Advertising Standards Canada
Consumer Drug Section
Therapeutic Comparative Advertising SOP

Part I: Directive &
Part II, Section 3: Comparison of Side Effect Profiles and Other Safety Information

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This Standard Operating Procedure (SOP) applies to consumer-directed advertisements for nonprescription drugs that contain therapeutic comparative claims. This SOP describes the steps ASC's Consumer Drug Section will follow to evaluate whether a therapeutic comparative claim complies with the Health Products and Food Branch's (HPFB) Policy: Therapeutic Comparative Advertising Directive and Guidance Document.

In addition to meeting the provisions of the HPFB's Directive and Guidance Document (March 2001) and ASC's corresponding SOP, consumer-directed therapeutic comparative advertising for nonprescription drugs must also meet the provisions of the *Food and Drugs Act* and *Regulations*, the *Consumer Drug Advertising Guidelines*, and other relevant HPFB policies, guidelines and procedures.

NOTE: ASC will review only those therapeutic comparative claims that are consistent with the HPFB Terms of Market Authorization[1] for each of the compared drugs/ingredients. Advertisers must submit new therapeutic claims to HPFB for review and approval.

[1] HPFB Definition: "Terms of Market/Product Authorization" / "Authorized Product Information": The Terms of Market Authorization are comprised of all information in the PM that accompanies the NOC and in the document that assigns a DIN and related product labelling for drugs that are subject to the requirements of Division 8, Part C of the Regulations (new drugs). For drugs that are not subject to Division 8, Part C of the Regulations, the Terms of Market Authorization are identified in the document that assigns a DIN and related product labelling. This information is derived from the review of information on the drug product that is required to be submitted for regulatory review and authorization, as outlined in the Food and Drugs Act and Regulations and interpretive guidelines and policies.

Part I: Directive Requirements

Desired Therapeutic Comparative Claim:

_____

_____

HPFB Directive Requirement 1:
1 (a) Compared drugs have an authorized indication for use in common, **and**
1 (b) The comparison is related to that use, **or**
1 (c) In addition to the common indication for use, a second authorized indication is claimed as an added benefit of the advertised drug.

Assessment:
Name of Advertised drug/ingredient:

_____

Authorized Indication(s) for Advertised drug/ingredient:

_____

Name of Comparator drug/ingredient:

_____

Authorized Indication(s) for Comparator drug/ingredient:

_____

Review Decision:
Based on foregoing assessment, do the compared drugs/ingredients have an authorized indication for use in common?

- ❑ **Yes:** Proceed with review. Go to next Review Decision.
- ❑ **No:** Resubmit/Reject Submission*

Review Decision:
Is the comparison related to the shared authorized indication for use?

- ❑ **Yes:** Proceed with review. Go to Directive Requirement 2.
- ❑ **No:** If no, then, in addition to common indication for use, is a second authorized indication being claimed as an added benefit of the Advertised drug?
  - ❑ **No:** Resubmit/Reject Submission*
  - ❑ **Yes:** If yes, is the second claimed indication consistent with the Terms of Market Authorization for the Advertised drug?
    - ❑ **Yes:** Proceed with review. Go to Directive Requirement 2.
    - ❑ **No:** Resubmit/Reject Submission*

* As per standard ASC clearance procedures, advertisers have the opportunity to discuss and respond to ASC concerns before a submission is rejected.

HPFB Directive Requirement 2:
The comparison is drawn between drugs under the same conditions of use, e.g. at equivalent part(s) of their authorized dosage ranges in a similar population.

Health Canada Note:
Directive Requirement 2 precludes Extra vs. Regular Strength comparisons between brands. However, should a manufacturer want to compare different dosage ranges within a brand, a case-by-case assessment should be done.

Assessment:
Claimed Conditions of Use of Advertised drug/ingredient:

Authorized Conditions of Use of Advertised drug/ingredient:

Review Decision:
Are the claimed and authorized conditions of use for the Advertised drug/ingredient consistent?
- ❑ **Yes:** Proceed with review. Go to next Assessment section.
- ❑ **No:** Resubmit/Reject Submission*

Assessment:
Claimed Conditions of Use of Comparator drug/ingredient:

Authorized Conditions of Use of Comparator drug/ingredient:

Review Decision:
Are the claimed and authorized conditions of use for the Comparator drug/ingredient consistent?

❑ **Yes:** Proceed with review. Go to Directive Requirement 3.

❑ **No:** Resubmit/Reject Submission*

HPFB Directive Requirement 3:
The claim does not conflict with the Terms of Market Authorization of the compared products.

Assessment:
Evaluate comparative claim against the authorized product information for advertised and compared product.

For drugs subject to Division 8, Part C of the Regulations, consult HPFB Policy: *"Changes to Marketed New Drugs".*

For drugs assigned a DIN but not subject to Division 8, Part C of the Regulations, consult section C.01.014.4 of the Regulations, provided the claim does not render the product subject to Division 8, Part C of the Regulations.

Health Canada Note:
If the parameters, including endpoints, on which authorization was based are the same, then this would not constitute an expansion of the Terms of Market Authorization. If claims on which comparisons were based were not contained in the Product Monographs or other authorized product information, then sponsors will be required to prepare a submission for Health Canada.

In instances where ASC is uncertain as to whether the claims are an expansion of the Terms of Market Authorization, ASC may consult MHPD for a decision.

Terms of Market Authorization for Advertised drug/ingredient:

_____

_____

Review Decision:
Does the claim conflict with the Terms of Market Authorization of the Advertised drug/ingredient?

❑ **Yes:** Resubmit/Reject Submission*. Sponsors must prepare a submission to HC.

❑ **No:** Proceed with review. Go to next Assessment section.

Assessment:
Terms of Market Authorization for Comparator drug/ingredient:

Review Decision:
Does the claim conflict with the Terms of Market Authorization of the Comparator drug/ingredient?

- ❑ **Yes:** Resubmit/Reject Submission*.
- ❑ **No:** Proceed with review. Go to Directive Requirement 4.

HPFB Directive Requirement 4:
The claim is of clinical relevance to humans, i.e., relevant to treatment selection, and where this is not readily apparent, its clinical relevance can be justified by the sponsor.

Assessment:
Evaluate the therapeutic comparative claim against the HPFB definition "Clinical Relevance to the Consumer":
"Clinical relevance to the consumer refers to the practical value of the claim itself in assisting consumers to select an appropriate therapy. Practical value means offering a clinically significant benefit or advantage which can easily be understood and seen by the consumer when one treatment is compared to another, e.g., lack of side effect, ease of administration, faster onset of action, longer lasting relief, etc".

Review Decision:
Does the claim describe a clinically significant benefit or advantage which can easily be understood and seen by the consumer when one treatment is compared to another? Where not readily apparent, consider Advertiser's rationale.

- ❑ **Yes:** Proceed with review. Go to Directive Requirement 5.
- ❑ **No:** Resubmit/Reject Submission*

HPFB Directive Requirement 5:
The evidence generated to substantiate the claim is conclusive based on:

(i) Consideration of all relevant data, and
(ii) Scientifically accurate, unbiased, reproducible data obtained from studies conducted and analyzed to current scientific standards using established research methodologies and validated end points, and
(iii) Appropriate interpretation of the data (Note: extrapolation beyond the actual conditions of the supporting studies is not acceptable).

Assessment:
ASC will deem HPFB Directive Requirement to be met, if the supporting data meets the requirements set out in the Guidance Document Efficacy sections: 1-1 Standards of Evidence, 1-2

Test and Reference Products, 1-3 Clinical Study Design / Methodology / Analysis, and 1-4 Interpretation (Refer to Part II: Guidance Document).

Note: As required, with prior consent from the Advertiser, ASC may have the clinical studies evaluated by an external expert selected from its Roster of Experts.

Go to Directive Requirement 6(i).

HPFB Directive Requirement 6: The claim and its presentation should:
(i) Identify the compared entities[2], **and**

Assessment:

How Advertised drug/ingredient is identified in ad:

Other products in Advertised drug/ingredient product line:

How Comparator drug/ingredient is identified in ad:

Other products in Comparator drug/ingredient product line:

Review Decision:

Does the ad clearly identify the **Advertised drug/ingredient**? (There should be no confusion with other products in the same product line, or with other similar products.)

- ❑ **Yes:** Proceed with review. Go to next Review Decision.
- ❑ **No:** Resubmit/Reject Submission*

[2] i.e. hanging comparisons such as "better", "faster acting" are unacceptable, as are vague statements such as "compared to the leading brand…"

Review Decision:
Does the ad clearly identify the **Comparator drug/ingredient**? (There should be no confusion with other products in the same product line, or with other similar products.)

❑ **Yes:** Proceed with review. Go to Directive Requirement 6(ii).

❑ **No:** Resubmit/Reject Submission*

HPFB Directive Requirement 6: The claim and its presentation should:
(ii) Identify the medicinal use related to the claim where this is not readily apparent[3]; **and**

Assessment and Review Decision:
Do the claim and its presentation identify the medicinal use related to the claim where this is not readily apparent?

❑ **Yes:** Proceed with review. Go to Directive Requirement 6(iii).

❑ **No:** Resubmit/Reject Submission*

HPFB Directive Requirement 6: The claim and its presentation should:
(iii) Not obscure the therapeutic use of the advertised product/ingredient[4], **and**

Assessment and Review Decision:
Is the therapeutic use of the Advertised product/ingredient obscured?

❑ **Yes:** Resubmit/Reject Submission*

❑ **No:** Proceed with review. Go to Directive Requirement 6(iv).

HPFB Directive Requirement 6: The claim and its presentation should:
(iv) Not attack the compared drug product(s)/ingredient(s) in an unreasonable manner, **and**

Assessment:
Evaluate the therapeutic comparative claim against section 9(1) of the Food and Drugs Act: *"No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety".*

For example, it is acceptable to promote that a particular drug has an additional therapeutic indication (due to an additional ingredient) that another product does not have. It is not acceptable, however, to suggest that the single ingredient, single indication product is not as effective or should not be used because it only relieves one symptom instead of two.

[3] Where the advertised entity has more than one indication for use, it should be clear to which use the claim refers
[4] i.e., the comparative claim should be afforded no more prominence than the therapeutic use.

It is misleading to claim superior efficacy for the CONDITION based on the presence of an additional active ingredient. It is misleading for the advertised product to claim superior efficacy for a multi-symptom CONDITION that the compared product was never intended to relieve.

For example:
Menstrual Product X contains an active ingredient for relief of menstrual cramps.
Menstrual Product Y contains the same active as X for menstrual cramps, along with an additional ingredient for bloating.

It is misleading to claim:
"Product Y is more effective than X for menstrual symptoms because it relieves cramps and bloating." This claim is misleading since Product X was never intended to relieve bloating.
The claim would be acceptable if reformulated to claim an added therapeutic benefit due to the presence of an additional active ingredient. For example: "Unlike Product X, which only relieves menstrual cramps, Product Y also relieves bloating".

Review Decision:

Does the comparative therapeutic claim create an erroneous impression regarding the character, value, quantity, composition, merit or safety of the **Comparator drug/ingredient?**

- ❑ **Yes:** Resubmit/Reject Submission*
- ❑ **No:** Proceed with review. Go to Directive Requirement 6(v).

HPFB Directive Requirement 6: The claim and its presentation should:
(v) Be expressed in terms, language and graphics that can be understood by the intended audience.

Assessment:

Review terms and language used to express comparative therapeutic claim.
Review graphics used to express comparative therapeutic claim (graphics should not require disclosure of study parameters or medical/scientific knowledge in order to be accurately interpreted).

Review Decision:

Is the comparative claim expressed in a manner that will be understood by the consumer audience?

- ❑ **Yes:** Proceed with review. Go to Guidance Document Requirement 1.
- ❑ **No:** Resubmit/Reject Submission*

ASC Therapeutic Comparative Advertising SOP
Part II: Guidance Document

Section 3: Comparison of Side Effect Profiles and Other Safety Information

Note: For Side Effect or Other Safety Information comparative claims, Advertisers must also meet the requirements set out in the HPFB Directive. See pages 1-8 of this SOP.

Desired Therapeutic Comparative Claim:

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_____

Guidance Document Excerpt:
*Statements that compare the side effect and safety profiles, of drug products or ingredients, may be made in consumer-directed advertising provided the general provisions of the **Directive**, this **Guidance Document** and this **Section** are met.*

Section 3-1

HPFB Guidance Document Requirement 3-1(a):
A comparison of side effects and other safety parameters may be done if the following conditions (where applicable) are met:
(a) the approved indications are disclosed in the advertisement;

Assessment:
Advertised Product/ingredient:

_____

Approved Indication(s)[5] of Advertised product/ingredient as per Terms of Market Authorization:

_____

_____

Advertised Indication(s) of Advertised product/ingredient:

_____

_____

[5] HPFB Definition: "Terms of Market Authorization" are comprised of information in the Product Monograph and the document that assigns a Drug Identification Number (DIN) (including related product labelling material and prescribing information) authorized by the HPFB upon issuance of the DIN.

Comparator Product/ingredient:

Approved Indication(s)[1] of Comparator product/ingredient as per Terms of Market Authorization:

Advertised Indication(s) of Comparator product/ingredient:

Review Decision:
Are the approved indications for each product/ingredient clearly identified in the advertisement?
❑ **Yes:** Proceed with review. Go to 3-1(b) (1).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(b):
3-1(b) (1): the side effect is self-limiting…

Assessment:
Review Advertiser's evidence to support that compared side effect is self-limiting (i.e., that it usually resolves on its own):

Review Decision:
Is the compared side effect self-limiting?
❑ **Yes:** Proceed with review. Go to 3-1(b) (2).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(b):
3-1(b) (2): …self-recognizable…

* As per standard ASC clearance procedures, advertisers have the opportunity to discuss and respond to ASC concerns before a submission is rejected.

Assessment 3-1(b) (2):
Review Advertiser's evidence to support that this side effect is self-recognizable (i.e., that consumer can accurately identify symptom without consulting a health care professional):

Review Decision:
Is the compared side effect self-recognizable?
❑ **Yes:** Proceed with review. Go to 3-1(b) (3).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(b):
3-1(b) (3): …understandable, and…

Assessment and Review Decision:
Is the compared side effect generally understandable to consumers? (Where not readily apparent, consider Advertiser's rationale.)
❑ **Yes:** Proceed with review. Go to 3-1(b) (4).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(b):
3-1(b) (4): …of clinical relevance to the consumer.
(e.g. dizziness, drowsiness, dry mouth)

Assessment and Review Decision:
Based on previously completed assessment of clinical relevance (Part I: Directive, HPFB Requirement 4), does the claim meet the criteria for "clinical relevance"?
❑ **Yes:** Proceed with review. Go to 3-1(c).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(c):
Given the broad spectrum of nonprescription drugs, all comparisons for products that
3-1(c) (1): …have complex side effect/safety profiles…

Assessment:
Consult Terms of Market Authorization for both products/ingredients.

In general, products/ingredients subject to a Category IV Monograph or Labelling Standard are considered to be "low risk" (i.e. "uncomplicated side effect/safety profile") products/ingredients, relatively speaking. Products/ingredients subject to Division 8 are generally considered to be more complex.

Review Decision:
Does the **Advertised product/ingredient** have a complex side effect/safety profile, (e.g., is medical or scientific knowledge required to understand the benefit/risk ratio of using the product/ingredient)?

❑ **Yes:** Go to 3-1(c) (2).
❑ **No:** Go to next Review Decision.

Review Decision:
Does the **Comparator/ingredient** have a complex side effect/safety profile, (e.g., is medical or scientific knowledge required to understand the benefit/risk ratio of using the product/ingredient)?

❑ **Yes:** Go to 3-1(c) (2).
❑ **No:** Proceed with review. Go to 3-1(d).

HPFB Guidance Document Requirement 3-1(c):
3-1(c) (2) …must present the benefits and the risks of each drug to provide an accurate, balanced and fair representation;

Assessment and Review Decision:
Does the advertisement present the benefits and risks of each drug to provide an accurate, balanced and fair representation?

❑ **Yes:** Go to 3-1(d).
❑ **No:** Resubmit/Reject submission*

HPFB Guidance Document Requirement 3-1(d):
As the complexity or seriousness of adverse effects and safety concerns increase, the access to easily understandable patient information for the sponsor's drug must increase and be readily available for consumers;

Assessment:
Review the Terms of Market Authorization for the Advertised product/ingredient.

In general, products/ingredients subject to a Category IV Monograph or Labelling Standard are considered to be "low risk" (i.e. "uncomplicated side effect/safety profile") products/ingredients, relatively speaking. Products/ingredients subject to Division 8 are generally considered to be more complex.

Review Decision:

Does the Advertised product/ingredient have a complex safety profile or possible serious adverse effects?

- ❑ **No:** Proceed with review. Go to 3-1(e).
- ❑ **Yes:** If yes, has the Advertiser provided a written attestation to ASC that easily understandable patient information is readily available to consumers for the advertised product?
  - ❑ **Yes:** Proceed with review. Go to 3-1(e).
  - ❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(e):

Sponsors should always provide easy access to the complete patient information on proper drug use, (e.g., patient package insert, Product Monograph) which may include simultaneous dissemination to targeted audiences in various mediums such as print, 1-800 information lines, broadcast, Internet etc. (the amount of information made available would increase especially as complexity of comparisons increase);

Assessment and Review:

Has the Advertiser provided a written attestation to ASC stating that the Advertiser has provided easy access to complete patient information on proper product/ingredient use of the advertised product?

- ❑ **Yes:** Proceed with review. Go to 3-1(f).
- ❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(f):

Comparisons that require medical/scientific knowledge to accurately interpret the results are to be avoided in consumer directed advertising;

Assessment and Review Decision:

Does the claim require medical/scientific knowledge to be accurately interpreted?

- ❑ **Yes:** Resubmit/Reject Submission*
- ❑ **No:** Proceed with review. Go to 3-1(g) (1).

HPFB Guidance Document Requirement 3-1(g):

3-1(g) (1): The advertisement should not impact negatively on patient compliance…

Assessment and Review Decision:
Does the advertisement impact negatively on patient compliance? (e.g., Does the advertisement suggest that one does not have to take or should not take an indicated medicine, or does not have to take it as directed)?

❑ **Yes:** Resubmit/Reject Submission*

❑ **No:** Proceed with review. Go to 3-1(g) (2).

HPFB Guidance Document Requirement 3-1(g):
3-1(g) (2): …nor deter or cause delay from seeking appropriate treatment…

Assessment and Review Decision:
Does the advertisement deter or cause delay from seeking appropriate treatment?

❑ **Yes:** Resubmit/Reject Submission*

❑ **No:** Proceed with review. Go to 3-1(g) (3).

HPFB Guidance Document Requirement 3-1(g):
3-1(g) (3): Provisions should be included to refer consumers to a qualified health professional (pharmacist, nurse, physician etc) if consumers require additional information or if symptoms persist;

Assessment and Review Decision:
Does the advertisement include provisions that refer consumers to a qualified health care professional if consumers require additional information or if symptoms persist?

❑ **Yes:** Proceed with review. Go to 3-1(h).

❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-1(h):
The advertisement does not attack the compared drug product(s)/ingredient(s) in an unreasonable, disparaging manner;

Assessment:
Assess whether the advertisement "attacks the compared drug product(s)/ingredient(s) in an unreasonable, disparaging manner", based on the following criteria extracted from the Guidance Document:

Guidance Document Excerpt:
Comparison of drug interactions, complex adverse reactions, contraindications, precautions, risks and other safety factors are difficult to present to consumers without being potentially misleading or deceptive.
3-1(h) (1): *This is especially difficult to achieve in most advertising media which are limited in time and length.*

Assessment and Review Decision:

Is the advertisement of sufficient time and length to present the comparison without being potentially misleading or deceptive?

❑ **Yes:** Go to 3-1(h) (2)

❑ **No:** Resubmit/Reject Submission*

Guidance Document Excerpt:

3-1(h) (2): *Furthermore, generalizations concerning comparisons of product effects may not always be applicable to each individual because other confounding factors such as the individual's medical conditions, use of multiple drug therapies etc, may directly impact on the selection of appropriate drug therapy.*

Assessment and Review Decision:

Does the advertisement make generalizations about the applicability of the comparison to all consumers?

❑ **No:** Go to 3-1(h) (3)

❑ **Yes:** If yes, is the generalization applicable to each and every consumer (consider whether confounding factors may be present such as the individual's medical condition, use of multiple drug therapies, etc)?

- ❑ **Yes:** Go to 3-1(h) (3)
- ❑ **No:** Resubmit/Reject Submission*

Guidance Document Excerpt:

3-1(h) (3): *It is considered misleading to focus on a comparison of one particular side effect or safety parameter to show a benefit, when in fact the product/ingredient may show other side effects or safety concerns that compare unfavorably with the comparator product*

Assessment and Review Decision:

Based on a comparison of the Terms of Market Authorization of both drugs, does the advertisement focus on a comparison of one particular side effect or safety parameter to show a benefit, when in fact the product/ingredient may show other side effects or safety concerns that compare unfavorably with the comparator?

❑ **Yes:** Resubmit/Reject Submission*

❑ **No:** Go to 3-1(h) (4)

Guidance Document Excerpt:

3-1(h) (4): *In most cases, a fair and balanced presentation of comparable effects can only be carried out when a complete comparison of the benefits and risks of two products/ingredients is done. The overall safety of a drug depends on many factors and to highlight only one aspect provides an incomplete picture of the product merit and may be inherently misleading.*

Assessment and Review Decision:
As evaluated under 3-1(c), is a complete comparison of the benefits and risks of each drug product necessary to ensure a fair and balanced comparison?

❑ **Yes:**If yes, has a complete comparison of the benefits and risks of each drug been presented?
- ❑ **Yes:** Go to 3-1(h) (5)
- ❑ **No:** Resubmit/Reject Submission*

❑ **No:** Go to 3-1(h) (5)

Guidance Document Excerpt:
3-1(h) (5): *Even in such a complete comparison, caution is required because the message may still be misleading or confusing to the consumer if evaluation requires medical/scientific knowledge to accurately interpret that information.*

Assessment and Review Decision:
Is medical/scientific knowledge required to accurately interpret the claim as presented?
❑ **Yes:** Resubmit/Reject Submission*
❑ **No:** Go to 3-1(h) (6).

Guidance Document Excerpt:
3-1(h) (6): *Claims based on differences that are subtle or require the disclosure of study parameters in order to accurately interpret the results, obviously should not be advertised to the public but only to the health professional who has the expertise to understand the scientific complexities and nuances.*

Assessment and Review Decision:
Is the claim based on differences that are subtle or that require the disclosure of study parameters in order to accurately interpret the results?
❑ **Yes:** Resubmit/Reject Submission*
❑ **No:** Go to 3-1(h) (7).

Guidance Document Excerpt:
3-1(h) (7): *Therefore, if such comparisons are targeted to the public, they must be considered with caution as the amount of information required to provide a fair and balanced view of the relative safety may exceed the amount of information that can reasonably be provided to and/or understood by the consumer in most consumer advertising messages.*

Assessment and Review Decision:
Does the amount of information required to provide a fair and balanced view of the relative safety of the advertised and the compared drugs exceed the amount of information that can be reasonably provided to and/or understood by the consumer in the submitted advertisement?
❑ **Yes:** Resubmit/Reject Submission*
❑ **No:** Go to 3-2.

Section 3-2
Standard of Evidence

HPFB Guidance Document Requirement 3-2(a):
3-2(a) (1): The side effects and safety parameters compared must be limited to those that are cited in the HPFB approved Terms of Market Authorization[6] and/or labelling of the products compared (for a product vs. product comparison),

Health Canada Note:
Only Health Canada may review and approve side-effect incidence claims for incidence greater than placebo. This applies to all drugs, not just new drugs.

Health Canada Note:
ASC has the authority to review and approve absence of side effect claims in consumer advertising i.e., side-effect incidence less than or equal to placebo.

Health Canada Note:
Claims based on side-effect or safety information that are found in the scientific literature or meet the requirements of 3-2(b), (c), or (d), but ARE NOT CITED in the Terms of Market Authorization are NEW therapeutic claims requiring HC approval.

Since post-market surveillance data and incidence of side effects evolve continuously, it is of paramount importance that ASC remains up-to-date regarding emerging new drug safety information disseminated by Health Canada.

Monographs may have ongoing reviews and new therapeutic and safety claims are subject to Health Canada market authorizations. Category IV Monographs and Labelling Standards have not been updated recently and cannot be used for comparative advertising purposes, as they are not representative of the available body of evidence. ASC should always consult with HC in case of doubt.

Assessment:
For Product to Product comparisons, go to next Assessment and Review Decision
For Ingredient to Ingredient comparisons, go to 3-2(a) (2).

[6] HPFB Definition: "Terms of Market Authorization" are comprised of information in the Product Monograph and the document that assigns a Drug Identification Number (DIN) (including related product labelling material and prescribing information) authorized by the HPFB upon issuance of the DIN.

Assessment:
Side effect and safety parameters compared:

Advertised product:
Side effect and safety parameters as per Terms of Market Authorization:

Comparator product:
Side effect and safety parameters as per Terms of Market Authorization:

Review Decision:
Is the comparison limited to side effects and safety parameters in the HPFB approved Terms of Market Authorization for the Advertised and Comparator products?

- ❑ **Yes:** Proceed with review
  - For Product to Product (Brand Name A to Brand Name B) comparisons, go to 3-2(b)
  - For Ingredient to Ingredient and Product to Ingredient comparisons, go to 3-2(c)
  - For Product/Ingredient to All Other Canadian Products/Ingredients for the Same Indication, go to 3-2(d)
- ❑ **No:** Resubmit/Reject submission*

HPFB Guidance Document Requirement 3-2(a): The side effects and safety parameters compared must be limited to those that are cited in the HPFB approved Terms of Market Authorization and/or labelling of the products compared (for a product to product comparison, **3-2(a) (2):** or of those currently required to be referenced in the HPFB approved PM or labelling of products containing only those ingredients compared (for an ingredient vs. ingredient comparison)

Assessment:
Side Effect and safety parameters compared:

Advertised Ingredient:
Side effect and safety parameters as per Terms of Market Authorization:

Comparator Ingredient:
Side effect and safety parameters as per Terms of Market Authorization:

Review Decision:
Are the side effects/safety parameters compared limited to those currently required to be referenced in the HPFB approved PM or labelling of products containing only those ingredients compared (for an ingredient to ingredient comparison)?

❑ **Yes:** Proceed with review
- For Ingredient to Ingredient and Product to Ingredient comparisons, go to 3-2(c)
- For Product/Ingredient to All Other Canadian Products/Ingredients for the Same Indication, go to 3-2(d)

❑ **No:** Resubmit/Reject submission*

Section 3-2(b)
Product to Product (Brand Name A vs. Brand Name B) Comparison

HPFB Guidance Document Requirement 3-2(b)(i):
To support product-to-product comparison of side effect and safety profiles, the evidence based on clinical or other studies must be supported by
3-2(b)(i) (1): at least two…

Health Canada Note:
*This requirement does not preclude the use of well-designed **retrospective** studies. Well-designed retrospective studies can be used as long as they are conducted according to current scientific standards, e.g., limitations and potential biases must be accounted for. Pharmaco-epidemiological expertise may be required to review such studies.*

Assessment and Review Decision:
Is claim supported by at least two studies?

❑ **Yes:** Proceed with review. Go to 3-2(b)(i) (2).

❑ **No:** If No, is the claim supported by one study?

❑ **Yes:** If yes,

Guidance Document Excerpt:

"*Reproducibility of efficacy or product superiority can normally be obtained through the internationally accepted standard of two independent, randomized clinical trials. At least two studies provide the confirmatory evidence required for a reasonable expectation that the results are accurate.*

However, the review Bureau[7] may determine that one large well-conducted *clinical trial adequately powered may suffice. In such circumstances, a rationale to use only one clinical trial must be provided and this must be discussed with the Health Products and Food Branch on a case-by-case basis. Also, the study must be designed in the very beginning to show superiority".*

Review Decision:

Has the Advertiser provided evidence to ASC that Health Products and Food Branch has determined that one large well-conducted adequately powered clinical trial designed to show superiority is sufficient to substantiate therapeutic comparative advertising claims?

❑ **Yes:** Proceed with review. Go to 3-2(b)(i) (3).

❑ **No:** Reject Submission*

[7] "Review Bureau" refers to the relevant Health Canada Bureau

HPFB Guidance Document Requirement 3-2(b)(i) (2):
… independent[8]…

Assessment and Review Decision:
Were the studies conducted on a different set of patients, in two separate trials (e.g., one study cannot be a subset of the other, or an interim analysis of the other)?
❑ **Yes:** Proceed with review. Go to 3-2(b)(i) (3).
❑ **No:** Resubmit/Reject submission* or Go to 3-2(b)(iii).

HPFB Guidance Document Requirement 3-2(b)(i) (3):
…well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards, which meet the conditions outlined in **Sections 1-1(b)…**

Assessment:
Complete assessment as per 1-1(b).

Review Decision:
Are the requirements of 1-1(b) met?
❑ **Yes:** Go to 3-2(b)(i) (4).
❑ **No:** Resubmit/Reject Submission* or go to 3-2(b)(iii).

HPFB Guidance Document Requirement 3-2(b)(i) (4):
…well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards, which meet the conditions outlined in Sections 1-1(b), **1-2…**

Assessment:
Complete assessment as per 1-2.

Review Decision:
Are the requirements of 1-2 met?
❑ **Yes:** Go to 3-2(b)(i) (5).
❑ **No:** Resubmit/Reject Submission* or go to 3-2(b)(iii).

[8] The term 'independent' is not meant to exclude company-sponsored clinical trials.

HPFB Guidance Document Requirement 3-2(b)(i) (5):
…well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards, which meet the conditions outlined in Sections 1-1(b), 1-2, **1-3(a)**…

Assessment:
Complete assessment as per 1-3(a).

Review Decision:
Are the requirements of 1-3(a) met?
❑ **Yes:** Go to 3-2(b)(i) (6).
❑ **No:** Resubmit/Reject Submission* or go to 3-2(b)(iii).

HPFB Guidance Document Requirement 3-2(b)(i) (6):
…well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards, which meet the conditions outlined in Sections 1-1(b), 1-2, 1-3(a) and **1-4(c)**.

Assessment:
Complete assessment as per 1-4(c).

Review Decision:
Are the requirements of 1-4(c) met?
❑ **Yes:** Go to 3-2(b)(ii).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-2(b)(ii):
3-2(b)(ii) (1): Sponsors must provide an attestation that the results of the supporting studies reflect the "body of available evidence"[9] in the public domain and have not been superseded by contradictory findings…

Assessment and Review Decision:
Has the Advertiser provided a written attestation that the results of supporting studies reflect the "body of available evidence" and have not been superseded by contradictory findings?
❑ **Yes:** Proceed with review. Go to 3-2(b)(ii) (3).
Note: If ASC is aware of evidence that might invalidate the attestation, this will be discussed with the Advertiser, subject to the limits of ASC's confidentiality policy.

[9] 'Body of available evidence' is defined as 'the information reasonably available as published or unpublished studies, other data in respected medical literature, generally available in the public domain at that point in time'.

❑ **No:** If no, request attestation.

If attestation is available, does it meet the requirements of 3-2(b)(ii) (1)?

❑ **Yes:** Go to 3-2(b)(ii) (3).

❑ **No:** Go to 3-2(b)(ii) (2).

If attestation is unavailable: Go to 3-2(b)(iii).

HPFB Guidance Document Requirement 3-2(b)(ii):
3-2(b)(ii) (2): …or, an explanation/justification of any difference should be provided for consideration.

Assessment and Review Decision:

Has the Advertiser provided sufficient justification for any deviation from the available body of evidence or for contradictory findings?

❑ **Yes:** If yes, is justification satisfactory based on methodologies used and recognized the scientific community?

❑ **Yes:** Proceed with review. Go to 3-2(b)(ii) (3).

❑ **No:** Resubmit/Reject Submission*

❑ **No:** Proceed with review. Go to 3-2(b)(iii).

HPFB Guidance Document Requirement 3-2(b)(ii):
3-2(b)(ii) (3): The "attestation" must contain the results of either a meta-analysis or a systematic review[10] to show that the two studies reflect the body of medical evidence, provided the conditions in Section 1-2 are met for International data.

Review Decision:

Does the attestation contain the results of either a meta-analysis or a systematic review[10] of the medical literature to show that the two studies reflect the body of medical evidence?

❑ **Yes:** Proceed with review. Go to next Review Decision.

❑ **No:** Resubmit/Reject Submission*

Review Decision:

For International data, do the results presented in the attestation meet the conditions in Section 1-2?

❑ **Yes:** Proceed with review. Go to 3-2(b)(iii).

❑ **No:** Resubmit/Reject Submission*

❑ **N/A:** Proceed with review. Go to 3-2(b)(iii).

[10] HPFB Definition: "Systematic Review": A summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies.

HPFB Guidance Document Requirement 3-2(b)(iii):
Comparison of the authorized product information may be used to support comparison of the side effect and safety profile of the advertised product in contrast to the compared product…

Assessment and Review Decision:
Is the claim supported by a comparison of the authorized product information for each product?
- ❑ **Yes:** Go to 3-2(b)(iii) (1).
- ❑ **No:** Go to 3-3.

HPFB Guidance Document Requirement 3-2(b)(iii):
…provided that:
3-2(b)(iii) (1): Effects unique to differences in formulation and route of administration have been accounted for;

Assessment and Review Decision:
Have any effects unique to differences in formulation and route of administration been accounted for?
- ❑ **Yes:** Go to 3-2(b)(iii) (2).
- ❑ **No:** Resubmit/Reject Submission*
- ❑ **N/A:** Go to 3-2(b)(iii) (2)

HPFB Guidance Document Requirement 3-2(b)(iii):
3-2(b)(iii) (2): The study populations, methodologies, dosing and measurement criteria are comparable;

Assessment and Review Decision:
Are the study populations, methodologies, dosing and measurement criteria comparable?
- ❑ **Yes:** Go to 3-2(b)(iii) (3)
- ❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-2(b)(iii):
3-2(b)(iii) (3): The side-by-side presentation of adverse events and safety data are comparable.

Otherwise, adverse event and safety data quoted from two or more Product Monographs, derived from studies that were not head-to-head and were not comparable are unacceptable.

Assessment and Review Decision:

Are the side-by-side presentation of adverse events and safety data comparable?

- ❑ **Yes:** Go to 3-3.
- ❑ **No:** Resubmit/Reject Submission*
- ❑ **N/A:** Go to 3-3.

Section 3-2(c)
Ingredient to Ingredient and Product to Ingredient Comparisons

HPFB Guidance Document Requirement:
In addition to the criteria outlined in Sections 3-2(a) and (b):

Assessment:
Complete assessment as per Sections 3-2(a) and (b).

Review Decision:
Do the supporting data meet the requirements of Section 3-2(a)?

❑ **Yes:** Proceed with review. Go to next Review Decision.

❑ **No:** Resubmit/Reject Submission*

Review Decision:
Do the supporting data meet the requirements of Section 3-2(b)?

❑ **Yes:** Proceed with review. Go to 3-2(c)(i).

❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-2(c)(i):
Statements that compare the side effect and safety profiles of drug ingredients in terms of their presence or absence[11] should be based on evidence obtained through a systematic review[12] relating to the compared ingredients.

Health Canada Note:
The requirements of 3-2(a) and 3-2(c)(i) are meant to be complementary. The expression "Systematic Review[13]" (in 3-2(c)) is used in order to ascertain that every body of available evidence is covered to preclude circumstances where the information would not yet be included in the Product Monograph or in the labelling but evidence exists in scientific literature. Section 3-2(c) covers ingredient to ingredient comparisons where specific products are not identified, therefore a systematic review must be done to gather all available evidence.

Note: *Health Canada to clarify whether comparisons of safety/side effect information that DO NOT appear in the TMA but meet the requirements of 3-2(b), (c) or (d) are consistent with the TMA and thus subject to review by ASC, or inconsistent with the TMA, and thus subject to review by HC.*

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[11] As per the requirements of the Consumer Drug Advertising Guideline (Amendment October 1991) Absence of Side Effects section, p. 21a-21c.

[12] It is recognized that it may not be possible to include a quantitative analysis. However, quantitative claims must be based on quantitative data.

Health Canada Note:
With respect to Terms of Market Authorization that list a side effect but do not quantify its incidence, only Health Canada may review and approve data that quantify side effect incidence.

[13] HPFB Definition: 'Systematic Review': A summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies.

Health Canada Note:
Only Health Canada may review and approve side-effect incidence claims for incidence greater than placebo. This applies to all drugs, not just new drugs.

Health Canada Note:
ASC has the authority to review and approve absence of side effect claims in consumer advertising i.e., side-effect incidence less than or equal to placebo.

Health Canada Note:
With respect to Terms of Market Authorization that list a side effect but do not quantify its incidence, only Health Canada may review and approve data that quantify side effect incidence.

Assessment and Review Decision:

Does the claim compare the side effect and/or safety profiles of ingredient in terms of their presence or absence?

- ❑ **No:** Proceed with review. Go to 3-2(c)(ii).
- ❑ **Yes:** If yes, is the claim based on evidence obtained through a systematic review of the medical literature relating to the compared ingredients?
  - ❑ **Yes:** Proceed with review. Go to next Assessment and Review Decision.
  - ❑ **No:** Resubmit/Reject Submission*

Assessment and Review Decision:

Does the claim compare side effect and/or safety profiles in terms of their absence?

- ❑ **No:** Proceed with review. Go to 3-2(c)(ii).
- ❑ **Yes:** If yes, are the requirements of the HPFB Policy: Absence of Side Effect Claims for Nonprescription Drugs (1990.06.20) met?
  - ❑ **Yes:** Proceed with review. Go to 3-2(c)(ii).
  - ❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-2(c)(ii):

With respect to a comparison of the incidence of side effects of ingredients, the method of quantifying the incidence must be identical for all compared entities, and the data and method of calculation must be provided.

Health Canada Note:
Only Health Canada may review and approve side-effect incidence claims for incidence greater than placebo. This applies to all drugs, not just new drugs.

Health Canada Note:
ASC has the authority to review and approve absence of side effect claims in consumer advertising i.e., side-effect incidence less than or equal to placebo.

Health Canada Note:
With respect to Terms of Market Authorization that list a side effect but do not quantify its incidence, only Health Canada may review and approve data that quantify side effect incidence.

Assessment:
As per the Health Canada Notes above, only HC may review and approve incidence claims. Therefore, if the incidence claim appears in the Terms of Market Authorization of a product containing only those ingredients compared (as per 3-2(a)), ASC will deem requirement 3-2(c)(ii) to be met.

Review Decision:
Does the incidence claim appear in the Terms of Market Authorization of a product containing only those ingredients compared?

- ❑ **No:** Resubmit/Reject Submission*
- ❑ **Yes:** Proceed with review. Go to 3-3.

Section 3-2(d)
Product/Ingredient to all Other Canadian Products/Ingredients for the Same Indication

HPFB Guidance Document Requirement 3-2(d)(i):
Evidence and data generated to support side effect and safety profiles of one product/ingredient versus all others for the same indication should be consistent with the requirements outlined for individual comparison in Section 3-2.

Assessment:
All other Canadian products/ingredients for the same indication:

Product/ingredient 1:_____

Product/ingredient 2:_____

Product/ingredient 3:_____

Product/ingredient 4:_____

Product/ingredient 5:_____

Review Decision:
Has the Advertiser provided to ASC data that compares the Advertised product/ingredient with **each** Canadian Comparator product/ingredient listed above?

❑ **No:** Resubmit/Reject Submission*

❑ **Yes:** If yes, evaluate the data for each of the products/ingredients listed above against the standards cited in Section 3-2.

Review Decision:
Do the data for the Advertised product vs. each of the Canadian Comparator products/ingredients meet the criteria in Section 3-2(a)?
❑ **Yes:** Proceed with review. Go to next Review Decision.
❑ **No:** Resubmit/Reject Submission*

Review Decision:
Refer to all that apply:
-For product to product comparisons:
Do the data for the Advertised product vs. each of the Canadian Comparator products meet the criteria in Section 3-2(b)?
❑ **Yes:** Proceed with review. Go to 3-3.
❑ **No:** Resubmit/Reject Submission*

- For Ingredient to Ingredient or Product to Ingredient comparisons:
Do the data for the Advertised product/ingredient vs. each of the Canadian Comparator ingredients meet the criteria in Section 3-2(c)?
❑ **Yes:** Proceed with review. Go to Section 3-3.
❑ **No:** Resubmit/Reject Submission*

Section 3-3
Test and Reference Products

HPFB Guidance Document Requirements 3-3:
3-3: Refer to Sections 1-2 and 2-2.

Assessment:
Complete assessment as per 1-2/2-2.
Note: The requirements for these sections are identical.

Review Decision:
Are the requirements of 1-2/2-2 met?
- ❑ **Yes:** Proceed with review. Go to 3-4.
- ❑ **No:** Resubmit/Reject Submission*

Section 3-4
Interpretation

HPFB Guidance Document Requirement 3-4(a):
3-4(a) (1): The minimum acceptable level of statistical significance of the measured difference between treatments is $p<0.05$;

Assessment:
Study 1: Level of statistical significance of measured difference between treatments:

Study 2: Level of statistical significance of measured difference between treatments:

Review Decision:
Is the level of statistical significance of the measured difference between the treatments at least $p<0.05$ in each of the studies?
❑ **Yes:** Proceed with review. Go to 3-4(a) (2).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-4(a):
3-4(a) (2): The 95% confidence intervals should also be stated;

Assessment and Review Decision:
Are the 95% Confidence Intervals stated for each of the studies?
❑ **Yes:** Proceed with review. Go to 3-4(b).
❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-4(b):
Evidence of clinical relevance should be presented in order to assist the consumer in selecting an appropriate therapy.[14]

[14] The independent preclearance agency will ensure that the number (e.g. %) representations of data are not misleading to the consumer. For example, in the case of adverse events this may be measured by one of the following: absolute risk reduction or ARR (the difference of the adverse event rates for the two products) or relative risk reduction or odds ratio* or RRR%(the adverse event rate for one product divided by the adverse event rate for the other product multiplied by 100). The number needed to treats (NNT) must also be considered. *Sackett SL, Strauss Se, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*; New York; Churchill Livingstone; Section Ed.:2000.

Assessment and Review Decision:
Based on previously completed assessment of clinical relevance (Part I: Directive, HPFB Requirement 4), does the claim meet the criteria for "clinical relevance"?

❑ **Yes:** Proceed with review. Go to 3-4(c).

❑ **No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 3-4(c):
Failure of the clinical studies to demonstrate a statistically significant difference in the measured effect is not sufficient to enable a claim of equivalence[15] between the compared treatments. Equivalence can only be established using hypotheses structured for assessing equivalence.[16]

Assessment and Review Decision:
Did the clinical studies demonstrate a statistically significant difference in the measured effect?

❑ **Yes:** Proceed with review. Go to ASC standard nonprescription drug advertising clearance review procedures.

❑ **No:** Resubmit/Reject Submission* (equivalence may not be claimed)

[15] HPFB Definition: "Equivalence": Product claims equal or identical performance to another product (Brand A works as well as Brand B at relieving heartburn).
[16] e.g., Section 3.3.2, ICH E9 document on Statistical Principles for Clinical Trials; Dunnett CW, Gent M. *Biometrics* 1977;33:509-602. Blackwelder WC. *Clin Trials* 1982;3:345-53.