FDA Background Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

October 24-25, 2018

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought "Guidance for Industry: Diabetes Mellitus--Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" and the cardiovascular risk assessment of drugs and biologics for the treatment of type 2 diabetes mellitus, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Division Director Memorandum:

To: Chair, Members, and Invited Guests
Endocrinologic and Metabolic Drugs Advisory Committee

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Subject: October 24-25, 2018 Advisory Committee Meeting

Thank you for your participation in the October 24-25, 2018 advisory committee meeting. This meeting is being held to discuss the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

Type 2 diabetes is a disorder of impaired glucose homeostasis which leads to hyperglycemia. As a consequence of chronic hyperglycemia, patients with type 2 diabetes are at increased risk for microvascular and macrovascular complications. Improved glycemic controls has been shown to improve clinical outcomes, and lowering glucose levels has been a target of clinical care and drug development.

While reduction of hyperglycemia is on target of clinical care for patients with type 2 diabetes, the management of patients with diabetes mellitus is encompasses many aspects and includes ophthalmic care, podiatric care, and management of other risk factors for cardiovascular disease. Previously, concerns were raised that treatment of patients with diabetes was too 'glucocentric' and that there may be therapies that lower blood glucose but that also increase the risk for adverse cardiovascular events.

The 2008 guidance was issued to ensure that new antidiabetic therapies to treat type 2 diabetes were not associated with an unacceptable increase in cardiovascular risk, and the recommendations in the guidance were applied to all new drug products intended to treat type 2 diabetes, irrespective of whether a signal of concern was identified in the development program. Over the past decade cardiovascular risk assessments for new antidiabetic drugs have been conducted in accordance with the recommendations outlined in the guidance.

We now have eight clinical trials conducted under the guidance. All eight have demonstrated no excess cardiovascular risk with any of the therapies studied. Notably, some of the trials have shown a reduced risk for adverse cardiovascular events.

Now that we have results of several trials and ten years of experience with drug development under the guidance, it seems apropos to review what we have learned and consider what changes to the approach, if any, are necessary.

This background document and the presentations that you will hear at the meeting are intended to provide a look back at why the guidance was issued, a description of how things have changed as a result of the guidance, and what we have learned as a result. You will also hear about the work that goes into the design and conduct of cardiovascular outcomes trials, a perspective on the benefits and costs of instituting the guidance, and some thoughts on different approaches to evaluating cardiovascular risk. Taking all of this into consideration we will ask you to provide your thoughts on the guidance and your recommendations for evaluating this concern moving forward.

We thank you for your service as part of this advisory committee and look forward to hearing your discussion and recommendations.

Draft Points for Discussion:

1. Discuss the impact of the recommendations in the 2008 Guidance for Industry: *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes mellitus.

2. For each recommendation described in the 2008 guidance, discuss its value in the evaluation of the safety of new antidiabetic drugs. The recommendations we would like you to consider are:

    a. Establishment of an independent cardiovascular endpoints committee for prospective adjudication.

    b. Inclusion of patients at higher risk for cardiovascular events in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk.

    c. Exclusion of 1.8 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio prior to approval.

    d. Exclusion of 1.3 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio to conclude that there is no unacceptable increase in cardiovascular risk.

3. Discuss how cardiovascular safety findings from members of a drug class should or should not be applied to all members of the drug class.

4. The 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes provided recommendations on excluding an unacceptable increase in cardiovascular risk for all new therapies to improve glycemic control in patients with type 2 diabetes regardless of the presence or absence of a signal for cardiovascular risk in the development program.

   Discuss whether an unacceptable increase in cardiovascular risk needs to be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for CV risk in the development program.

   a. If 'Yes', provide your rationale. Include in your discussion what changes, if any, you would recommend to the 2008 guidance and why, and what kind of assessment would be appropriate and when it should be conducted (i.e., pre-market, post-market, both).

   b. If 'No', provide your rationale. Include in your discussion what might constitute a signal of cardiovascular risk that would warrant conduct of a cardiovascular outcomes trial or other form of cardiovascular risk assessment.

History of the Guidance

Diabetes mellitus is a serious, chronic disease of impaired glucose homeostasis. Generally, there are considered to be two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM). In T1DM, there is an absence of insulin production resulting in a need for insulin replacement therapy. In T2DM, there is insulin resistance and relative insulin deficiency. In both types, the resulting chronic hyperglycemia increases the risk for complications, both microvascular (e.g., diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) and macrovascular (e.g., myocardial infarction, stroke, death). Based on the results of large, prospective, controlled clinical trials, improving glycemic control, as demonstrated by reducing hemoglobin A1c (HbA1c), is expected to improve clinical outcomes (e.g., reduced risk of diabetic retinopathy [1, 2]).

Development of drugs to treat diabetes mellitus, particularly T2DM, has focused on demonstrating that a drug product has the ability to lower blood glucose and can improve glycemic control. This, in turn, is expected to lead to improved clinical outcomes. However, there have been instances where a signal of cardiovascular risk has been reported either with specific drug products or in the setting of intensive glycemic control in selected patient populations (Table 1).

[1] The Diabetes Control and Complications Trial Research Group. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". NEJM, 1993; 329 (14): 977-986.
[2] UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". Lancet, 1998; 352 (9131): 837-853.

Table 1: Selected examples of findings that raised concern for cardiovascular risk

UGDP [a]	University Group Diabetes Program reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality.
Muraglitazar [b]	Evaluation based on pool of 5 phase 2 and 3 clinical trials. In the muraglitazar-treated patients, death, MI, or stroke occurred in 35 of 2374 (1.47%) patients compared with 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone treatment groups (controls) (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; P=.03). For the more comprehensive outcome measure that included TIA and CHF, the incidence was 50 of 2374 (2.11%) for muraglitazar compared with 11 of 1351 (0.81%) for controls (RR, 2.62; 95% CI, 1.36-5.05; P=0.004). Relative risks for each of the individual components of the composite end point exceeded 2.1 but were not statistically significant. Incidence of adjudicated CHF was 13 of 2374 (0.55%) muraglitazar-treated patients and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; P=0.053).
Rosiglitazone [c]	A meta-analysis of 42 trials suggested an increased the risk of myocardial infarction by 43% and cardiovascular mortality by 64% compared to placebo and other anti-diabetic agents.
ACCORD Trial [d]	In this randomized trial comparing intensive glucose lowering (target HbA1c ≤ 6%) with 'standard' therapy (target HbA1c 7% to 7.9%) with a primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04).

[a] Meinert CL, et al. "A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality Results". *Diabetes*. 1970; 19 (Suppl): 789-830.
[b] Nissen SE, et al. "Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus". *JAMA*. 2005; 294 (20): 2581-2586.
[c] Nissen SE, and Wolski S. "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes". *N Engl J Med*. 2007; 356: 2457-2471.
[d] The Action to Control Cardiovascular Risk in Diabetes Study Group. "Effects of intensive glucose lowering in type 2 diabetes". *N Engl J Med*. 2008; 358: 2545-2559.

In 2008, the FDA convened an Advisory Committee meeting to discuss the role of cardiovascular risk assessment in the preapproval and postapproval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus [3]. Advice that was conveyed at

[3] See May 22, 2008 Federal Register Notice (https://www.federalregister.gov/documents/2008/05/22/E8-11449/endocrinologic-and-metabolic-drugs-advisory-committee-notice-of-meeting) and meeting materials for the

that meeting included a need for additional assessment of cardiovascular risk compared to the procedures in place at the time. Recommendations included standardization and ruling out excess cardiovascular risk. An upper bound to the hazard ratio of 1.2 to 1.4 was felt to be reasonable by a majority of the committee members. Trials of longer duration and enrollment of diabetic patients with higher cardiovascular risk were suggested.

Following that meeting, a Guidance for Industry was issued outlining recommendations on the evaluation of cardiovascular risk for new antidiabetic therapies (see Appendix 1). To establish the safety of new antidiabetic therapies to treat type 2 diabetes, developers of drug products should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. Recommendations included:

- Establishment of an independent cardiovascular endpoints committee to adjudicate cardiovascular events
- Phase 2 and phase 3 trials should include patients at higher risk for cardiovascular events in order to obtain sufficient endpoints to allow a meaningful estimate of risk
- Prior to marketing, the upper bound of the 2-sided 95% confidence interval should be less than 1.8 with a reassuring point estimate.
- A postmarketing trial [4] may be necessary to show that the upper bound of the 2-sided 95% confidence interval is less than 1.3.

July 1 and 2, 2008 Endocrinologic and Metabolic Drugs Advisory Committee Meeting (https://wayback.archive-it.org/7993/20170403222224/https://www.fda.gov/ohrms/dockets/ac/cder08 html#EndocrinologicMetabolic)

[4] Under the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901 [also 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)]

Cardiovascular Risk Assessment Prior to the 2008 Guidance

Before the Guidance for Industry was issued, the evaluation of adverse cardiovascular events was based on reported adverse event terms and populations not necessarily at a high risk for cardiovascular events. Clinical trials were also often relatively short (duration 6 to 12 months). Typically, there were small numbers of cardiovascular events to consider.

The development programs for saxagliptin, liraglutide, and alogliptin offer some perspective on the data available for consideration of cardiovascular risk before the 2008 Guidance. These three drug products were under review at the time the 2008 Guidance was issued and provide examples of the preapproval data available for assessing risk before 2008. All three products were also required to in a postapproval study that that the upper bound of the 2-sided 95% confidence interval for major adverse cardiovascular events was less than 1.3.

A summary of the cardiovascular risk assessment for these three drug products is provided in Table 2. Each program utilized the same strategy for identification of cardiovascular events. Adverse cardiovascular events were identified using investigator reported adverse events. Both a broad search and a custom/narrow search were conducted.

Table 2: Examples of Cardiovascular Risk Assessments Prior to 2008 Guidance for Industry on Evaluating Cardiovascular Risk in New Antidiabetic Drugs

	Saxagliptin [a] N=3356, PY=3753	***All Comparator N=1251, PY=1289***
Broad SMQ [++]		
➢ Events (%)	100 (3.1)	41 (3.2)
➢ Per 1000 patient-years	28	32
➢ Odds Ratio (95% CI)	0.96 (0.65, 1.42)	
Custom Query [#]		
➢ Events (%)	23 (0.7)	17 (1.3)
➢ Per 1000 patient-years	6	13
➢ Odds Ratio (95% CI)	0.52 (0.26, 1.04)	

	Liraglutide [b] *N=4257, PY=2882*	*All Comparator N=2381, PY=1486*
Broad SMQ		
➢ Events (%)	69 (1.62)	45 (1.89)
➢ Per 1000 patient-years	23.94	30.27
➢ Odds Ratio (95% CI)	0.86 (0.59, 1.24)	
Custom Query		
➢ Events (%)	21 (0.49)	17 (0.71)
➢ Per 1000 patient-years	7.29	11.44
➢ Odds Ratio (95% CI)	0.71 (0.39, 1.3)	
	Alogliptin [c] *N=3489, PY=1537*	*All Comparator N=1213, PY=505*
Broad SMQ		
➢ Events (%)	24 (0.69)	8 (0.66)
➢ Per 1000 patient-years	1.56	1.59
➢ Odds Ratio (95% CI)	0.9 (0.4, 1.9)	
Custom Query		
➢ Events (%)	14 (0.4)	4 (0.33)
➢ Per 1000 patient-years	0.91	0.79
➢ Odds Ratio (95% CI)	0.8 (0.3, 2)	

N = number of patients; SMQ = standardized MedDRA Query; CI = confidence interval

++ 'Broad SMQ' consists of cardiovascular death and all preferred terms in the 'Myocardial Infarction' and 'Central Nervous System Haemorrhages and Cerebrovascular Accidents' SMQs. Included terms can be found in Appendix 2

'Custom Query' consists of a subset of 'Broad SMQ. Included terms can be found in Appendix 2

Source: [a] adapted from Table 12 and Table 16 of the Joint Clinical and Statistical Briefing Document for the April 1, 2009 Advisory Committee Meeting; [b] adapted from Table II.C.10 and Table II.C.11 of the Clinical Briefing Document for the April 2, 2009 Advisory Committee Meeting; [c] Adapted from Table 11 and Table 12 of Dr. Hylton Joffe's May 27, 2009 Cross-Discipline Team Lead Review

In all three programs, there were relatively few events (particularly using the custom/narrow search strategy) for consideration. This, in part, reflects the design and demographics of the phase 3 programs. The trials were generally of 26 weeks duration with some continuing to 52 weeks and generally enrolled younger patients and did not include a significant proportion of patients with cardiovascular disease. Characteristics of the safety database at the time of original NDA submission for each of these drug products are described below.

Saxagliptin

The safety database for the original NDA submissions consisted of 8 phase 2/3 trials. In the phase 3 trials, mean ages ranged from 51.8 to 55.36 years. Less than 20% of patients were ≥ 65 years old. Mean duration of diabetes ranged from 2.1 to 2.3 years in studies of saxagliptin as monotherapy. In studies of saxagliptin as add-on to other drug products, the mean duration of diabetes was longer (5.1 to 7.1 years). Mean HbA1c was 7.8 to 7.9% in the studies of

saxagliptin as monotherapy, and was slightly higher in studies of saxagliptin as add-on therapy to other drug products (8 to 8.5%). In a study of initial combination therapy with metformin, mean baseline HbA1c was 9.4 to 9.6%. A low proportion of patients had a baseline history of coronary artery disease (3 to 13% of patients in phase 3 trials).

Liraglutide

The safety database for the original NDA submission included 38 clinical trials (phase 1/2/3) with the bulk of the data coming from 5 phase 3 trials. In the phase 3 trials, mean ages ranged from 52 to 57.7 years. Mean duration of diabetes ranged from 5.2 to 5.6 years in the study of liraglutide as monotherapy. In studies of liraglutide as add-on to other drug products, the mean duration of disease was longer (6.8 to 8.1 years in add-on to 1 oral anti-diabetic drug trials and 8.9 to 9.7 years in add-on to 2 oral antidiabetic drug trials). Mean baseline HbA1c ranged from 8.3 to 8.6%. Patients with significant cardiovascular disease were excluded from the trials.

Alogliptin

The safety database for the original NDA submission 8 phase 2/3 trials. In the phase 3 trials, mean ages ranged from 52.6 to 57.1 years. The majority of patients were < 65 years old (80-85%). Mean duration of diabetes ranged from 2.8 to 4.3 years in the study of alogliptin as monotherapy. In studies of alogliptin as add-on to 1 or more oral antidiabetic drugs, the mean duration of disease was longer (5.9 to 7.8 years). The mean duration of disease was longest in the study of alogliptin as add-on to insulin (12.1 to 13.4 years). Mean baseline HbA1c ranged from 7.9 to 8.1% in the monotherapy and add-on to oral antidiabetic drug studies. It was slightly higher in the add-on to insulin study (9.3%). Patients with myocardial infarction or coronary intervention in the preceding 6 to 12 months were excluded, as were patients with New York Heart Association Class III/IV heart failure.

Summary of Results from Completed Cardiovascular Outcomes Trials

Since the 2008 Guidance for Industry was issued, thirteen non-insulin drug products (not including fixed combination drug products) to improve glycemic control in patients with type 2 diabetes have been approved (see Appendix 3). A total of eight drug products have completed a cardiovascular outcomes trial to address the 2008 Guidance for Industry. Each of those trials is briefly described here along with findings from those trials. While each of the trials is described as being placebo-controlled, it is worth noting that the comparator arm was not a true placebo as additional glucose-lowering therapies were allowed.

SAVOR-TIMI

SAVOR-TIMI was an event-drive, randomized, prospective, double-blind, placebo-controlled trial comparing saxagliptin on top of standard of care vs. placebo on top of standard of care in patients with type 2 diabetes mellitus. Other anti-diabetic therapy was allowed (with the exception of dipeptidyl peptidase-4 [DPP-4] inhibitors or glucagon-like peptide-1 [GLP-1] receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 16,492 subjects were randomized 1:1 to saxagliptin or placebo. Study subjects either had a history of established cardiovascular disease or multiple risk factors for vascular disease (i.e., age $\geq$ 55 years for males or $\geq$ 60 years for females, and at least one of the following: dyslipidemia, hypertension, active smoking). The primary composite endpoint was time to first occurrence of a major adverse cardiovascular event (MACE) defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

In SAVOR-TIMI, the mean age was 65 years with approximately 14% of patients being greater than 75 years old. The mean duration of diabetes was 12 years with approximately 18% of patients having a diagnosis of diabetes > 20 years. Nearly 80% of patients had a history of established cardiovascular disease. Mean HbA1c at baseline was 8%. Median duration of follow-up was 2.1 years.

Findings for the primary composite endpoint showed no increased risk with saxagliptin for MACE (Table 3).

Table 3: Findings from SAVOR-TIMI for MACE

	Saxagliptin + SOC N=8280	*Placebo + SOC N=8212*	*HR (95.1% CI)*
3-Point MACE [n (%)]	613 (7.4)	609 (7.4)	1 (0.89, 1.12)
➢ Cardiovascular Death [n (%)]	245 (3)	234 (2.8)	
➢ Non-fatal MI [n (%)]	233 (2.8)	260 (3.2)	
➢ Non-fatal Stroke [n (%)]	135 (1.6)	115 (1.4)	

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from prescribing information for saxagliptin

In the trial, 289 (3.5%) of saxagliptin treated patients and 228 (2.8%) of placebo treated patients were hospitalized for heart failure. The risk of hospitalization for heart failure was higher in the saxagliptin treated group (estimated hazard ration 1.27; 95% confidence interval 1.07 to 1.51).

EXAMINE

EXAMINE was an event-driven, randomized, prospective, double-blind, placebo-controlled trial comparing alogliptin on top of standard of care vs. placebo on top of standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome. Other anti-diabetic therapy was allowed (with the exception of DPP-4 inhibitors or GLP-1 receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 5,380 subjects were randomized 1:1 to alogliptin or placebo. Study subjects had to have experienced an acute coronary syndrome event within 15 to 90 days prior to randomization. The primary composite endpoint was time to first occurrence of a major adverse cardiovascular event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

In EXAMINE, the mean age was around 61 years with approximately 35% of patients being greater than 65 years old. The mean duration of diabetes was 9.1 years. All patients had a recent acute coronary syndrome event. The majority of index events (greater than 80%) were

myocardial infarctions. Mean HbA1c at baseline was 7.6%. Median duration of follow-up was 1.5 years.

Findings for the primary composite endpoint showed no increased risk with alogliptin for MACE (Table 4).

Table 4: Findings from EXAMINE for MACE

	Alogliptin + SOC N=2701	*Placebo + SOC N=2679*	*HR (95% CI)*
3-Point MACE [n (%)]	305 (11.3)	316 (11.8)	0.96 (0.8, 1.16)
➢ Cardiovascular Death [n (%)]	89 (3.3)	111 (4.1)	
➢ Non-fatal MI [n (%)]	187 (6.9)	173 (6.5)	
➢ Non-fatal Stroke [n (%)]	29 (1.1)	32 (1.2)	

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from prescribing information for alogliptin

In the trial, 106 (3.9%) of the alogliptin treated patients and 89 (3.3%) of the placebo treated patients were hospitalized for heart failure, yielding an estimated hazard ratio for hospitalization for heart failure with alogliptin of 1.18.

EMPA-REG OUTCOME

EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled, parallel-group, event driven trial designed to compare the safety and efficacy of 10 mg empagliflozin once daily and 25 mg empagliflozin once daily versus placebo as add-on to standard of care treatment for diabetes and other cardiovascular risks in patients with T2DM. Other anti-diabetic therapy was allowed (with the exception of sodium glucose cotransporter-2 [SGLT-2] inhibitors) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 7020 patients were randomized 1:1:1 and treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo. The patient population was enriched for cardiovascular events by enrolling patients with high cardiovascular risk. High cardiovascular risk was defined as:

- Confirmed history of MI
- Evidence of multi-vessel CAD, irrespective of the revascularization status
- Evidence of single vessel CAD with:

  - Stenosis of at least 50% of one major coronary artery in patients not subsequently successfully revascularized, and
  - At least one of the following: positive non-invasive stress test, or a hospital discharge diagnosis of unstable angina within 12 months prior to selection
- Unstable angina with evidence of multi-vessel, or single vessel CAD
- History of ischemic or hemorrhagic stroke
- Presence of peripheral artery disease

The primary endpoint was time to occurrence of a major cardiovascular event (MACE) defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The two empagliflozin treatment arms were pooled for the analysis of cardiovascular events.

In EMPA-REG OUTCOME, the mean age was 63 years. More than half (~57%) of the patients had a diagnosis of diabetes for greater than 10 years. The population was enriched for high cardiovascular risk (i.e., essentially all subjects had history of cardiovascular disease), with approximately 75% of patients having coronary artery disease, and approximately 23% had a history of stroke. Mean HbA1c at baseline was 8%. Median duration of follow-up was 3.1 years.

Findings for the primary composite endpoint showed no increased risk with empagliflozin for MACE (Table 5). A statistically significant reduced risk of first occurrence of the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was seen. The treatment effect was driven by a reduction in the risk of cardiovascular death in subjects randomized to empagliflozin.

Table 5: Findings from EMPA-REG OUTCOME for MACE

	Empagliflozin + SOC N=4687	***Placebo + SOC N=2333***	***HR (95% CI)***
3-Point MACE [n (%)]	490 (10.5)	282 (12.1)	0.86 (0.74, 0.99)
➢ Cardiovascular Death [n (%)]	173 (3.7)	137 (5.9)	0.62 (0.49, 0.77)
➢ Non-fatal MI [n (%)]	213 (4.5)	121 (5.2)	0.87 (0.7, 1.09)
➢ Non-fatal Stroke [n (%)]	150 (3.2)	60 (2.6)	1.24 (0.92, 1.67)

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from prescribing information for empagliflozin

ELIXA

ELIXA was a randomized, double-blind, placebo-controlled study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide on top of standard of care in patients with type 2 diabetes mellitus after a recent acute coronary syndrome event. Other anti-diabetic therapy was allowed (with the exception of DPP-4 inhibitors or GLP-1 receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 6068 patients were randomized 1:1 to either placebo or lixisenatide and were included in the primary analyses. Study subjects had experienced an acute coronary syndrome event within 180 days prior to screening. The primary composite endpoint was time to first occurrence of a major adverse cardiovascular event defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (i.e., MACE+).

In ELIXA, the mean age was 60 years. The mean duration of diabetes was 9.3 years. The population was enriched for high cardiovascular risk by including patients with a recent acute coronary syndrome event. The majority of index events (greater than 80%) were myocardial infarctions. Mean HbA1c at baseline was 7.6%. Median duration of follow-up was 25 months.

Findings for the primary composite endpoint showed no increased risk with lixisenatide for MACE+ (Table 6Table 4).

Table 6: Findings from ELIXA for MACE

	Lixisenatide + SOC N=3034	***Placebo + SOC N=3034***	***HR (95% CI)***
MACE + [n (%)]	406 (13.4)	399 (13.2)	1.02 (0.89, 1.17)
➢ Cardiovascular Death [n (%)]	88 (2.9)	93 (3.1)	
➢ Non-fatal MI [n (%)]	255 (8.4)	247 (8.1)	
➢ Non-fatal Stroke [n (%)]	54 (1.8)	49 (1.6)	
➢ Hosp. for unstable angina [n (%)]	10 (0.3)	9 (0.3)	

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction; Hosp. = hospitalization
MACE + = composite endpoint consisting of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina
Source: Adapted from prescribing information for lixisenatide

LEADER

LEADER was a multi-center, double-blinded trial comparing the risk for major adverse cardiovascular events in patients treated with liraglutide or placebo on top of standard of care treatments for type 2 diabetes. Other anti-diabetic therapy was allowed (with the exception of DPP-4 inhibitors or GLP-1 receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 9,340 patients were randomized 1:1 to liraglutide or placebo in addition to standard of care therapy. Patients eligible to enter the trial were 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (80% of the enrolled population), or were 60 years of age or older and had other specified risk factors for cardiovascular disease (20% of the enrolled population). The primary composite endpoint consisted of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

In LEADER, the mean age was 64 years. The mean duration of diabetes was approximately 13 years. The majority of patients (81%) had established cardiovascular disease. Slightly more than half (53%) of patients had a history of ischemic heart disease, and approximately 30% of patients had a history of a myocardial infarction. Mean HbA1c at baseline was 8.7%. Median duration of follow-up was 3.5 years.

Findings for the primary composite endpoint showed no increased risk with liraglutide for MACE (Table 7). A statistically significant reduction in the time to first occurrence of MACE was seen.

Table 7: Findings from LEADER for MACE

	Liraglutide + SOC N=4668	***Placebo + SOC N=4672***	***HR (95% CI)***
3-Point MACE [n (%)]	608 (13)	694 (14.9)	0.87 (0.78, 0.97)
➢ Cardiovascular Death [n (%)]	219 (4.7)	278 (6)	0.78 (0.66, 0.93)
➢ Non-fatal MI [n (%)]	281 (6)	317 (6.8)	0.88 (0.75, 1.03)
➢ Non-fatal Stroke [n (%)]	159 (3.4)	177 (3.8)	0.89 (0.72, 1.11)

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from prescribing information for liraglutide

SUSTAIN-6

SUSTAIN-6 was a multi-center, double-blinded trial comparing the risk for major adverse cardiovascular events in patients treated with liraglutide or placebo on top of standard of care treatments for type 2 diabetes. This trial was conducted as a pre-marketing trial and was designed to exclude a hazard ratio of 1.8 from the upper bound of the 2-sided 95% confidence interval. Other anti-diabetic therapy was allowed (with the exception of DPP-4 inhibitors, or GLP-1 receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 3,297 patients were randomized 1:1 to semaglutide or placebo in addition to standard of care therapy. Patients eligible to enter the trial were either ≥ 50 years old with clinical evidence of cardiovascular disease [5], or ≥ 60 years old with subclinical evidence of cardiovascular disease [6]. The primary composite endpoint consisted of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The trial was designed to continue until at least 122 primary composite endpoint events occurred or the last randomized patient had been followed for 2 years (whichever occurred later).

In SUSTAIN-6, the mean age was 64.6 years. The mean duration of diabetes was approximately 14 years. The majority of patients (83%) had clinical evidence of cardiovascular disease. Approximately 60% of patients had a history of ischemic heart disease, and nearly 33% of patients had a history of a myocardial infarction. Mean HbA1c at baseline was 8.7%. Median duration of follow-up was 2.1 years.

Findings for the primary composite endpoint showed no increased risk with semaglutide for MACE (Table 8). A statistically significant reduction in the time to first occurrence of MACE was seen.

[5] Defined as at least one of the following: prior myocardial infarction, prior stroke or transient ischemic attack, prior coronary, carotid, or peripheral arterial revascularization, > 50% stenosis of coronary, carotid, or lower extremity arteries, history of symptomatic coronary heart disease, asymptomatic cardiac ischemia, New York Heart Association class II-III chronic heart failure, chronic renal impairment with eGFR < 60 mL/min/1.73 m^2

[6] Defined as at least one of the following: persistent microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction on imaging, ankle-brachial index < 0.9

Table 8: Findings from SUSTAIN-6 for MACE

	Semaglutide + SOC N=4668	*Placebo + SOC N=4672*	*HR (95% CI)*
3-Point MACE [n (%)]	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95)
➢ Cardiovascular Death [n (%)]	44 (2.7)	46 (2.8)	0.98 (0.65-1.48)
➢ Non-fatal MI [n (%)]	47 (2.9)	64 (3.9)	0.74 (0.51, 1.08)
➢ Non-fatal Stroke [n (%)]	27 (1.6)	44 (2.7)	0.61 (0.38, 0.99)

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from Table 1 of N Engl J Med 2016; 375:1834-44.

In the trial, 50 (3%) of semaglutide treated patients and 29 (1.8%) of placebo treated patients experienced an event of diabetic retinopathy (estimated hazard ratio 1.76, 95% confidence interval 1.11-2.78).

CANVAS and CANVAS-R

CANVAS and CANVAS-R were a pair of cardiovascular outcome trials conducted to evaluate the cardiovascular safety of canagliflozin [7]. Both trials were randomized, placebo-controlled trials comparing the patients treated with canagliflozin or placebo on top of standard of care. Other anti-diabetic therapy was allowed (with the exception of SGLT inhibitors) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 10,142 patients were enrolled in the CANVAS program. In CANVAS, patients were randomized 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or placebo. In CANVAS-R, patients were randomized 1:1 to canagliflozin (starting at 100 mg with option to increase to 300 mg) or to placebo. Patients eligible for participation were either ≥ 30 years old with a history of cardiovascular event, or ≥ 50 years old with a high risk for cardiovascular events. The primary composite endpoint for both trials consisted of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

In the CANVAS program, the mean age of patients was 63.3 years. The mean duration of diabetes was 13.5 years. Mean HbA1c was 8.2%. Approximately two-thirds of patients had a

[7] Neal B, et al. "Canagliflozin and cardiovascular and renal events in type 2 diabetes". N Engl J Med 2017; 377: 644-57.

history of cardiovascular disease. The median duration of follow-up was 126.1 weeks (mean follow-up of 295.9 weeks in CANVAS and 108 weeks in CANVAS-R).

The analysis of major adverse cardiovascular events from the CANVAS program was based on a pre-specified integrated analysis of the two trials (Table 9). No increased risk for major adverse cardiovascular events was seen with canagliflozin.

Table 9: Findings from CANVAS Program for MACE

	Canagliflozin + SOC N=5795	*Placebo + SOC N=4347*	*HR (95% CI)*
3-Point MACE [per 1000 patient-years]	26.9	31.5	0.86 (0.75, 0.97)
➢ Cardiovascular Death [per 1000 patient-years]	11.6	12.8	0.87 (0.72, 1.06)
➢ Non-fatal MI [per 1000 patient-years]	9.7	11.6	0.85 (0.71, 1.05)
➢ Non-fatal Stroke [per 1000 patient-years]	7.1	8.4	0.9 (0.71, 1.15)

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from Figure 3 of N Engl J Med 2017; 377:644-57.

In the CANVAS Program, an increased risk for toe, foot, and leg amputations was observed (Table 10).

Table 10: Findings for Amputations in the CANVAS Program

	Canagliflozin + SOC	*Placebo + SOC*	*HR (95% CI)*
CANVAS program [per 1000 patient-years]	6.3	3.4	1.97 (1.41, 2.75)
➢ CANVAS [per 1000 patient-years]	5.9	2.8	
➢ CANVAS-R [per 1000 patient-years]	7.5	4.2	

SOC = standard of care; HR = hazard ratio; CI = confidence interval
Source: Adapted from N Engl J Med 2017; 377:644-57 and the May 16, 2017 FDA Drug Safety Communication (https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm)

EXSCEL

The EXSCEL trial [8] was a randomized, double-blind, placebo-controlled, event-driven trial comparing the risk of major adverse cardiovascular events in patients treated with exenatide

[8] Holman RR, et al. "Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes". N Engl J Med 2017; 377: 1228-1239.

extended-release or placebo on top of standard of care treatment for type 2 diabetes mellitus. Other anti-diabetic therapy was allowed (with the exception of DPP-4 inhibitors or GLP-1 receptor agonists) and could be adjusted at the investigator's discretion based on local treatment guidelines. Management of other CV risk factors (e.g., blood pressure, lipids) was also based on local treatment guidelines.

A total of 14,752 patients were randomized 1:1 to exenatide extended-release or placebo in addition to standard of care therapy. Patients eligible to enter the trial were adults with type 2 diabetes mellitus and an HbA1c between 6.5 to 10%. The trial was designed such that approximately 70% of the population had a prior cardiovascular event (defined as a history of a major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease). The remaining 30% were not to have had previous cardiovascular events. Patients with recurrent severe hypoglycemia, end-stage renal disease or estimated glomerular filtration rate < 30 mL/min/1.73 m^2 were excluded. The primary composite endpoint consisted for death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (i.e., MACE).

In EXSCEL, the mean age was 62 years. The median duration of diabetes was 12 years. Approximately 73% of patient had a prior cardiovascular event. The median HbA1c was 8%. Median duration of follow-up was 3.2 years.

Findings for the primary composite endpoint showed no increased risk with exenatide extended-release MACE (Table 11).

Table 11: Findings from EXSCEL for MACE

	Exenatide extended-release + SOC N=7356	***Placebo + SOC N=7396***	***HR (95% CI)***
3-Point MACE [n (%)]	839 (11.4)	905 2.2)	0.91 (0.83, 1)
Exploratory Secondary Outcomes			
➢ Cardiovascular Death [n (%)]	340 (4.6)	383 (5.2)	0.88 (0.76, 1.02)
➢ MI (fatal or nonfatal) [n (%)]	483 (6.6)	493 (6.7)	0.97 (0.85, 1.1)
➢ Stroke (fatal or nonfatal) [n (%)]	187 (2.5)	218 (2.9)	0.85 (0.7, 1.03)

N = number of patients; HR = hazard ratio; CI = confidence interval; SOC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction; Hosp. = hospitalization
3-Point MACE = composite endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke
Source: Adapted from Table 1 of N Engl J Med 2017; 377: 1228-1239.

Discussion of Cardiovascular Risk Assessments

The approach to evaluating cardiovascular risk has changed substantially over the last ten years.

Prior to the 2008 guidance, the cardiovascular risk assessment was conducted based on small numbers of investigator-reported adverse event that were observed in relatively short clinical trials that enrolled patients at relatively low risk for cardiovascular events. The guidance changed all of that.

Since the 2008 guidance, events have been evaluated with much more rigor. Potential events are identified and data around the event are collected before being reviewed and adjudicated. This has yielded more specificity in the events considered in the assessment of cardiovascular risk.

The amount of data (i.e., number of events) to consider has also changed. Before the guidance, there were generally a limited number of events to consider, and smaller, shorter trials. The populations were also generally of relatively low cardiovascular risk. The saxagliptin, liraglutide, and alogliptin programs serve as examples of how different the data were prior to the guidance compared to what was available to consider after the guidance.

Based on the narrower, custom query developed for review of these three products in 2008, there were a total of 40, 38, and 18 cardiovascular events in the saxagliptin, liraglutide, and alogliptin programs, respectively. Compare that to the number of events accrued in the cardiovascular outcome trials for these three drug products (1,222 in SAVOR-TIMI, 1,302 in LEADER, and 621 in EXAMINE). The greater number of events allowed for greater certainty when considering the relative risk associated with each drug.

The patient populations were also generally at lower cardiovascular risk. The proportion of patients with known cardiovascular disease was relatively small, and patients with recent or advanced cardiovascular disease were excluded. Patients also tended to have a relatively short duration of diabetes. In the CVOTs for these three products, nearly all patients had known cardiovascular disease and, on average, had been diagnosed with diabetes for a longer period of time.

Overall, the assessment of cardiovascular risk as recommended by the guidance has led to greater specificity, more data for consideration, and additional data in a population of patients that was not well represented previously.

Discussion of Findings from Completed Clinical Trials

The 2008 CV Guidance has provided cardiovascular safety data for eight anti-diabetic drugs from three different therapeutic classes. None of the trials discussed here demonstrated an increased risk for MACE (as defined by each trial). Of interest, a reduced risk for MACE was observed in some of the trials.

In considering the trials where a reduced risk for MACE was seen it is worth noting that findings from the GLP-1 receptor agonists show some heterogeneity in terms of the conclusions. Findings from LEADER supported a conclusion of reduced risk whereas the ELIXA trial and EXSCEL trial supported a conclusion of no increased risk. Data from the completed trials with SGLT-2 inhibitors point towards similar overall conclusions, but within the composite endpoint different trends were seen. The component in EMPA-REG OUTCOMES that served as the primary driver for a reduced risk was CV death. The other two components either did not demonstrate a marked reduction (i.e., nonfatal MI) or hinted at an increased risk (i.e., nonfatal stroke). In contrast, the reported findings from the CANVAS program showed a relative consistency across the individual components and the primary composite.

It is not clear whether these observed differences are due to inherent differences between the drug products, chance, or differences in the approach to evaluating cardiovascular risk. While on the surface these trials appear the same (i.e., double-blind, placebo-controlled on top of standard of care in patients at risk for cardiovascular events), in looking more closely there are differences.

Patients included in these trials were at risk for cardiovascular events, but how this population was defined differed between the trials. Some trials included patients at very high risk for cardiovascular events (e.g., EXAMINE and ELIXA included patients with recent acute coronary syndrome event) while others included sub-populations with lower degrees of risk (e.g., LEADER and EXSCEL specified subpopulations without a history of cardiovascular events). Subsequently, event accrual was different in the different trials and some trials had shorter durations of exposure and follow-up.

Differences in the duration of the trial could have affected the results of the trial. As an example, compare ELIXA with LEADER. There was an additional 1.5 years of exposure and follow-up in LEADER, as well as more events (1,302 in LEADER, 805 in ELIXA). Whether continued study

of the patients in ELIXA and accrual of additional events would have changed the conclusions for lixisenatide is unknown.

The question of whether differences between the studies could have affected results is also relevant for some of the safety findings from the trials.

A nominally statistically significant increased risk for hospitalization for heart failure was observed in SAVOR-TIMI. In EXAMINE, the other study with a DPP4 inhibitor, the observed relative risk for hospitalization was of a similar magnitude to that seen in SAVOR-TIMI but it was not statistically significant. EXAMINE was a shorter trial, and it is unknown whether longer follow-up and accrual of additional heart failure events would have led to similar findings for alogliptin.

Similarly, an of increased risk for amputations was seen in the CANVAS program. No such finding was seen in EMPA-REG OUTCOMES [9]. While acknowledging that there were differences in the approach to capturing events, there was a greater duration of exposure and follow-up in the CANVAS program. Whether this contributed to differences in the findings for these two trials is unknown.

Overall, the completed trials have provided reassurance that the studied drugs are not associated with an increased risk for adverse cardiovascular events. The differences in how each study was designed resulted in differences between studies in terms of duration and number of events, but these differences did not impact conclusions with respect to an absence of cardiovascular risk. Where these differences raise interesting questions is in the consideration of some of the other findings (e.g., reduced risk for cardiovascular events, differences in safety findings). Whether these findings are due to product specific differences or due to differences in the approach to study of the drug product is unknown.

[9] Inzucchi SE, Iliev H, Pfarr E, and Zinman B. "Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial". Diabetes Care 2018; 41:e4-e5.

Appendix 1: Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Food & Drug Administration
10903 New Hampshire Avenue
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Contains Nonbinding Recommendations

Guidance for Industry[1]
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.[2] Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

In March 2008, the FDA issued the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.[3] Concerns related to cardiovascular risk will be addressed in the final version of that guidance. In the meantime, we are issuing this final guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs. We will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For discussion of general issues of clinical trial design or statistical analysis, see the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www fda.gov/cder/guidance/index htm.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although several drug treatments currently are available, we recognize the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs and therapeutic biologics).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure). Both type 1 and type 2 diabetes have a heritable basis. Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.[4] Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.[5]

There are also compelling data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control. Glycemic control in these studies has been based on changes in HbA1c. This endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. Therefore, reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus. However, diabetes mellitus is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population.
Although this excess cardiovascular risk is present in both type 1 and type 2 diabetes, the

[4] See N Engl J Med, 1993, 329:977-986.

[5] See Diabetes, 2006, 55:3556-3565.

absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. For type 2 diabetes, the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings. After considering the discussion at this meeting as well as other available data and information,[6] we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

[6] See Lancet, 1998, 352:837-853 and 854-865.

controlled trials, and to preserve the study level randomized comparison but include, when possible in the meta-analysis, important identifiers of study differences or other factors (e.g., dose, duration of exposure, add-on drugs). It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.

- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.[7]

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary.

[7] See the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901. This section will become section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A).

- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings.

Sponsors are encouraged to contact the division to discuss specific issues that arise during the development of a new antidiabetic therapy to treat type 2 diabetes.

Appendix 2: MedDRA Terms from Broad SMQ and Custom Query

	Broad SMQ	Custom Query
Myocardial Infarction Terms		
Acute coronary syndrome	X	
Acute myocardial infarction	X	X
Agonal rhythm		
Blood creatine phosphokinase abnormal	X	
Blood creatine phosphokinase increased	X	
Blood creatine phosphokinase MB abnormal	X	
Blood creatine phosphokinase MB increased	X	
Cardiac arrest		
Cardiac death		
Cardiac enzymes increased	X	
Cardio-respiratory arrest		
Coronary artery embolism	X	
Coronary artery occlusion	X	
Coronary artery reocclusion	X	
Coronary artery thrombosis	X	X
Coronary bypass thrombosis	X	
Electrocardiogram Q wave abnormal	X	
Electrocardiogram ST segment abnormal	X	
Electrocardiogram ST segment elevation	X	
Electrocardiogram ST-T segment elevation	X	
Electromechanical dissociation		
Infarction	X	
Myocardial infarction	X	X
Myocardial reperfusion injury	X	
Papillary muscle infarction	X	X
Postinfarction angina	X	
Postprocedural myocardial infarction	X	X
Scan myocardial perfusion abnormal	X	
Silent myocardial infarction	X	X
Sudden cardiac death		
Sudden death		
Troponin I increased	X	
Troponin increased	X	

	Broad SMQ	Custom Query
Troponin T increased	X	
Vascular graft occlusion	X	
Ventricular asystole		
Stroke Terms		
Agnosia	X	
Amaurosis fugax	X	
Angiogram cerebral abnormal	X	
Aphasia	X	
Balint's syndrome	X	
Basal ganglia hemorrhage	X	
Basilar artery occlusion	X	
Basilar artery stenosis	X	
Basilar artery thrombosis	X	X
Brain stem hemorrhage	X	
Brain stem infarction	X	X
Brain stem ischemia	X	
Brain stem stroke	X	X
Brain stem thrombosis	X	X
Capsular warning syndrome	X	
Carotid aneurysm rupture	X	
Carotid arterial embolus	X	X
Carotid arteriosclerosis	X	
Carotid artery aneurysm	X	
Carotid artery bypass	X	
Carotid artery disease	X	
Carotid artery dissection	X	
Carotid artery insufficiency	X	
Carotid artery occlusion	X	
Carotid artery stenosis	X	
Carotid artery stent insertion	X	
Carotid artery thrombosis	X	X
Carotid endarterectomy	X	
Central pain syndrome	X	
Cerebellar artery occlusion	X	
Cerebellar artery thrombosis	X	
Cerebellar embolism	X	
Cerebellar hemorrhage	X	
Cerebellar hematoma	X	
Cerebellar infarction	X	X

	Broad SMQ	Custom Query
Cerebellar ischemia	X	
Cerebral aneurysm ruptured syphilitic	X	
Cerebral arteriosclerosis	X	
Cerebral arteriovenous malformation hemorrhagic	X	
Cerebral artery embolism	X	X
Cerebral artery occlusion	X	
Cerebral artery stenosis	X	
Cerebral artery thrombosis	X	X
Cerebral hematoma	X	
Cerebral hemorrhage	X	
Cerebral hemorrhage fetal	X	
Cerebral hemorrhage neonatal	X	
Cerebral infarction	X	X
Cerebral infarction fetal	X	
Cerebral ischemia	X	
Cerebral thrombosis	X	X
Cerebral vasoconstriction	X	
Cerebral venous thrombosis	X	
Cerebrovascular accident	X	X
Cerebrovascular accident prophylaxis	X	
Cerebrovascular disorder	X	
Cerebrovascular insufficiency	X	
Cerebrovascular spasm	X	
Cerebrovascular stenosis	X	
Charcot-Bouchard microaneurysms	X	
Diplegia	X	
Dysarthria	X	
Embolic cerebral infarction	X	X
Embolic stroke	X	X
Hematomyelia	X	
Hemiparesis	X	
Hemiplegia	X	
Hemorrhage intracranial	X	
Hemorrhagic cerebral infarction	X	X
Hemorrhagic stroke	X	X
Hemorrhagic transformation stroke	X	X
Intracerebral aneurysm operation	X	
Intracerebral hematoma evacuation	X	

	Broad SMQ	Custom Query
Intracranial aneurysm	X	
Intracranial hematoma	X	
Intraventricular hemorrhage	X	
Intraventricular hemorrhage neonatal	X	
Ischemic cerebral infarction	X	X
Ischemic stroke	X	X
Lacunar infarction	X	X
Lateral medullary syndrome	X	X
Meningorrhagia	X	
Millard-Gubler syndrome	X	
Monoparesis	X	
Monoplegia	X	
Moyamoya disease	X	X
Paralysis	X	
Paralysis flaccid	X	
Paraparesis	X	
Paraplegia	X	
Paresis	X	
Postprocedural stroke	X	X
Precerebral artery occlusion	X	
Putamen hemorrhage	X	
Quadriparesis	X	
Quadriplegia	X	
Red blood cells CSF positive	X	
Reversible ischemic neurologic deficit	X	
Ruptured cerebral aneurysm	X	
Spastic paralysis	X	

Source: Adapted from Table 9 of the Joint Clinical and Statistical Review of Major Adverse Cardiovascular Events from the FDA Briefing Materials for the April 1, 2009 Endocrinologic and Metabolic Drugs Advisory Committee meeting

Appendix 3: Drugs Currently Approved to Improve Glycemic Control

Drug Class	Approved Products
Insulin products	Insulin human Insulin human isophane suspension Insulin lispro Insulin aspart Insulin glulisine Insulin glargine Insulin detemir Insulin degludec[++] Insulin human inhalation powder[++]
Sulfonylureas	Tolbutamide Acetohexamide Chlorpropamide Glipizide Glyburide Glimepiride
Biguanides	Metformin
Alpha-glucosidase inhibitors	Acarbose Miglitol
Thiazolidinediones	Rosiglitazone Pioglitazone
Meglitinides	Repaglinide Nateglinide
Amylin mimetics	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine receptor agonists	Bromocriptine
Dipeptidyl peptidase-4 inhibitors	Sitagliptin Saxagliptin[++] Alogliptin[++] Linagliptin[++]
Glucagon-like peptide-1 receptor agonists	Exenatide Liraglutide[++] Exenatide extended-release[++] Albiglutide[++] Dulaglutide[++] Lixisenatide[++] Semaglutide[++]
Sodium glucose cotransporter inhibitors	Canagliflozin[++] Dapagliflozin[++] Empagliflozin[++] Ertugliflozin[++]
[++] indicates a drug product approved after publication of 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes	

Appendix 4: Links to FDA Background Documents from Prior Advisory Committee Meetings Where CVOT Results Were Discussed

Trial:	Hyperlink:
SAVOR-TIMI	https://wayback.archive-it.org/7993/20170404151612/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM442060.pdf
EXAMINE	https://wayback.archive-it.org/7993/20170404151612/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM442062.pdf
EMPA-REG OUTCOME	https://wayback.archive-it.org/7993/20170404151458/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM508422.pdf
ELIXA	https://wayback.archive-it.org/7993/20170404151509/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM502558.pdf
LEADER	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM563334.pdf
SUSTAIN-6	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM580460.pdf