Guidance Regarding Duration of Clinical Trials Used as Reference Support in Advertising

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For healthcare products that do not have Terms of Market Authorization (TMA) limitations on duration, the following may be considered as reference support for advertising messages provided they meet all of the requirements in this advisory:

- Out-of-label studies evaluating a duration of use that is longer than the product's pivotal trials for the corresponding condition
- Published, pre-planned extensions and subsequent interim and final analyses of randomized, controlled trials (RCTs)

1. The study is consistent with the TMA

Clinical trials used as reference support in advertising should be consistent with the TMA of the promoted product as per s. 3.1 of the PAAB Code. When assessing consistency with the TMA, the PAAB considers:

- Indication
- Patient population
- Limitations and directions for handling/use
- Dosing or use regimen/administration
- Magnitude and direction of effect

Limitations in duration of therapy identified in the TMA, such as might be stated in the dosing and administration section of the TMA, must be reflected in the out-of-label study in order for it to be accepted as reference support for advertising claims.

Example: The TMA states that the product is given for 18 cycles. Out-of-label studies examining more than 18 cycles of treatment will not be acceptable as reference support for advertising claims.

2. The study meets standards for high quality evidence

Clinical trials must meet all requirements for evidence outlined in the PAAB Code and PAAB guidelines.

For a list of some of the key relevant resources & guidances CLICK HERE.

Published, pre-planned extensions or subsequent interim/final analyses that do not meet all requirements for evidence in the PAAB Code and PAAB guidelines may also be acceptable as reference support in advertising provided that:

- The original RCT meets PAAB Code requirements for evidence.
- The presented endpoints from the extension/subsequent analysis are endpoints that were acceptable from the original RCT
- Findings from the extension/subsequent analysis are presented separately from and following the presentation of relevant findings from the RCT
- Findings from the extension/subsequent analysis are presented in a neutral manner with no claims

A note about published, pre-planned extensions or subsequent interim/final analyses of pivotal trials in the TMA: If the pivotal trial would not have been accepted as reference support for advertising if it had not been in the TMA (e.g. study population is not entirely on-label, dosing is not completely on-label, etc.), presentations of data from the extension or subsequent interim/final analysis may not be accepted and/or PAAB may need to consult with Health Canada.

3. The study duration must not increase the potential for harm relative to:

i. the information in the TMA

The Market Authorization Holder (MAH) is most aware of current and emerging safety data for its products. PAAB will require a signed letter from the medical department (or equivalent) attesting that the MAH is unaware of data, whether published or unpublished, suggesting that use of the product for the promoted study's duration might introduce new health risks or increase the frequency/severity of the health risks conveyed in the TMA.

ii. current medical practice:

All healthcare products have the potential to cause harm. This potential tends to increase with longer durations of exposure. Studies that are of longer duration than those of the studies in the TMA can only be used to inform HCPs about efficacy and safety when they are of **a duration of treatment that is already expected or typical for patients taking the product (or those from the same product class/category) for a given condition.**

> The MAH's medical department (or equivalent) should provide an attestation that the typical or expected duration of treatment with a product or product class is not shorter than that of the out-of-label study and that they are unaware of factors that could impair applicability of this information to the promoted product.

Notwithstanding receipt of these attestations, the PAAB may consult with Health Canada on an as needed basis.

4. Existing directions for use in the TMA must enable the product to be safely and effectively used in the manner promoted in the APS

As an example, the PAAB may not accept clinical trials as evidentiary support for representations in advertising if their duration exceeds the time frame for which monitoring instructions are presented in the TMA.

Fictitious explanatory case for this requirement:
The longest study duration in Product XYZ's TMA is 6 months. A 2-year study evaluating efficacy in patients with the corresponding medical condition is submitted. The TMA

contains a warning regarding red blood cell count and directs HCPs to measure the patient's red blood cell count according to one of the following schedule:

Scenario A *"At month 0, month 3, and month 6. Additional data is required to determine optimal testing frequency after 6 months of use".*		(The TMA must be updated prior to inclusion of data based on study duration that is beyond BOTH the longest pivotal trial for the corresponding use and 6 months).
Scenario B *"At month 0, month 3, and month 6".*		(The study may be considered. Additional considerations will be whether the MAH can provide evidence that monitoring is intended to end at 6 months. PAAB may need to consult with Health Canada)
Scenario C *"At baseline and every 3 months thereafter".*		(The study can be considered assuming all other requirements are met)
Scenario D *"Prior to treatment; further monitoring should be based on signs and symptoms"*		(The study can be considered assuming all other requirements are met)

5. The APS must include appropriate disclosures

Any disclosures necessary to ensure that the presentation is both truthful AND non-misleading must be prominently included in the APS.

As an example, cautions or directions relating to extended use must be disclosed.

Example: A statement similar to "The duration of this study is longer than that of data in the TMA" must be included.

Example: If the TMA indicates that the risk of an adverse outcome or toxicity increases with treatment duration, this information must be included.