The Critical Path & Cardiac Safety 2009

An Industry Perspective

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- The views and opinions expressed here are my own
- They do not reflect the positions, policies or activities of my employer, the organizers of this meeting, or any of the organizations contributing to CSRC

Critical Path Initiative and CV Safety

Goals of CPI*

- Close the gap between discoveries to better treat e.g., diabetes, cancer and Alzheimer's, and translation into innovative medical treatments
- To bring new products to patients in a “more timely and affordable” way
- How? By modernizing the “sciences and tools through which FDA-regulated products are developed, evaluated, manufactured, and used”
- For drug products in particular, to better assess safety and efficacy through “smaller but smarter” clinical trials

Have we made progress?

- Oral antidiabetic drugs: case in point
  - Lots of research activity in response to unmet medical need
  - PPAR’s held promise but safety issues changed the landscape
  - Current regulatory environment emphasizes evaluation of safety risks

*From FDA CPI website: 2008 CPI Annual Report and FAQ’s

Antidiabetic Drug Therapy and CV Safety

Goals of treatment

- Normalization or near normalization of glucose levels with the intent of forestalling diabetic complications
  - Microvascular outcomes (retinopathy, nephropathy, neuropathy)
  - Macrovascular outcomes (CV death, MI, stroke, etc.) – leading cause of morbidity and mortality in the diabetic patient population

Regulatory standards revised 2008 because of increasing safety concerns

- HbA1c remains the primary efficacy endpoint for approval of drugs to treat hyperglycemia secondary to diabetes mellitus
- Wide range of antidiabetic therapies provides opportunity to evaluate effects on CV risk, enabling more informed treatment decisions
- Guidance recommended that concerns about cardiovascular risk should be more thoroughly addressed during drug development

Adapted from FDA Guidance document, “Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”, Dec 2008

“Traditional” Oral Antidiabetic Drug Development

- Small to moderately-sized studies to demonstrate glycemic efficacy
  - Size typically dictated by power calculation on efficacy endpoint
  - Multiple trials to address different indications (monoRx, add-on, etc.)
  - Combined safety database considered adequate to document pre-registration safety profile
- Most patients with early disease (treatment-naïve, failed monotherapy)
  - Patients on Insulin Therapy or 2 OAD’s not typically part of NDA registration
  - Few elderly patients
- Patients at high cardiovascular risk such as recent CV event often excluded
  - Low annual CV event rate (< 1% for MACE)
- CV risk factors (BP, Lipids) were studied but establishing CV safety was not a predefined objective
- Overall program size more recently driven mainly by safety exposure requirements – Feb 2008 FDA draft Guidance
  - ≥2,500 subjects exposed to investigational agent
  - ≥ 1,300 to 1,500 exposed for at least 1 year
  - ≥ 300 to 500 exposed for at least 18 months

FDA Guidance on New Antidiabetic Drug Development Dec 2008

- Independent committee should prospectively and blindly adjudicate MACE
- Phase 2/3 design should permit and prespecify meta-analysis of MACE
- Trials should include patients at increased risk for CV events
- Trial duration(s) should be >6 months to obtain enough events and provide long-term data
  - UL(95%CI) <1.8 criterion should be assessed on ≥1,300-1,500 patients with ≥1 year exposure (FDA presentation, DMEP and PhRMA meeting June 3, 2009)

How does this translate into drug development reality?

- Complying with CV guidance requirements = “Chasing” CV events
- Biggest hurdle in meeting the guidance: observing enough CV events provides a reliable Relative Risk estimate with an Upper Limit (95% CI) <1.8
- Development programs will shift their focus from general safety and efficacy to targeting an adequate number of events to meet the filing requirement

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

α=0.05; 90% power; **5-year trial**; 2-year recruitment

(From Joy Mele, FDA Biostatistician, DMEP and PhRMA meeting, June 3, 2009)

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FDA Guidance – Likely Impact on Drug Development

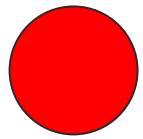
- Likely impact on Phase 2 development
  - More robust and comprehensive
  - Greater scrutiny of possible effects on CV risk factors
  - Dose exploration to be completed in Phase 2
  - Special populations (renal failure, insulin) studied earlier

- Expected changes in Phase 3 development
  - All CV events will be adjudicated across Phase 2/3
  - Expect greater harmonization of trial designs/procedures across phase 2/3 (to aid planned meta-analysis)
  - Blinded extensions to gain longer term safety data will be common
  - High CV risk patients will be included

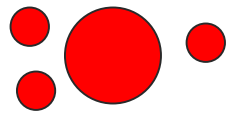
How do we best comply with CV Guidance requirements while simultaneously trying to deliver appropriate indications/claims?

Ways to meet FDA CV Guidance in Phase 3

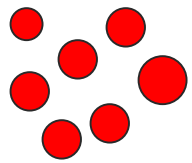
- A single large (event driven) CV Outcome study



- Indication seeking efficacy trials plus a dedicated CV event study



- Indication seeking efficacy trials incorporating high risk patients



FDA Guidance – Likely Impact on Phase 3 Development

- Additional considerations
  - Monitoring CV events: Competing interests of safety surveillance vs. integrity of the ongoing program (related to maintaining the blind)
  - Statistical Issues: “Spending alpha” for interim look(s) of CV events in trials with different stop/start times
  - Should the exact same CV event categories be used irrespective of the drug’s MOA?
  - What is an “adequate” # of events even when the 1.8 criterion is met?

- Likely Impact on Phase 3 Development
  - Longer duration programs *(not faster!)*
  - Bigger programs *(not smaller!)*
  - More expensive programs *(not cheaper!)*

All of the above with a relatively greater uncertainty towards successful registration within a reasonable timeframe

Consequences of FDA guidance on T2DM Drug Development

- Intended Consequences
  - New requirements will provide more (meaningful) data to estimate CV risk associated with new antidiabetic agents
  - Phase 2/3 larger, more comprehensive, will include high-risk patients
  - Expect to see creative study designs to meet the guidance
- Unintended Consequences
  - Will the time, money and resources spent to address a “theoretical CV risk” for a new drug take away from the work-up of other drug specific risks/issues?
  - Will the CV risk hurdle keep rising?
    - Approved drugs with favorable CV risk point estimate may challenge new drugs in development to aim for lower point estimates
  - Potential time, cost and risk implications will limit incentives for companies to develop new antidiabetic therapies
  - Fewer companies may be able to develop diabetes drugs
  - Fewer diabetes drugs may be developed

Is this consistent with the goals of the CPI?