A Path Towards
Globally First-in-Class Health Product Advertising Directed to HCPs

Caveat

Please note that this document is for initial consultation only. It has been developed with oversight from a committee of industry experts in real world evidence. We aim to co-create the specific standards in collaboration with HCPs (healthcare professionals) and the industry to ensure that the guidance is valuable from a multi-stakeholder perspective prior to consultation with Health Canada. Depending on the resulting standards, the guidelines could inform/require modification to the PAAB Code.

1. Background

In a perfect world, all clinical decisions would be supported by gold-standard evidence. However, in the real world, HCPs don't typically have the luxury of deferring therapeutic decisions until the highest possible quality of evidence is available; they must make decisions based on the best data available at the time. With the proposed approach outlined below, we aim to facilitate the delivery of the best data currently available to HCPs to inform healthcare decision-making. This guidance document pertains to Advertising/Promotion Systems (APS) that are directed to health professionals.

Canada has a unique preclearance mechanism for HCP advertising: an impartial review conducted by a specialized body that is completely independent from the manufacturer. This puts Canada's health product industry in a unique position to leverage potential health benefits from advertising content that goes beyond gold-standard evidence, when it is in the interest of Canadians, while maintaining a long-standing tradition of truthful and trustworthy advertising.

The guidance proposed herein could further promote informed clinician decision-making by ensuring that all data is presented responsibly and that the limitations of the data are prominently disclosed.

2. Scope

This proposed guidance document applies to health product advertising directed to health professionals. It is important to note; however, that it does not apply to:

- **Class B opioids:** In adherence with Health Canada's Terms and Conditions on advertising for opioids, the advertising for such products is restricted to verbatim extractions from the TMA.
- **NOC/c products:** For products authorized under Notice of Compliance with Conditions (NOC/c), advertising presentations relating to efficacy/effectiveness/safety must be sourced from the TMA. CLICK HERE for additional applicable guidance. The evidentiary and disclosure requirements for NOC/c products differ from those for Notice of Compliance (NOC) products.

For the purposes of this guidance document, the PAAB considers the following sources of Real-World Evidence/Data (RWE/RWD) as the basis for APS presentations of health product effectiveness and/or safety:

- pragmatic trials

- cohort studies (prospective and retrospective)
- case control studies
- variants of the above three designs

The PAAB considers these same sources in addition to cross-sectional studies for disease information presentations in APS. Note that neither individual case studies nor case-series are acceptable as evidentiary basis for APS messaging.

RWD from recognized/validated market data providers can be considered for market share and retention/persistence presentations.

3. Proposed Approach

PAAB's evidentiary standards for marketing benefit claims are unchanged by this guidance document. For a list of some of the key relevant resources & guidances CLICK HERE. From this point forward, this guidance document uses the phrase "evidence which meets (or does not meet) the PAAB's standards for marketing benefit claims" to refer to standards discussed throughout the linked list of Code sections and guidance documents.

Study data presentations based on evidence which does not meet the PAAB's standards for therapeutic claims of benefit may appear as informational APS presentations in the following circumstances:

- The evidentiary support meets the requirements outlined in section 3.1
- The APS presentation of the results meets the requirements outlined in section 3.2

3.1 Requirements pertaining to the references used as evidentiary basis for informational APS presentations aligned with the standards in section 3.2 of this document

i. Consistency with the Terms of Market Authorization (TMA)

As is true of APS presentations based on Randomized Controlled Trials (RCTs), presentations based on RWE/RWD must be consistent with the sponsor product's TMA. Neither presentations based on RCTs nor those based on RWE/RWD may contradict anything in the TMA. Assessment of consistency with the TMA entails consideration of:

Indicated disease/condition:
Information relating to management of a different disease/condition than that for which the product is indicated is not permissible in advertising. Additionally, efficacy or effectiveness presentations in APS must NOT be based on use of the sponsor's product to manage different severity, stages, or manifestations of a disease than those conveyed in the TMA.

Patient population:
The APS presentation must be derived from analysis of patients that fall within the indicated population and are aligned with any relevant contraindications from the TMA. In instances where an overall study

population exceeds the product's indication, it may be possible to present data from a pre-planned patient subset which reflects the indicated patient population.

Dosing/administration, limitations (e.g., statement of treatment duration limits), and directions for handling/use:
The manner in which the respective health products are utilized to generate evidence/data must not contradict the TMA (e.g., dosage, administration route, titration schedule where protocol driven, duration of use, and so on).
Where the TMA does not contain statements of treatment duration limits and the study exceeds the duration of the longest relevant study in the TMA, the principles outlined in the guidance on study duration apply. CLICK HERE for more information.

Endpoints/Outcomes:
During industry consultation on the first draft of this guidance document, we received numerous questions about whether APS would be limited to the particular endpoints in the TMA. Regardless of whether the evidentiary basis for the presentation is RWE/RWD or an RCT, endpoints are not generally limited to those explicitly included within the TMA for non-opioid products that have NOC approval (i.e., NOC without conditions). Endpoints/Outcomes must be "consistent with" (though not necessarily "the same as") those in the TMA. Though the approach for RWE/RWD mirrors that for RCTs in this respect, the following examples are intended to clarify questions received during the consultation process.

Example 1.
A hypothetical health product is indicated for the treatment of adult patients with type 2 diabetes mellitus (T2D) to improve glycemic control. The TMA contains the following efficacy endpoint: HbA1C.

- Can data pertaining to Fasting Blood Glucose in patients with T2D be considered in the APS? Yes.
- Can data pertaining to reduced risk of cardiovascular complications in patients with T2D be considered in the APS? No.

Example 2.
A hypothetical health product is indicated for the treatment of advanced solid-state tumors. The TMA contains the following efficacy endpoints: Objective Response Rate and Complete Response Rate.

- Can data pertaining to quality of life in patients with advanced solid-state tumors be considered? Yes.
- Can data pertaining to overall survival in patients with advanced solid-state tumors be considered? Yes.
- Can data pertaining to rate of development of second primary neoplasms (SPN) in patients with advanced solid-state tumors be considered? No.

Additional guidance pertaining to BOTH patient population and dosing
It is understood that real-word evidence tends to evaluate more heterogenous populations and tends to be less protocol driven than RCTs. It is not unusual for a small proportion of the study population to deviate from the Terms of Market Authorization. With this in mind, no APS presentation may be derived from an evidentiary source where > 20% of patients are not aligned with the relevant indication,

contraindications, limitations of use, or dosing/administration recommendations from the TMA. This threshold applies to the patients from the particular analysis from which the APS presentation is derived, not necessarily the overall study population. For example, a study's overall population may exceed the aforementioned threshold as long as the **pre-defined** sub-population upon which an APS presentation is based adheres to the threshold.

ii. Published and peer-reviewed.

All APS presentations based on RWE or RWD must be published and peer-reviewed with the following exceptions:

- Presentations based on non-comparative retention/persistence data or adherence data from the sponsor's patient support program (PSP).
  Note that the retention/persistence rate or adherence should be attributed to the health product's support program (rather than being framed as a direct/sole result of the health product in and of itself). Where this data is not published and peer-reviewed, the submission must include sufficient information for PAAB to validate the methods relating to data measurement, recording, analysis, and reporting. Comparisons across patient programs (i.e., versus PSPs offered by competitors) are not acceptable.
- Comparative or non-comparative data from recognized/validated market data providers (for market share and retention/persistence data).
- The study is not presently published but has been peer-reviewed and accepted for publication at a future date. A copy of the Author Accepted Manuscript (AAM) must be submitted to PAAB as the basis for review. Note that the AMM is also sometimes referred to as the author's manuscript or the accepted manuscript. For the purposes of this document, it is intended to refer to the version of the article that follows completion of the peer review process and approval for publication (but often prior to copyediting and typesetting).

Where a reference within those listed exceptions has not been published at the time of use in advertising, the sponsor is still required to make the reference available to a healthcare professional on request per PAAB Code s3.2. The healthcare professional may be asked to sign a non-disclosure agreement where required.

Abstracts, posters, and slides presented at congresses are not acceptable. If the data has been peer-reviewed and accepted for future publication, then the manuscript that has been accepted for publication must be used as the data source (not the abstract/poster/slides).

iii. Disclosure of methodologic information

Transparency is a key characteristic of high-quality research. The evidentiary source must provide comprehensive details on how data was collected and analyzed. The following two-part litmus test is a fair guide for advertisers on comprehensiveness.

Litmus test: The published paper contains sufficient methodologic information to likely enable:

- PAAB to identify key study limitations (as these are required to be listed in the APS)

- Healthcare professionals to assess the study and determine if it is sufficiently robust for them to consider incorporating the findings into their clinical practice.

Manufacturers are *encouraged* to assess studies according to recognized national or international reporting standards where appropriate/relevant (e.g., the STROBE checklist or the upcoming CADTH guidance *or equivalent*), *particularly in regards to criteria relevant to the research question and methodology.*

iv. Pre-planned methodology

The methodology is predefined. Any amendments to the methodology should be justifiable (i.e., are required and have scientific merit) and will be disclosed in the APS when warranted. Data derived from data-mining activities that are not BOTH based on pre-defined research questions and peer-reviewed are not acceptable in advertising. In response to questions that arose during the consultation process, this does not necessarily preclude use of retrospective analysis with pre-defined methodologies.

Pre-planned secondary endpoints must clearly be identified as secondary endpoints per PAAB Code s3.10.

v. The data is collected from empirical observation

The data is collected from empirical observation (i.e., as opposed to predictive modeling and simulated data where the model/simulation design and implementation is not independent from the sponsor (i.e., where it occurs in a sponsored study).

vi. Relevant to medical practice in Canada

In RWE/RWD, clinician decisions can potentially be impacted by factors that are local to the study's jurisdiction (e.g., the healthcare system structure, the manner in which clinical care is practised, distribution of co-variables relating to patient/disease characteristics) to a larger extent than they would be in RCTs by virtue of the fact that RWE/RWD tends to be less protocol-driven. Consequently, although RWE often has the benefit of generalizability to the corresponding real-world clinical context, it can be perilous to generalize the study's findings to other jurisdictions.

For RWE from other jurisdictions, the sponsor should provide an attestation letter signed by personnel from the medical/regulatory department confirming that the study is relevant to the Canadian practice. It is understood that the letter will be signed by personnel considered by the sponsor to have sufficient knowledge and authority to make such attestation.

The APS explanatory statement (accompanying the icon discussed below) will include prominent disclosure of the non-Canadian study jurisdiction(s).

vii. Comparable treatment between study groups

Where the study includes one or more comparators (whether active or inactive), the methodology must be equivalent for each study group.

While the APS presentation is not required in principle to include all study comparators, at least one of the comparators must be included for comparative effectiveness studies AND the presentation must not be overly-selective per PAAB Code s5.12. All comparators included in the APS presentation must have been evaluated in a manner consistent with their respective TMA's. The principles outlined in section 3.1.i above apply to both the sponsor's products and the comparators. Where none of the evaluated comparators meet this requirement, presentation of the study will not be permitted. A single arm presentation cannot be derived from a study that was designed to be comparative.

Statistical analysis is required for comparative studies. The p-value and/or confidence interval must be included in the APS presentation.

Single arm trials can be considered as the basis for data presentations pertaining to adherence/compliance, persistence/retention, and safety. When published and peer-reviewed single arm studies are included in APS for effectiveness endpoints, the discussion of key limitations in the body of the presentation must include disclosure statements conveying that the methodology may make it difficult to differentiate between:

- drug effects and the natural history of the disease
- drug effects and placebo effects

For single arm studies, sample size and a measure of sample dispersion must be presented within the body of the presentation.

viii. Disclosure of contradictory data (or removal of the RWE)

While there is no requirement for sponsors to perform systematic analyses prior to including RWE in APS, where a published contradictory comparative statistical inference is known to exist, the RWE presentation should disclose that fact in body copy. Alternatively, the sponsor has the option of removing the RWE presentation from the APS.

> i.e., The sponsor's study demonstrated that Drug A is statistically superior to Drug B on endpoint ABC while a separate study demonstrated that Drug B was statistically superior to drug A for a similar endpoint and population.
>
> Had the separate study demonstrated that Drug A was statistically non-inferior to Drug B (or that Drug B was statistically non-inferior to Drug A), this disclosure provision would not apply. The provision also would not apply if the separate study had instead demonstrated that p=NS with respect to that comparison (i.e., a failure to attain statistical significance).

In response to questions raised during the consultation process, this standard is not expected to introduce new significant burdens onto health product manufacturers. In fact, manufacturers already have a vested interest in maintaining awareness of published studies demonstrating that a competitor

was statistically superior to their product in relation to endpoints and populations that are featured in the manufacturer's ongoing advertising campaigns.

If the PAAB is made aware of credible contradictory data after approval of the APS, the PAAB may require the APS to be updated with the relevant disclosures accordingly.

Where the contradictory data comes from a published and peer-reviewed, well-controlled RCT, the contradictory data should be included in the presentation for balance. The studies must appear as separate and distinct presentations so as not to appear to be a cross-study comparison. The sponsor has the OPTION to also include a factual and balanced description of the overall study design/parameters for the contradictory study. No direct comparisons should be drawn to the sponsor's study design/parameters.

Where the contradictory data comes from a published and peer-reviewed RWE or meta-analysis, it is sufficient to include a disclosure statement indicating the existence of the contradictory RWE or meta-analysis with a cross-reference to the citation list item identifying the study. However, the sponsor is welcome to exceed this minimum disclosure standard.

ix. Inform PAAB of review by other Canadian bodies

The advertiser must inform PAAB during initial review of any study included in the APS that has undergone review by an authoritative Canadian body (e.g., CADTH, INESSS, Health Canada). The initial submission must include the relevant conclusions from the review of the RWE.

3.2 Proposed key principles relating to presentation of data

- The presentation is informational and claim neutral. The data is not used as the basis for EITHER overt claims of benefit OR creative imagery
- Three key elements required in a data presentation based on evidence that does not meet gold standards are:
    - The presentation is boxed (e.g. shading or line)
    - The presentation begins with an icon and an explanatory statement on the data source
    - The presentation discloses key study limitations
- Repetition of the data requires repetition of the icon, explanatory statement and disclosure of key study limitations. This sort of data presentation does not lend itself well to a summary page since it cannot be reduced into a concise/summary format.
- The RWE presentation standards are not required for data presentations that are exclusively based on content from the TMA. This applies EVEN if they aren't considered gold standard evidence in and of themselves, they conflict with other study findings, and/or they don't pertain to the specific product promoted in the APS.

The icon

- The icon should be presented prominently at the top of the presentation
- The icon must, at a minimum, meet the sizing standards outlined in the icon style guide. See www.paab.ca/resources/pdfs/RWE-icon for the RWE Disclaimer Icon Guidelines.
- The alt tag for the icon is "Attention"

The explanatory statement on the data source

- The statement should be presented prominently at the top of the presentation.
- An example of an explanatory statement is “The data in this box is from an observational study. It should be interpreted cautiously as it is not a randomized controlled trial or in the product monograph”.

Disclosure of key study limitations

- The statement appears as body copy (i.e., at least 75% of font size of main body copy)

Considerations for audio/video presentations

- Video:
  - The explanatory statement on the data source may be included on a title/divider screen prior to the presentation of results instead of on every screen where the data is presented
  - A closing statement similar to “The presentation from the observational study is now concluded” should be included to indicate the end of the presentation
- Audio:
  - The icon and explanatory statement should be included in the audio. The icon can be read as “Attention”. A single tone may be included prior to the reading of the explanatory statement to provide a break from the regular background noise or pace of audio, thus alerting the listener to pay attention to the audio that immediately follows the tone. (The intention of this tone is to help break up the audio, in a similar way that a visual break would be created in a layout).

Recommended Icon Use:

- Minimum size
  - The icon should be scaled to a minimum of 225% of the body copy cap-height in the corresponding box. PAAB will base the calculation on the larger of the text in the copy or the text in images (e.g., graphics). For an explanation of cap-height, see Guidance on Indication and Fair Balance Font Size.
  - NOTE: This is a minimum, not a standard size. The icon must be large enough to always stand out in the presentation.
- Safety area
  - The safety area is equivalent to the height of the exclamation point, without its point.

3.3Examples:

Examples will be updated per changes above upon final draft

Postcard example

<visual>

Letter example

<visual>

Fax example

<visual>

Email and mobile*† examples

<visual>

*Grey boxes bleed all the way to the edges on email and mobile templates only.
†Study parameters can appear anywhere on the spread or through a digital link. The footnote would elaborate on the study description. The sponsor may include additional features of the study (i.e., not limited to shortcomings); these should be presented in a neutral/non-promotional tone.

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Glossary

Health product

A substance or mixture of substances manufactured, sold or represented by a specific manufacturer for in vivo use in the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof; or in restoring, correcting or modifying function(s) in humans. This includes: drugs listed on all schedules of the Food & Drugs Act and Regulations that have a Drug Identification Number (DIN) assigned by Health Canada; and Natural Health Products that includes traditional herbal medicines; traditional Chinese, Ayurvedic (East Indian) and Native North American medicine; homeopathic preparations; and vitamin and mineral supplements that have a Health Canada assigned NPN or DIN-HM and “pharmaceutical products”.

This excludes medical devices and cosmetics (except for therapeutic cosmetics) as defined in the Food and Drugs Act and Regulations; products used for in vitro diagnosis of conditions, both normal (pregnancy test kits) or in connection with disordered states of health (blood glucose monitoring devices for diabetes, contact lens solutions, etc.); and food and vitamins being promoted purely for the maintenance of normal health.

Marketing benefit claims

A statement that is designed to promote the sale of a health product. It often highlights a specific product attribute i.e. “longer lasting” or “tastes great”.

A promotional statement designed to inform about the product's availability and benefits so as to form/alter the audience's opinion of the medication. It can be explicit (i.e. text) or implicit (i.e. images), comparative or non-comparative. It can relate to pharmacological or non-pharmacological properties of the product.

Not all statements about a product are "marketing claims of benefit". Common examples of product messaging which are not considered marketing benefit claims include product reconstitution instructions, monitoring instructions, dosing modifications for special populations and storage instructions when these are presented as instructions/burdens rather than features/ benefits (i.e. presented to instruct rather than alter/form the audience's opinion of the medication in a positive way). How a statement is framed can sometimes affect whether it is a marketing benefit claim. For example, the copy "Arbace: Convenience of a single daily dose" is a marketing benefit claim, while "Patients should be instructed to take a single dose daily at the same time each day" is not.

APS
Advertising/Promotional Systems

PSP or PAP
Patient Support Program or Patient Assistance Program
Programs that exist to provide patient timely access to medication, information, and resources intended to help patients stay on track of their therapy.

Real World Data (RWD)
Real world data are data relating to patient status and/or the delivery of health care routinely collected from a variety of sources in real-world settings.

Real World Evidence (RWE)
Real world evidence is the evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of real-world data.