



**Prescription Drug User Fee Act
(PDUFA) Reauthorization
Public Meeting**



Meta-Analysis of Randomized Controlled Clinical Trials for Safety Evaluation

Docket Number FDA-2013-N-1276

November 25, 2013

Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)
Department of Health and Human Services

Agenda

- | | |
|-----------------|--|
| 7:30 – 8:00 am | Registration |
| 8:00 – 8:05 am | Welcome, Introductions and Logistics
Patrick Frey
Director, Office of Program and Strategic Analysis, (OPSA), CDER, FDA
Indira Hills
Project Manager, Office of Translational Sciences (OTS), CDER, FDA |
| 8:05 – 8:15 am | Opening Remarks
Doug Throckmorton, MD
Center Deputy Director for Regulatory Programs, CDER, FDA |
| 8:15 – 8:25 am | Introduction and Charge
Lisa LaVange, Ph.D.
Director, Office of Biostatistics (OB), OTS, CDER, FDA |
| 8:25 – 9:00 am | FDA Presentation: Meta-Analysis of Randomized Controlled Clinical Trials for Safety Evaluation: FDA Examples
Mark Levenson, Ph.D.
Deputy Director, Division of Biometrics VII, OB, OTS, CDER, FDA |
| 9:00 – 10:15 am | Panel Session 1: Bias and Multiplicity

FDA often needs to weigh evidence from meta-analyses conducted internally and/or externally to determine if a regulatory action concerning a product's safety is needed. Potential sources of bias that lead to erroneous conclusions are of considerable concern to the agency, as are tendencies for the results of a meta-analysis to be over-stated due to multiplicity of analyses, outcomes or objectives. Please discuss the following questions in this context.

<ol style="list-style-type: none">How can researchers guard against or account for the bias introduced by prior knowledge of the findings of relevant clinical trials that are included in a meta-analysis? How can the agency be confident that this source of bias has been avoided or at least minimized?Quantifying a safety risk may involve evaluating multiple endpoints reflecting the events of concern or patient subgroups with different risk profiles. When these multiple objectives are investigated in a single meta-analysis, what approaches do you recommend to address multiplicity? How would you balance the need to address multiplicity with the concern about the power to detect a rare event? |

- c. It may be the case that a safety signal is observed in a trial, and a meta-analysis is planned to further investigate the signal. In this case, what is your recommendation for whether or not to include in the meta-analysis the study that provided the initial signal, what methods of analysis are most appropriate, and how is interpretation impacted?
- d. Are there other important sources of bias and multiplicity that should be addressed? Please do not focus on aspects of the individual studies, which will be discussed in a later session.
- e. To account for known sources of bias as well as multiplicity, suggestions have been made in the literature for the use of a more stringent criteria for controlling uncertainty such as a statistical test size (e.g., $\alpha=0.01$ or lower) in a meta-analysis. What is your recommendation, given our concern here is with meta-analyses of safety risks?

10:15 – 10:30 am **Audience Questions and Comments on Panel Session 1**

10:30 – 10:45 am **BREAK**

10:45 – 11:45am **Panel Session 2: Statistical Methods**

Statistical methods for meta-analysis are well-developed, but the regulatory requirements for evaluating safety risks present unique challenges. Please discuss the following questions in this context.

- a. Is either a fixed- or random-effects model preferable? How should generalizability versus precision of the meta-analysis results be balanced in the regulatory context?
- b. How should individual studies that have large influence on the meta-analysis due to their size or number of events be handled in the meta-analysis?
- c. Some have suggested the use of cross-validation methods for meta-analysis in which a random subsample of the data is used for hypothesis generation, and the remainder for validation. What are your recommendations regarding this approach?
- d. What are the advantages and disadvantages of frequentist and Bayesian methods in the present context?
- e. What methods are preferred for sparse events? How should trials with no events in either or all treatment arms be handled?

11:45 – 12:00 pm **Audience Questions and Comments on Panel Session 2**

12:00 – 12:45 pm **LUNCH** (On your own)

12:45 – 1:45 pm **Panel Session 3: Individual Study Quality**

Meta-analysis provides the ability to summarize information from individual trials, usually with greater precision and/or generalizability. They cannot, however, be expected to overcome issues with individual trial quality. Please discuss the following questions in this context.

- a. What aspects of the choices of exposure and outcome definitions in the individual trial are important for the quality of the meta-analysis? Should trials that were designed for other purposes than the objective of the meta-analysis be included, and if so, how?
- b. How important is the availability of patient-level data from individual trials? Are there situations for which trial-level data may suffice?
- c. What other aspects of the individual trials are important?
- d. What are the advantages and disadvantages of the inclusion criteria of (i) trials conducted for regulatory development with availability of patient-level data versus (ii) trials from an exhaustive publication search?
- e. How should large trials designed specifically to address the objectives of the meta-analysis be handled? Should they be included in the meta-analysis or should they provide stand-alone independent information?

1:45 – 2:00 pm **Audience Questions and Comments on Panel Session 3**

2:00 – 3:00 pm **Panel Session 4: Overall Meta-Analysis Quality**

In this session, we would like to discuss some broad issues that affect the overall quality of the meta-analysis. Please discuss the following questions in this context.

- a. What documentation should be required to evaluate the quality of the overall meta-analysis and the strength of its findings? Discuss documentation that could be required during both the planning and the reporting phases of the meta-analysis.
- b. What infrastructure, if any, currently exists to register and archive documents associated with a meta-analysis? If one is named, is this infrastructure sufficient for regulatory purposes? If one is not named, do you have any suggestions for how such an infrastructure might be developed and its use advocated?
- c. What are the key sensitivity analyses needed to support the conclusions of a meta-analysis?
- d. What are your recommendations for establishing a hierarchy of evidence that could be used to judge the quality and strength of findings from a meta-analysis?

3:00 – 3:15 pm

BREAK

3:15 – 4:15pm

Audience Questions and Comments on Panel Session 4 and Open Public Speakers Session

4:15 – 4:45 pm

Summary of Discussions and Next Steps

Lisa LaVange, Ph.D.

Director, Office of Biostatistics, OTS, CDER, FDA

Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov> and <http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm>

Written and electronic comments will be accepted after the hearing until January 25, 2014, Docket Number FDA-2013-N-1276. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers lane, Ro. 1051, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.