Guidance Document for The Use of Subgroup Analysis In Advertising

January 2013

Subgroup Analysis Checklist

Item No	Checklist Item (clients can use this tool to help make decisions regarding use of subgroup analysis data in advertising claims)	√
Considerations		
3.1	Consistency with Terms of Market Authorization	
3.2	Predefined Endpoints	
3.3	Baseline comparability	
3.4	Subgroup analysis must be confirmatory in nature	
3.5	Consistent with effects seen in overall study population	
3.6	Claim should identify that the presentation relates to a subgroup	

1. Key Benefits:

Subgroup analyses can provide clinically relevant insight into heterogeneity of treatment effect in relation to various parameters including: pathophysiology (e.g. comorbidities, biologic/genetic markers), medical history, concomitant treatments, treatment history, gender…etc.

2. Key Pitfalls:

Real effects can be missed because the original studies were not designed to detect them (i.e. false negatives), and identified effects can be false because of multiple testing and natural within-trial variability. Also, efficacy/safety may not have been assessed by Health Canada in that subgroup.

3. Managing Pitfalls:

The following checklist provides 6 helpful principles to guide industry and the PAAB staff in determining whether a subgroup analysis presentation may appear within advertising/promotional systems (APS). The checklist relates only to factors specific to subpopulations. Refer to the PAAB code for general factors relating to acceptability of a study.

□ 3.1 Consistency with Terms of Market Authorization

Principle:
Drug advertising should be consistent with the Health Canada approved Terms of Market Authorization (TMA).

Rationale:
Advertising content which is inconsistent with the TMA would contravene section 9.1 of the Food and Drugs Act.

Application:
The subgroup(s) must be part of the population segment covered by the product indication AND the specific patient group(s) must be consistent with the TMA. Claims relating to subgroups can only appear after prominent presentation of the relevant Health Canada approved indication (i.e. disclosure of the overall indicated population). The observation must not contradict anything in the TMA (with respect to magnitude, direction, or duration).

□ 3.2 Predefined Endpoints

Principle:
Claims should be based on assessments which were designed to measure the observed outcomes.

Rationale:
To minimize biases (e.g. selection and measurement bias).

Application:
The subgroup and the method/number of analysis must be pre-defined in the study protocol. Data on file, such as the statistical analysis plan, may be used to demonstrate that this requirement has been met.

□ 3.3 Baseline comparability

Principle:
Baseline features should be comparable across the subgroups and the overall study population.

Rationale:
This is important to avoid selection bias and an imbalance in the prognostic factors.

Application:
The subgroup variable(s) must be measured prior to randomization of the overall population.

□ 3.4 The promoted outcome must be confirmatory in nature

Principle:
Exploratory analyses are not accepted.

Rationale:
Planned confirmatory analysis empowers a priori decisions on how to control the risk of type 1 error

Application:
Must meet all following criteria:

- Must have similar results to those seen in other studies
- Must have results that are consistent with a biologic rationale
- The statistical analysis must discuss how the risk for type 1 error was minimized

□ 3.5 Consistent with effects seen in overall study population

Principle:
For claims of benefit, the results of a subgroup analysis must demonstrate consistency of effect to the overall study population.

Rationale:
The study is powered to assess the primary endpoint. A subgroup analysis in a secondary endpoint cannot salvage a failed study.

Application:
Outcome must be directionally consistent with the overall study population.

□ 3.6 Claim should identify that the presentation relates to a subgroup

Principle:
The claim must not mislead.

Rationale:
The message should not lead the reader to misinterpret the subgroup analysis to be the primary endpoint.

Application:
The APS must clearly identify that the outcome is a subpopulation (i.e. within the claim, not a footnote) except where this assessment was the primary endpoint.