development program accrue a minimum number of relevant adverse events to exclude a meaningful degree of risk. Adjudication of these adverse events may also be needed. The Agency expects that situations where the collection of these additional safety data is necessary will be identified and discussed before phase 3 trials are initiated.
- Sponsors should include data safety monitoring boards or committees to provide independent oversight of the safety findings from the clinical trials.