

# **Integrating Cardiac & Vascular Safety: Expanding our Assessment Horizons for Prospectively Excluding Unacceptable Risks**



**Dedicated to your information and advancement.**

**J. Rick Turner, PhD, MICR CSci, MTOPRA  
Senior Director, Cardiovascular Safety  
Quintiles ECG Services**

**Quintiles Transnational Corporation**

**&**

**Visiting Fellow, Center for Medicine in the Public Interest**

## Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.

## Integrating Cardiac & Vascular Safety: Starting Points

- The 2005 ICH Guideline E14 [1] provided a useful example by discussing the exclusion of unacceptable QT/QTc interval prolongation (as a surrogate for unacceptable risk of *Torsades de Pointes*).
- This approach has three central components:
  - Clinical science: clinical judgments concerning absolute and relative risks;
  - Regulatory science: thresholds of regulatory interest;
  - Statistical science: accepted methodology for data analysis involving these thresholds, inferential statistical analysis, and confidence intervals.
- See also the paper by Brass et al, 2006:
  - Risk assessment in drug development for symptomatic indications: A framework for the prospective exclusion of unacceptable cardiovascular risk. [2]

## Expanding our Assessment Horizons for Prospectively Excluding Unacceptable Risks

- Attention is now expanding to a much broader array of cardiac and vascular risk factors. Borer et al, 2007 [3] included discussion of the following parameters:
  - Body weight;
  - Blood pressure;
  - Blood lipid concentrations;
  - Coagulation profiles;
  - Cardiac dimensions;
  - Left ventricular size and function;
  - Interaction between drug effects and specific genomic or proteomic characteristics (to the extent feasible);
  - Other ECG parameters (in addition to QT interval).

## Expanding our Assessment Horizons for Prospectively Excluding Unacceptable Risks

- The December 2008 FDA Guidance for Industry on evaluating CV risk for new drugs for T2DM [4] included:
  - Cardiovascular mortality;
  - Myocardial infarction (non-fatal)
  - Stroke (non-fatal)
  - Hospitalization for acute coronary syndrome;
  - Urgent revascularization procedures;
  - And “possibly other endpoints.”
- This guidance also adopts the methodology of inferential statistical testing incorporating thresholds of regulatory interest and confidence intervals for the exclusion of unacceptable risk (point estimates are also explicitly addressed).

## December 2008 FDA Guidance: Endpoints

- The traditional Major Adverse Cardiovascular Events (MACE) composite endpoint is acceptable to the FDA. This includes:
  - Non-fatal myocardial infarction;
  - Non-fatal stroke;
  - Cardiovascular death.
- An expanded MACE endpoint (secondary endpoints) might include:
  - Hospitalization for unstable angina;
  - Urgent percutaneous coronary intervention/coronary artery bypass graft surgery;
  - Carotid revascularization;
  - Lower extremity amputations/revascularization.
- Endpoints must be **adjudicated**.

## December 2008 FDA Guidance: The Meta-analysis

- Once (planned) Phase II and III trials are completed, a meta-analysis is to be conducted.
- Since the cardiac and vascular safety of the test drug is judged against that of a comparator, a risk ratio is of interest.
- A random-effects model should be used (there is likely to be heterogeneity between the studies even when care is taken *a priori* to design them as similarly as possible).
- The upper limit of a two-sided 95% confidence interval placed around the risk ratio point estimate given by the meta-analysis is of interest.

## December 2008 FDA Guidance: The Meta-analysis

- Three scenarios concerning the upper limit of the CI are discussed:

If this upper bound is equal to or greater than 1.8, the drug would be deemed to have an unacceptable risk. In this case, “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.

## December 2008 FDA Guidance: The Meta-analysis

If the upper bound is equal to or greater than 1.3 and also less than 1.8, and the overall risk-benefit analysis presented at submission supports marketing 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.”

If the upper bound is less than 1.3 and the overall risk-benefit analysis presented at submission supports marketing approval, “a postmarketing cardiovascular trial generally may not be necessary.”

- See Caveney and Turner [5] for further discussion.

## Challenges as we Expand our Assessment Horizons

- Which (and how many) parameters should we assess?
  - Issues of multiplicity;
- Clinical (hard) endpoints vs. biomarkers:
  - Frequency of clinical endpoints (e.g., *Torsades* is exceedingly rare);
  - Validation of biomarkers (whatever that means);
  - Internal go/no-go decisions vs. regulatory submissions.
- Thresholds of regulatory concern/interest:
  - How are these decided upon?
  - What is ‘normal’? Epidemiological data; data collected on placebo (effectively regarded as off-drug).
- Of the three components of our model (clinical, regulatory, and statistical):
  - Statistical aspects are likely the most straightforward, but considerable care in execution of analytical strategies is still appropriate.

Thank you for your attention.

## References

- [1] ICH Guideline E14, May 2005. *The Clinical Evaluation of QT/QTc Interval Prolongation and proarrhythmic Potential for Non-antiarrhythmic Drugs.*
- [2] Brass et al, 2006, Risk assessment in drug development for symptomatic indications: A framework for the prospective exclusion of unacceptable cardiovascular risk. *Clinical Pharmacology & Therapeutics*, 79:165-172.
- [3] Borer et al, 2007, Cardiovascular safety of drugs not intended for cardiovascular use: Need for a new conceptual basis for assessment and approval, *European Heart Journal*, 28:1904-1909.
- [4] FDA Guidance for Industry, December 2008. *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Drugs to Treat Type 2 Diabetes.*
- [5] *Caveney and Turner (in preparation and accepted)*, Assessing Cardiovascular Safety during the Development of New Antidiabetic Therapies for Type 2 Diabetes: A Review of FDA Guidance. *Global Forum*, to appear in the December 2009 issue.