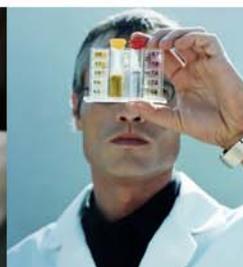




THE WORLDWIDE LEADER IN PHARMACEUTICAL SERVICES



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Prospectively Excluding Unacceptable Cardiac & Vascular Risks during Integrated Pharmaceutical Medicine

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Diversity of Expertise and Perspective within the CSRC

More than 20 Member organizations:

• Tremendous diversity of expertise, experiences, and perspectives.

From our website—Areas of Focus:

This consortium will address cardiac safety in cardiovascular and non-cardiovascular medical products. While the initial focus will be on the proarrhythmic risk of products, the intent of this collaboration is to develop evaluative tools, standards, validated tests and cardiovascular biomarkers related to broader aspects of cardiac safety including, but not limited to arrhythmia, thrombosis, myocardial infarction, and heart failure.

Moving into vascular safety:

• Stroke, urgent revascularizations.

Other potential areas for consideration:

• “Hot topics” in general medical product safety and patient safety:

- ▶ Training in Experimental Psychology & Cardiovascular Behavioral Medicine:
- ▶ Throughout my almost 30 years in experimental clinical research I have maintained an interest in behavioral aspects of successful interventions.

Integrated Pharmaceutical Medicine

This talk spans a wide range of issues:

Hopefully, provide some different topics for subsequent discussion.

Two conceptual frameworks for this range:

Lifecycle drug development [1]:

- ▶ Drug discovery/design (including *in silico* simulation);
- ▶ Nonclinical development program;
- ▶ Preapproval clinical development program*;
- ▶ Postapproval clinical trials and postmarketing surveillance.

Integrated pharmaceutical medicine [2]:

- ▶ Preapproval work leading to registration/marketing approval*;
- ▶ Communicating relevant information to physicians and patients*;
- ▶ Pharmacotherapy;
- ▶ Modifications to the drug following postmarketing information;
- ▶ Medication errors*;
- ▶ Adherence*.

Prospectively Excluding Unacceptable Cardiac & Vascular Risks

ICH Guideline E14 [3] provides an instructive example:

- Addresses the exclusion of unacceptable QT/QTc interval prolongation (as a surrogate for unacceptable risk of *Torsades de Pointes*).

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. *Clinical Pharmacology & Therapeutics*, 79:165-172.

This approach has three central components:

- Clinical science;
- Regulatory science;
- Statistical science.

Components of a Risk Exclusion Model

Clinical Science:

- Clinical judgments concerning absolute and relative risks (more later);

Regulatory science:

- Thresholds of regulatory concern/interest;

Statistical science:

- Accepted methodology for data analysis involving these thresholds, confidence intervals, and inferential statistical analysis;

- (Similar approaches in equivalence and noninferiority trials where equivalence and noninferiority margins must be established).

First two components have complex interplay:

- Well-being at the individual level and the public health level.

Third component is relatively straightforward, but:

- Consistency within/across guidances useful?;

- Considerable care must be taken when conducting meta-analysis.

Very Quick Review of Confidence Intervals in ICH E14 and CV/T2DM Guidance—and Looking Ahead

ICH E14 (focus here on 10 msec, but assay sensitivity component is same logic):

Guidance mixes discussion of upper limit of two-sided 90% CI and upper bound of one-sided 95% CI;

No numeric effect: they lie at precisely the same location;

Since no real interest in the lower limit of the two-sided 90% CI, use of the upper bound of the one-sided 95% CI allows this statement:

- ▶ We can declare with 95% confidence that the true but unknown population treatment effect is less than [the upper bound], and our best estimate is [the point estimate].

T2DM guidance [4]:

Uses two-sided 95% CIs with regard to meta-analysis;

Since no real interest in the lower limit of the two-sided 95% CI, use of the equivalent one-sided 95% CI allows this statement:

- ▶ We can declare with 97.5% confidence that the true but unknown population treatment effect is less than [the upper bound], and our best estimate is [the point estimate].
- ▶ Point estimate explicitly of interest here (not in ICH E14).

consistency moving forward useful or not?

Meta-analysis Methodology in General

Like any experimental study, a meta-analysis must be conducted according to an *a priori* protocol:

“To ensure that a meta-analysis is scientifically valid it is necessary to plan and conduct the analysis in an appropriate way. It is not sufficient to retrospectively go to a bunch of studies that you like the look of and stick them together!” [5]

“If all of the components involved in conducting a meta-analysis are performed appropriately, and the extent to which the results are helpful are not overstated (that is, any limitations are appropriately acknowledged and shared whenever and wherever communicating the results), these results can be informative and instructive. Unfortunately, however, it is easier than one might suspect to conduct a meta-analysis inappropriately and then to overstate the results in a variety of circumstances.” [6]

Meta-analysis Considerations Specifically for T2DM

Conduct a meta-analysis at the end of the (planned) preapproval clinical development program.

Use a random-effects model:

There is likely to be heterogeneity between the studies even when care is taken *a priori* to design them as similarly as possible.

A random-effects model is likely to give wider confidence intervals, more accurately representing the true range of the treatment effect of interest (here, captured as a risk ratio).

If a test for heterogeneity is not statistically significant, meta-analysts often proceed on the grounds that the studies are not heterogeneous, i.e., that a fixed-effects model is acceptable.

Turner and Durham [6] discussed the fragility of this argument, i.e., regarding the absence of statistically significant evidence of heterogeneity as a statement of its complete absence.

The FDA prefers to see results from a random-effects model even if the test for heterogeneity is nonsignificant.

Sponsors are also advised to discuss exact tests with the FDA.

Alternate Indices of Delayed Repolarization

Transmural dispersion of repolarization:

Drugs that have differential effects on epicardial, mid-myocardial, and endocardial cells are particularly prone to inducing *Torsades de Pointes*, since they can lead to “arrhythmogenic spatial dispersion of repolarization.” [7]

M-cells are “exquisitely responsive” to pharmacological agents that block the *hERG* cardiac potassium ion channel (and decrease I_{Kr}). [7]

T-wave morphology [8-10]:

Principal component analysis;

T-peak to T-end (Tp-Te) interval, T wave flatness, T wave symmetry, and T wave notch.

RIaD---triangulation, reverse use dependence, and stability [11].

Imaging Techniques for Atherosclerosis

Several recent papers [12-14] discuss this topic primarily from the efficacy perspective for drugs to combat atherosclerosis:

Application to vascular safety research also of interest.

Modalities include:

• Vascular ultrasound imaging techniques:

- ▶ Carotid intima-media thickness (CIMT)
- ▶ Intravascular ultrasound (IVUS) of the coronary arteries;

• Optical coherence tomography (OTC);

• Magnetic resonance imaging (MRI);

• Multislice spiral computed tomography (MSCT).

Bottom line:

• Their value awaits confirmation.

Biochemical Markers

Cardiac troponin:

Cardiac troponins (cTns) are established biomarkers of ischemic heart disease in humans;

Evaluation of value as biomarkers of drug-induced cardiac injury is of interest [15, 16].

Others:

Glycogen phosphorylase BB (GPBB): superior to CTns? [17]

Likely that a univariate approach is not optimum:

Many multiple regression models provide a simple precedent;

Not surprising that the same is true with biomarkers [18].

Biomarker working groups:

Biomarker Consortium of the Foundation for the NIH (FNIH)---
Atherosclerosis Working Group;

Health and Environmental Sciences (HESI)--- Cardiac Troponins
Biomarker Working Group.

CSRC White Paper on Evaluation of Ventricular Arrhythmias in Early Drug Development

Evaluation of Ventricular Arrhythmias in Early Clinical Pharmacology Trials and Potential Consequences for Later Development. [19]

Different approach from guidances discussed:

- Don't really have a good grasp of what is 'normal,' i.e., background occurrence of event(s) of interest;
- Therefore, hard to judge if occurrences during trials are drug-induced;
- Hence, addresses gaps in knowledge rather than a methodology for ruling out unacceptable risk.

SCR can be instrumental in the establishment of basic knowledge in such areas:

- Paper makes suggestions for collaborative research.

General point:

- For any future guidance, good information to guide choice of regulatory

Decision Making: Systematic or Nonsystematic?

omarkers:

May currently be better for internal decision making than as 'evidence' in submission to regulators. [20]

Consequences of 'no-go' decision:

Available resources (human, financial) for other projects;

Potential loss for patients and Sponsor:

- ▶ By definition, will never know the 'postmarketing story'---could have been huge win for patients (great treatment profile) and Sponsor (financial).

How best to make decisions?

Quantitative method of decision analysis: [21]

Advisory Committees---Decision Making Process:

Had privilege of addressing the joint meeting of the Endocrinologic & Metabolic Drugs, and Drug Safety & Risk Management, July 30th 2007:

Presentations, then 23 members discussed the evidence/presentations;

Votes were 20-3 and 22-1. However, what are the potential effects of group dynamics in more contentious cases?

Benefit and Risk Communication

How best to use numerical representations of biologically relevant information to facilitate health?

Risks quantified during lifecycle drug development pertain to study population(s). However, the assumer of the risk information and the actual risk is the individual patient.

Considerations at the public health level:

- Medical product labeling;
- Risk Communication Advisory Committee.

Considerations at the individual patient level:

- Helping patients reconcile averages derived from populations and their meaning to individual cases; [22]
- What should a physician say in cases where 'failure' may equate to death: A procedure has a 95% success rate, or a 5% failure rate?

Relative risk vs. absolute risk

- I believe this critical issue gets far too little attention.

Behavioral (Cardiovascular) Drug Safety

Adverse consequences of drug misuse dwarf clinical trial adverse events and adverse drug reactions:

- ▶ Medication errors: prescribing, dispensing, and/or administration:
 - ▶ ~100,000 deaths per year;
 - ▶ Additional costs of inpatient care: ~\$3 billion per year;
 - ▶ Not just pharmaceutical... ~4,000 wrong-side surgeries per year.

Well-known IOM publications on safety: [23-25]

- ▶ Some improvement in safety systems, but still way less effective than other industries;
- ▶ Need to consider individual, and human-machine-system interfaces.

FDA's Safety First/Safe Use Initiative: [26]

- ▶ Persuasion, not regulation.

Adherence (non-adherence), accidental and deliberate:

- ▶ Arguably the single biggest problem in pharmacotherapy;
- ▶ Case study: activity at UC San Francisco in early 1990s.

What's in a Name? (That which we call a rose...

Cardiac...

Cardiac and vascular...

Cardiovascular...

Same acronym... (cf. EMEA)

Three more syllables...

??? 😊

Thank you for your attention.

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