Reviewer's report

Title: Phase IV non-inferiority trials and additional claims of benefit

Version: 3  Date: 12 November 2012

Reviewer: Jörg Zinserling

Reviewer's report:

Major comments/ Major Compulsory Revisions

1. The authors present a manuscript on an analysis of non-inferiority (NI) trials which can be considered Phase IV trials in a broader sense. The research question is how “additional benefit” is addressed in the trials and on which basis “additional claims” are justified. The research question is relevant.

2. The sample of studies included in the author’s analysis is originating from the selection of studies used for a previous review of the group. The selection procedure is comprehensively described and the selection process leading to the selection of 15 definite Phase IV and 35 post-authorization studies is adequate. Further classification into pharmaceutical industry sponsored and non-industry sponsored studies is helpful. The authors adequately address the limitation of the sample size in the discussion. Some aspects of the terminology and statements by the authors need further explanation.

3. It is not clear to me how the authors define the term “formal test” as used in the results section (p. 5). In the context of inferential statistics in my understanding a formal (statistical) test could be a test with pre-defined hypotheses that are stated in advance and evaluated with assessment of p values size and precision of the treatment effect and its clinical relevance. This would be a formal test needed in an adequately controlled trial with confirmatory objective and documented sample size estimation (cf. ICH E9 on Trial Context). A formal statistical test could also meant be used in an exploratory sense where choice of hypotheses may be at least in part data dependent like in trials which use not only descriptive statistics for the secondary endpoints. The authors need to clarify what they mean by “formal test”.

4. I would not agree with the authors that Phase IV NI trials (with assay sensitivity secured) need in principle to have additional benefit claims that are to be based on confirmatory “formal tests”. Trials with the primary objective to show NI to a comparator can contribute to the “improvement of therapeutic interventions” (p. 7) also by exploratory analyses based on statistical tests which would not be expected to be confirmatory in nature (see comment 2). Furthermore, assessment of the safety profile is usually not based on pre-specified hypotheses with claims stated in advance. The authors need to clarify in which sense the term “additional claim” is meant.

5. The authors limited their analysis of trials to NI Phase IV trials. If “additional
claims” would be meant by the authors to be based on formal tests in a confirmatory sense a trial with this objective could just as well be a trial aimed to show superiority as a primary objective. By definition, superiority Phase IV trials are not included in the presented analysis. The authors should comment on this in the context of answers to the comments 3. and 4. and possibly include this aspect in the discussion.

Minor Comments/ Discretionary Revisions

1. The authors should comment on the possibility to include phase IV trials that are not explicitly non-inferiority trials in their review.

2. The message that Phase IV trials should be improved in methodology is supported by this reviewer.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests