The Pharmaceutical Advertising Advisory Board

REVIEW

By Ray Chepesiuk, Commissioner

Evidence or Artful Manipulation?

"There once was a biased clinician,
Who rejected the wise statistician.
By flogging his data with α and ß,
He satisfied all his ambition."
(author unknown)

Claims in drug advertising should be evidence-based. Published, peer-reviewed studies are a good starting point to demonstrate this statement. However, the final evaluation of whether a study is sound enough to support a claim can be a complex matter. Two of the learned skills PAAB reviewers possess are the ability to perform a critical review of literature and, in particular, the ability to analyze clinical studies to see if they are scientifically sound. Clinical studies should be objective, and should possess solid scientific rigour. Reviewers must ascertain that the claims in pharmaceutical advertising adhere to the requirements of PAAB Code sections 2, 3, 4, and 5. It is important to note that the often complex, time-consuming review process is particular to advertising directed to health professionals.

What makes a good clinical study?

If the study-based claim is within the Health Canada-approved product monograph, PAAB reviewers will look for the components of a good clinical trial protocol. They will seek the trial's designed purpose. Any data, analyses, opinions, and conclusions that do not correspond with the original design or intent are not suitable evidence for advertising. So, what do reviewers look for?

First, they will look at the study's objective and purpose. What is the scientific rationale for performing the clinical trial? What are the expected benefits? What are the primary and secondary objectives with respect to safety and efficacy? Can these be tested statistically? Reviewers will look at the manner in which the study was conducted, as well as the measures that were taken to minimize bias. Was the study randomized or stratified? Was it double-blind, placebo-controlled, or parallel? The treatments and their respective dosages are scrutinized. The duration of trial periods and the types of participating subjects are important factors. Discontinuation rules should be predefined.

With respect to subject selection, reviewers will look for:

- inclusion and exclusion criteria;
- screening and enrolment procedures; and
- withdrawal and replacement protocols.

They will look at subject treatment, in terms of:

- medications used,
- doses and dosing schedules,
- administration routes,
- treatment periods (including followups),
- permitted and excluded concomitant medications, and
- compliance-measuring procedures.

Reviewers also look at the assessment, recording, and analysis of both efficacy and safety.

The statistical analysis plan should include:

- the variable types of statistical methods and their justifications,
- the timing of any interim analysis,
- the sample size and rationale,
- the level of significance and rationale,
- the stopping criteria, and
- the handling of missing data and deviations.

Reviewers will look for the intention to treat numbers, and they will verify that subgroup analysis was a primary part of the study. Interim analyses can help the study sponsor determine if the study is worthwhile, and if it should be continued. However, published studies of interim analysis results should not be used to support advertising claims.

The International Conference on Harmonization (ICH) guidelines are today's dominant regulatory documents. They cover statistics in clinical trials, and a choice of control groups. They include discussions on superiority, non-inferiority, and equivalence studies. Regulatory agencies generally prefer clinical, non-inferiority studies over equivalence studies. The guidelines can be accessed online at *http://www.fda.gov/cder/guidance.*

Clinical study designs can include parallel or crossover designs, titration experiments, and experiments that are factorial, group sequential, or multiple stage. Parallel design is the most common in pivotal trials. Crossover designs are good for chronic diseases, where a drug may modulate, but will not permanently change the disease. This design is also good for drugs with a short half-life and for equivalency studies. It is very unusual for a statistician to perform an analysis that reveals an important drug effect when careful examination of the raw data does not. However, it is commonplace for a statistician to design a study that shows exactly what is needed.

Open-label studies are generally not accepted as evidence for claims in drug advertising. The exception would be the ability to demonstrate to PAAB reviewers that the study could not be conducted in a blinded manner, and/or the results could not be biased, either because of the chosen end points or because of the measurement method.

Meta-analysis should be as rigorously designed as a clinical trial. It is not simply a pooling of data that is analyzed every which way until something useful comes up. It is not possible for meta-analysis to replace large, well-conducted, randomized, clinical trials (RCTs). In rigorous meta-analysis studies, you should be:

- including all relevant trials,
- entering RCTs into central and accessible registries,
- starting the meta-analysis with a rigorous protocol,
- making exhaustive attempts to obtain complete individual patient data from each trial, and
- obtaining an agreement among trialists on the definitions of end points and the data collection process.

Large, well-conducted meta-analyses carry weight, whereas small, poorly-conducted meta-analyses carry stigma.

Nothing but the truth

If you torture data long enough, it will say what you want it to say. The PAAB Code requires good, solid evidence to support claims in drug advertising. It is the responsibility of all advertisers to use this principle as a starting point. We prefer that the truth be told. CPM

If you have any questions or comments about the review process, you can contact PAAB commissioner, Ray Chepesiuk, at (905) 509-2275.