



U.S. Food and Drug Administration

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Clinical Perspectives on FDA Guidance for Industry: Diabetes Mellitus – Evaluating CV Risk in New Anti- diabetic Therapies to Treat T2DM

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Outline of Presentation

- **Overview of T2DM**
 - **Why is CV risk assessment important**
- **Prior FDA regulatory requirements for approval of anti-diabetic therapies**
- **Recent Guidance for Industry**
 - **How is it different from prior requirements**
- **Implementing the Guidance**
- **Future developments**

Overview of T2DM

- **Affects > 24 million in the U.S.**
- **Leading cause of kidney failure, blindness, non-traumatic amputations**
- **2 to 4-fold increase in CV death**
- **Chronic disease with need for multiple drug therapy over time**
- **Multiple co-morbid conditions (obesity, renal disease, HTN, heart disease)**
- **Rising prevalence includes a wide spectrum of age**

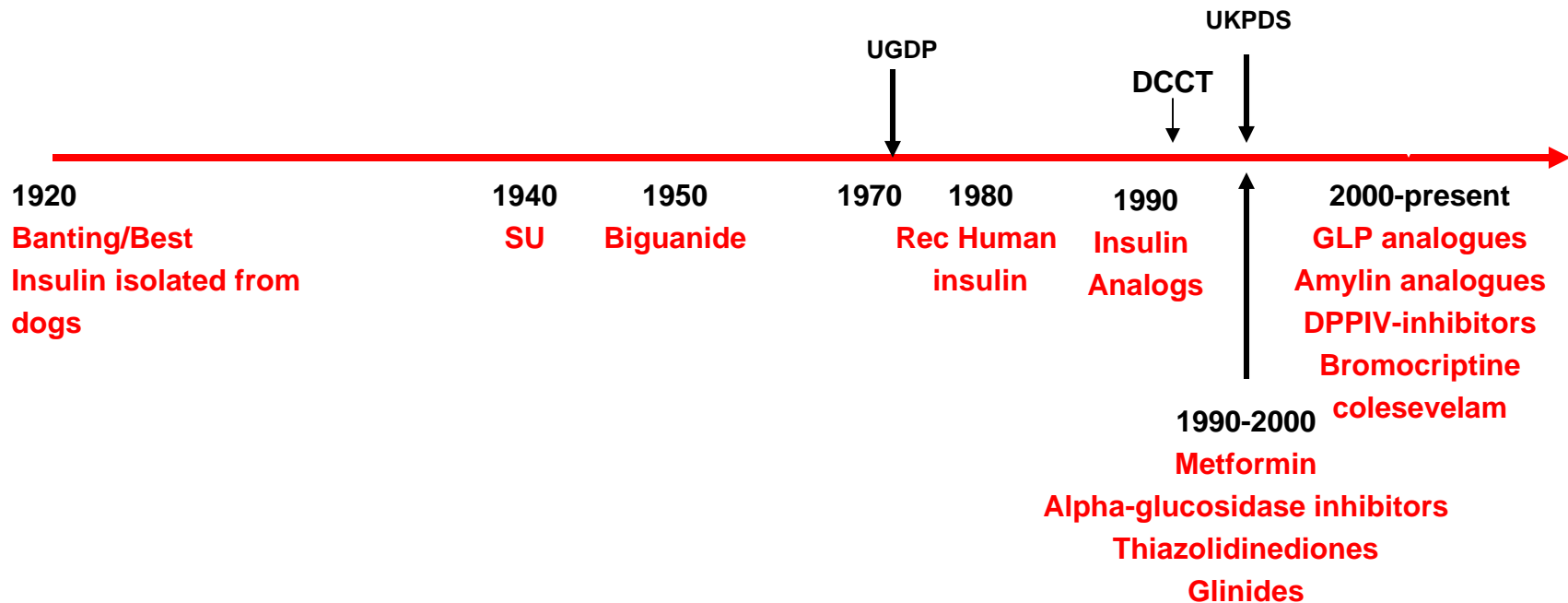
Trials Prior to December 2008 Guidance

- **HbA1c, as a measure of glycemic control, is the efficacy endpoint for approval of anti-diabetic therapies**
- **Trials supporting marketing application:**
 - 6-month PC or AC with open-label extension
 - Monotherapy and combination therapy
- **Patient population:**
 - CVD often an exclusion criterion
 - Few patients with renal disease enrolled
 - Treatment-naïve or short duration of diabetes
 - Discontinuations for glycemic rescue medications

Trials Prior to December 2008 Guidance

- **Cardiovascular risk assessment collected through adverse experiences reported by investigators**
 - **No central, blinded adjudication process**
 - **No planned analyses**
 - **These represent the types of studies included in recent retrospective meta-analyses to make conclusions on CV safety of certain drugs**
- **Safety database had patient exposures of 3000-5000 patients, mostly uncontrolled long-term data**

Timeline of Anti-diabetic Approvals



Prior to Diabetes Guidance

- **Regulatory path for approval enabled the availability of 11 classes of anti-diabetic therapies – 9 since 1990; 5 within past 5 years**
- **Multiple drugs available enabled the conduct of several long-term landmark diabetes trials (e.g., ACCORD, VADT, BARI-2D)**
- **No single anti-DM agent or multi-drug regimen has provided conclusive evidence of macrovascular risk reduction**
- **Absence of macrovascular risk reduction with these therapies challenges approval requirements when CV safety of a few agents capture media attention**

Trials Prior to December 2008 Guidance

	Total Number Exposed to Drug	Patient-year Exposure to Drug	Death/MI/Stroke
Drug A	4327	1908	22 / 16 NF / ?
Drug B	3226	2648	19 / 8 / 3
Drug C	3586	1854	9/ 2 ACS / 2
Drug D	3276	1339	7 / 1 / 4

MI = myocardial infarction

NF = non-fatal

ACS = acute coronary syndrome

July 2008 Advisory Committee Meeting

- Discussed pre- and post-approval cardiovascular assessment for therapies for type 2 diabetes
- Presentations by experts in endocrinology and cardiology
- Panel included endocrinologists, diabetologists, cardiologists, statisticians, drug safety experts

Transcript at www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic

July 2008 Advisory Committee Meeting

- **Panel members affirm importance of glycemic control and microvascular risk reduction**
 - HbA1c remains primary efficacy endpoint for drug approval
- **Diabetes is a metabolic disorder with multiple co-morbidities increasing overall risk of CVD. Glycemic control alone will be difficult to demonstrate CV risk reduction as observed in numerous outcomes trials.**
 - CV benefit not a requirement for approval of these drugs

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

Diabetes Cardiovascular Guidance: Specific Recommendations

- **For new clinical studies in the planning stage:**
 - Establish an independent CV endpoints committee for prospective adjudication of all Phase 2 and 3 trials
 - Events of interest should include CV death, MI, and stroke
 - Can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints
 - Patient population should include those at higher risk for a CV event (longer duration of DM, elderly, renal impairment)
 - Studies are designed and conducted such that a MA can be performed
 - Protocol describing statistical methods for the proposed MA should be submitted

Diabetes Cardiovascular Guidance: Specific Recommendations

- **For completed studies, before submission of the NDA/BLA:**
 - Compare incidence of CV events with investigational agent to incidence in control group obtained through
 - A meta-analysis of phase 2 and 3 trials
 - A single, large safety trial

Diabetes Cardiovascular Guidance: Specific Recommendations

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
CI=confidence interval *with a reassuring point estimate	

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 lowering HbA1c reduces long-term microvascular complications**

From Joy Mele, FDA Biostatistician

Annual Event Rate (Drug)	Annual Event Rate (Comparator)	Total Sample Size to Rule Out Increased Risk of 1.2, 1.3, 1.8		
		1.2	1.3	1.8
2%	2%	16,500	8,000	1,600
2%	1.75%	>100,000	34,000	2,800
3%	3%	11,200	5,400	1,100
3%	2.8%	29,300	10,100	1,400
4%	4%	8,600	4,100	800
4%	3.6%	49,000	12,000	1,300
5%	5%	7,000	3,400	700
5%	4.5%	40,000	9,800	1,000

$\alpha=0.05$; 90% power; 5-year trial; 2-year recruitment

Implementing the Guidance

- **Greatest concern raised was that new requirement would delay approval of effective therapies**
 - Saxagliptin approved 7/09 and Liraglutide approve 1/10
 - Exceptions because NDAs already filed and pending before FDA when Guidance was issued
 - Both approved but have PMR to conduct dedicated CV safety trial to establish upper bound of 95%CI < 1.3
- **Programs with completed Phase 2/3 programs**
 - Proposing a meta-analysis but not a prospectively planned program
- **Programs still in the planning stage**
 - Designing Phase 2/3 program to address CV risk assessment
 - Prospective meta-analysis planned
- **Appears that all have planned or will have to conduct a dedicated CV safety trial to meet Guidance recommendations as PMR under FDAAA**

Implementing the Guidance

- **Some proposals have included:**
 - A superiority trial to show cardiovascular benefit
 - A dedicated trial in patients with recent acute coronary syndrome to show cardiovascular safety
 - A standard phase 2/3 program plus a dedicated cardiovascular safety trial
 - Substudies for glycemic efficacy within a dedicated cardiovascular safety trial
- **Some rejected proposals:**
 - Performing multiple looks to see if 1.8 has been met without controlling type 1 error
 - Choosing a primary MACE endpoint that is too broad
 - < 1 yr duration of exposure in high-risk patients only

Challenges in Trial Design

- **Choice of comparator (active control, add-on to pbo control)**
- **Worsening glycemic control in long-term CV safety trial**
- **Controlling other CV risk factors**
- **Choice of CV endpoint**
 - **Primary endpoint – MACE or MACE plus hospitalization for unstable angina**
- **Individual contribution of a component to the overall composite endpoint**
- **Maintaining trial integrity with interim analyses**

What to expect in the near future?

- **Guidance has only been out for a little over a year. Too soon to:**
 - be modified without information from programs developed under these new recommendations
 - debate whether the 10th agent in a class should be held to the same standard as the first 2 with no evidence of CV harm
- **Expect larger and longer duration of patient exposure that will inform us beyond CV safety**
 - Other rare adverse events (e.g., pancreatitis, liver safety, hypersensitivity reactions, cancer)
 - Data in more vulnerable patient population
- **Guidances are not Regulations. Adapt as we learn, but learn we must.**



Thank you