

Advertising Standards Canada Consumer Drug Section Therapeutic Comparative Advertising SOP

Part I: Directive & Part II, Section 1: Comparative Efficacy

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 Authorization¹ 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 entities², **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*

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*

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

HPFB Directive Requirement 6: The claim and its presentation should:
(ii) Identify the medicinal use related to the claim where this is not readily apparent³; **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/ingredient⁴, **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.

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.

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.

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.

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*

Part II: Guidance Document

Section 1 Comparative Efficacy

HPFB Guidance Document Requirement 1:

“Statements may be made regarding the comparative **efficacy** of drug products/ingredients in meeting the claimed indication for use provided the general provisions of the directive, this guidance document and this section are met. The Guidance Document does not include provisions for the use of comparative **effectiveness** data. The science in this area is constantly evolving and it is deemed premature to include this data for comparative advertising purposes at this time.”

Assessment and Review Decision:

Is the therapeutic comparative claim an “efficacy⁵ claim” rather than an “effectiveness⁶” claim?

Yes: Proceed with review. Go to next Assessment and Review Decision.

No: Resubmit/Reject Submission*

Assessment and Review Decision:

Is the claim supported by efficacy⁵ (not effectiveness⁶) data?

Yes: Proceed with review. Go to Section 1-1.

No: Resubmit/Reject Submission*

⁵ Definition of “Efficacy” (provided by HPFB*):

“The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized controlled trial”.

⁶ Definition of “Effectiveness” (provided by HPFB*):

“The extent to which a specific intervention, procedure, regimen, or service, when deployed in the field, does what it is intended to do for a defined population.”

(*ref: Rawson NSB. ‘Effectiveness’ in the evaluation of new drugs: A misunderstood concept? Can J Clin Pharmacol 2001; 8(2):61-2.)

Section 1-1 Standard of Evidence

Assessment and Review Decision:

Does the comparative efficacy claim appear in the Terms of Market Authorization of the Advertised or the Compared product?

- Yes:** Approve (provided all other requirements re: consumer drug advertising and therapeutic comparisons are met)
- No:** Proceed with review. Go to 1-1(a) (1).

HPFB Guidance Document Requirement 1-1(a) (1)

For drugs that are subject to the requirements of Division 8 of the *Food and Drugs Regulations* the efficacy parameters measured in the comparative studies should be the same as those that were evaluated in the context of premarket submission review, and upon which market authorization was based.

As medical knowledge progresses, newer criteria may also be appropriate for therapeutic comparison. However their usage is to be in addition to and not in place of the traditional measures and sufficient justification of their usage must be present. In addition, the use of the new outcome measures for comparison must not result in new therapeutic claims.

In the case of drugs bearing a DIN but not subject to Division 8, the parameters measured should be consistent with those generally used to establish the efficacy of the relevant ingredient(s) that support the claimed indication for use.

Health Canada Note:

In most circumstances, relevant data to substantiate comparisons will be accessible in the respective Product Monographs. However, if evidence is unavailable in the PM or in the published scientific literature, the sponsor will have to provide ASC with appropriate clinical trials as per 1-1(b), 1-1(c) or 1-1(d).

Health Canada Note:

Where the premarket endpoints are different between the advertised and compared drugs, clinical trials studying the same endpoints have to be conducted to substantiate a comparison.

Health Canada Note:

Whether a drug is regulated under Division 1 or Division 8 is irrelevant since comparative claims must be based on clinical data, which support those claims. Head to head studies need to be conducted for comparative claims, because these types of studies were rarely conducted in the past.

Assessment:

Comparative Efficacy Studies: Efficacy parameters studied:

Advertised drug/ingredient: Efficacy parameters evaluated in premarket submission review:

Compared drug/ingredient: Efficacy parameters evaluated in premarket submission review:

Review Decision:

Are the premarket efficacy parameters different between the advertised and compared drug/ingredient?

- Yes:** Clinical trials studying the same endpoints have to be submitted as per 1-1(b), 1-(c), or 1-1(d). 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.
- No:** Approve comparative claim if it appears in authorized product information for either the advertised or compared drug/ingredient (provided all other requirements re: consumer drug advertising and therapeutic comparisons are met).

Assessment and Review Decision:

Have newer therapeutic criteria been used?

- No:** Proceed with review.
 - Go to 1-1(b) for Product-to-Product Comparison.
 - Go to 1-1(c) for Ingredient-to-Ingredient or Product-to-Ingredient Comparisons.
 - Go to 1-1(d) for Product/Ingredient to all other Canadian products/ingredients for the same indication.
- Yes:** If yes, is their usage in addition to and not in place of the traditional measures?
 - Yes:** Proceed with review. Go to next Review Decision.
 - No:** Resubmit/Reject Submission*

Review Decision:

If yes, has the Advertiser provided sufficient justification for their usage?

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

Assessment:

If yes, assess newer therapeutic criteria as per *Changes to Marketed New Drugs Policy*.

Review Decision:

Has the use of the new outcome measures resulted in new therapeutic claims?

Yes: Resubmit/Reject Submission*

No: Proceed with review.

- Go to 1-1(b) for Product-to-Product Comparison.
- Go to 1-1(c) for Ingredient-to-Ingredient or Product-to-Ingredient Comparisons.
- Go to 1-1(d) for Product/Ingredient to all other Canadian products/ingredients for the same indication.

Assessment:

Efficacy parameters (methodologies used and recognized by the scientific community) generally used to establish efficacy of the relevant ingredient(s) that support the claimed indication for use:
As per Advertiser’s submission to ASC:

Efficacy parameters used to establish efficacy in submitted comparative studies:

Review Decision:

Based on the above assessment, are the efficacy parameters used in the submitted comparative studies consistent with those generally used (methodologies used and recognized by the scientific community) to establish the efficacy of the relevant ingredient(s) that support the claimed indication for use?

Yes: Proceed with review

- Go to 1-1(b) for Product-to-Product Comparison.
- Go to 1-1(c) for Ingredient-to-Ingredient or Product-to-Ingredient Comparisons.
- Go to 1-1(d) for Product/Ingredient to all other Canadian products/ingredients for the same indication.

No: Resubmit/Reject Submission*

Section 1-1(b)
Product to Product (Brand Name A to Brand Name B) Comparison

Note: Whenever a brand name is mentioned in a comparative ad, this will be considered a brand to brand ad. Data for ingredient-to-ingredient comparisons cannot be used to make direct or indirect brand-to-brand comparisons. For example, brand-to-brand data (and not ingredient-to-ingredient data) is required to claim “Substance X, the active ingredient in brand Y, is more effective than substance A, the active ingredient in brand B”.

HPFB Guidance Document Requirement 1-1(b)(i) (1):

Statements that make an **equivalence, parity, or a superior efficacy** claim must be supported by **at least two...**

Assessment and Review Decision:

Is claim supported by at least two studies?

Yes: Proceed with review. Go to 1-1(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 Bureau⁷ 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 1-1(b)(i) (3).

No: Reject Submission*

No: Go to 1-1(b)(iii).

⁷ “Review Bureau” refers to the relevant Health Canada Bureau

HPFB Guidance Document Requirement 1-1(b)(i) (2):
... independent⁸...

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 1-1(b)(i) (3).

No: Go to 1-1(b)(iii).

HPFB Guidance Document Requirement 1-1(b)(i) (3):

...well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards (see Section 1-3(a)).

Assessment:

Will be assessed under Section 1-3(a). Go to 1-1(b)(i) (4).

HPFB Guidance Document Requirement 1-1(b)(i) (4):

The two studies must be specifically designed *a priori*, and of sufficient sample size, measurable endpoint(s) and power, to clearly demonstrate product superiority for a specific claim(s); **and**

Guidance Document Excerpt:

The review Bureau may determine that one large well-conducted clinical trial, adequately powered showing an unintended consequence of superiority, could be used as one of two clinical studies to support the newly found superiority claim. The second clinical trial must be appropriately designed to demonstrate superiority. In such circumstances, a rationale must be provided to this exception and discussed with the Health Products and Food Branch on a case-by-case basis.

Assessment and Review Decision:

Based on currently accepted clinical research standards in this therapeutic area, is Study 1 specifically designed *a priori*, and of sufficient sample size, measurable endpoint(s) and power to demonstrate superiority, equivalence or parity for the advertised claim?

Yes: Proceed with review. Go to next Assessment and Review Decision.

No:

If no, has the advertiser provided evidence to ASC that Health Products and Food Branch has determined that one large well-conducted adequately powered clinical trial showing an unintended consequence of superiority may be used as one of the two studies to substantiate therapeutic comparative advertising claims?

Yes: Proceed with review. Go to 1-1(b)(ii).

No: Go to 1-1(b)(iii)

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

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.

Assessment and Review Decision:

Based on currently accepted clinical research standards in this therapeutic area, is Study 2 specifically designed *a priori*, and of sufficient sample size, measurable endpoint(s) and power to demonstrate superiority, equivalence or parity for the advertised claim?

- Yes:** Proceed with review. Go to 1-1(b)(ii).
- No:** Go to 1-1(b)(iii).

HPFB Guidance Document Requirement 1-1(b)(ii):

1-1(b)(ii) (1): Sponsors should provide an attestation that the results of supporting studies reflect the “body of available evidence”⁹ and have not been superseded by contradictory findings¹⁰ ...

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 1-2.
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.
- No:** If no, request attestation. If attestation is available, does it meet the requirements of 1-1(b)(ii) (1)?
 - Yes:** Go to 1-2.
 - No:** Go to 1-1(b)(ii) (2).If attestation is unavailable: Go to 1-1(b)(iii).

HPFB Guidance Document Requirement 1-1(b)(ii):

1-1(b)(ii) (2): ...or, a justification of any difference should be provided for consideration; **or**

Assessment and Review Decision:

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

⁹ HPFB Definition: ‘Body of available evidence’: ‘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’.

¹⁰ Intended to ensure that the results are viewed in the context of all available information.

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

Yes: Proceed with review. Go to 1-2.

No: Go to 1-1(b)(iii)

No: Go to 1-1(b)(iii).

HPFB Guidance Document Requirement 1-1(b)(iii):

1-1(b)(iii) (1): If conditions i) and ii) are not presented, then data reported in the public domain (e.g., articles in peer reviewed¹¹, reputable scientific journals that are used to support a product-to-product comparison) or data in product monographs should pertain to the products cited in the claim...

Assessment and Review Decision:

Do the submitted supporting data pertain to the products cited in the claim?

Yes: Proceed with review. Go to 1-1(b)(iii) (2).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(b)(iii):

1-1(b)(iii) (2): ...such data are also subject to the standards cited in Sections 1-1(b)(i) and (ii).

Assessment:

Complete assessment as per Sections 1-1(b)(i) and (ii).

Review Decision:

Do the studies meet the requirements of Section 1-1(b)(i)?

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

No: Resubmit/Reject Submission*

Review Decision:

Do the studies meet the requirements of Section 1-1(b)(ii).

Yes: Proceed with review. Go to 1-2.

No: Resubmit/Reject Submission*

¹¹ Peer review of published articles is not all conducted to the same standard.

Section 1-1(c)
Ingredient to Ingredient or Product to Ingredient Comparisons

Note: Whenever a brand name is mentioned in a comparative ad, this will be considered a brand to brand ad. Data for ingredient-to-ingredient comparisons cannot be used to make direct or indirect brand-to-brand comparisons. For example, brand-to-brand data (and not ingredient-to-ingredient data) is required to claim “Substance X, the active ingredient in brand Y, is more effective than substance A, the active ingredient in brand B”.

Guidance Document Excerpt:

“The ability to make comparative efficacy claims for ingredient to ingredient or product to ingredient comparisons may be limited since most randomized clinical studies are actually conducted on specific products or brand names. The ability to extrapolate results for specific products to ingredients in comparative advertising claims is acknowledged. A meta-analytic approach may be the only option available, but must be subject to rigorous methods. The meta-analysis must include individual trials that were subject to the standards cited in Section 1-1(b)(i) and (ii).”

HPFB Guidance Document Requirement 1-1(c)(i):

1-1(c)(i) (1): Statements that make an **equivalence, parity or superior efficacy claim of one drug ingredient to another drug ingredient, or of one drug product to another drug ingredient** may be supported by a systematic review and meta-analysis of published and sponsor-generated data from studies in which the conditions of use of the compared drugs are consistent with those authorized in Canada; and...

Assessment:

Conditions of use (as per HPFB definition) of compared drugs in studies used in meta-analysis:

Study 1:

Study 2:

Authorized conditions of use in Canada of drug/ingredient 1:

Authorized conditions of use in Canada of drug/ingredient 2:

Review Decision:

Based on the above assessment, are the conditions of use of the compared drugs in the meta-analytic studies consistent with the authorized conditions of use in Canada for both drugs?

- Yes:** Proceed with review. Go to 1-1(c)(i) 2.
- No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(i) (2):

...Such data are also subject to the standards cited in Sections 1-1(b)(i) and (ii).

Assessment:

Complete assessment as per Sections 1-1(b)(i) and (ii).

Review Decision:

Do the studies meet the requirements of Section 1-1(b)(i)?

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

Review Decision:

Do the studies meet the requirements of Section 1-1(b)(ii)?

- Yes:** Proceed with review. Go to 1-1(c)(ii).
- No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii): The systematic review should adhere as closely as possible to the following methodological guidelines¹²:

1-1(c)(ii) (1): The research plan should be documented *a priori*, and...:

Assessment and Review Decision:

Was the research plan documented *a priori*?

- Yes:** Proceed with review. Go to 1-1(c)(ii) (1.1).
- No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (1): The research plan should include:

1-1(c)(ii) (1.1): the question(s) to be addressed by the review;

¹² Consistent with the principles expressed in Cook DJ, Sackett DL and Spitzer WO. Methodologic Guidelines for Systematic Reviews of Randomized Controlled Trials in Health Care from the Potsdam Consultation on Meta-analysis. *J Clin Epidemiol* 1995; 48:167-71.

Assessment and Review Decision:

Does the research plan include the questions to be addressed by the review?

Yes: Proceed with review. Go to 1-1(c)(ii) (1.2).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (1): The research plan should include:
1-1(c)(ii) (1.2): a reproducible and robust method for finding all relevant studies for review¹³, with search parameters stated;

Assessment and Review Decision:

Is the method for finding all relevant studies for review, with search parameters stated, reproducible and robust?

Yes: Proceed with review. Go to 1-1(c)(ii) (1.3).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement: 1-1(c)(ii) (1): The research plan should include:
1-1(c)(ii) (1.3): a reproducible method for selecting studies, from those retrieved, for detailed review (inclusion and exclusion criteria, with a list of excluded studies);

Assessment and Review Decision:

Did the plan include a reproducible method for selecting the studies for detailed review?

Yes: Proceed with review. Go to 1-1(c)(ii) (1.4).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (1): The research plan should include:
1-1(c)(ii) (1.4): a reproducible method for evaluating the scientific quality of studies;

Assessment and Review Decision:

Did the plan include a reproducible method for evaluating the scientific quality of the studies?

Yes: Proceed with review. Go to 1-1(c)(ii) (1.5).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (1): The research plan should include:
1-1(c)(ii) (1.5): a reproducible method for extracting evidence from studies;

¹³ With respect to a product vs. ingredient comparison, every effort should be made to locate, include and identify all studies in which the advertised product was compared.

Assessment and Review Decision:

Did the plan include a reproducible method for extracting evidence from the studies?

- Yes:** Proceed with review. Go to 1-1(c)(ii) (1.6).
- No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (1): The research plan should include:
1-1(c)(ii) (1.6): identification of proposed subgroup analyses

Assessment and Review Decision:

Does the research plan identify the proposed subgroup analyses?

- Yes:** Proceed with review. Go to 1-1(c)(ii) (2).
- No:** Resubmit/Reject Submission*
- N/A:** Proceed with review. Go to 1-1(c)(ii) (2).

HPFB Guidance Document Requirement 1-1(c)(ii) (2): The systematic review should adhere as closely as possible to the following methodological guidelines – i.e.:
1-1(c)(ii) (2): a documented justification to support any changes in the predetermined plans for data retrieval and subgroup analyses;

Assessment and Review Decision:

Are there any differences between the predetermined and the actual plan for data retrieval and subgroup analyses?

- No:** Proceed with review. Go to 1-1(c)(ii) (3).
- Yes:** If yes, does the study contain and/or has the Advertiser provided to ASC, a documented justification that adequately supports any changes in the predetermined plans for data retrieval and subgroup analyses:
 - Yes:** Proceed with review. Go to 1-1(c)(ii) (3).
 - No:** Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (3): The systematic review should adhere as closely as possible to the following methodological guidelines – i.e.:
1-1(c)(ii) (3): labelling of all subgroup analyses according to whether they are *a priori* or *a posteriori*

Assessment and Review Decision:

Are all subgroup analyses labelled according to whether they are *a priori* or *a posteriori*?

- Yes:** Proceed with review. Go to 1-1(c)(ii) (4).
- No:** Resubmit/Reject Submission*
- N/A:** Proceed with review. Go to 1-1(c)(ii) (4).

HPFB Guidance Document Requirement 1-1(c)(ii) (4): The systematic review should adhere as closely as possible to the following methodological guidelines – i.e.:

1-1(c)(ii) (4): use of sensitivity analyses to test the robustness of results relative to features of the primary studies and to key assumptions and decisions made in the selection, analysis and presentation of studies and their findings;

Assessment and Review Decision:

Does the research plan include sensitivity analyses that test the robustness of results relative to features of the primary studies and to key assumptions and decisions made in the selection, analysis and presentation of studies and their findings?

Yes: Proceed with review. Proceed with review. Go to 1-1(c)(ii) (5).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(ii) (5): The systematic review should adhere as closely as possible to the following methodological guidelines – i.e.:

1-1(c)(ii) (5): the results of the systematic review and meta-analysis should be provided.

Review Decision:

Are the results of the systematic review and meta-analysis provided?

Yes: Proceed with review. Go to 1-1(c)(iii).

No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-1(c)(iii):

Data quoted from two or more Product Monographs, derived from studies that were head-to-head, are acceptable support for comparative claims of clinical efficacy. Factors such as study methodologies, patient populations, dosing and measurement criteria used in the separate trials must be similar. The side-by-side presentation of efficacy data must be comparable, otherwise it could leave a misleading impression.

Assessment and Review Decision:

Are the compared data comparable?

Yes: Proceed with review. Go to 1-3.

No: Resubmit/Reject Submission*

Section 1-1(d)
Product/Ingredient to All Other Canadian Products/Ingredients
for the Same Indication

HPFB Guidance Document Requirement 1-1(d)(i):

Evidence and data generated to support equivalence, parity, or superiority claims of one product/ingredient over all others for the same indication should be consistent with the requirements for individual comparisons and subject to the standards cited in Sections 1-1(b) and (c).

Assessment:

Advertised product/ingredient:

All other Canadian products/ingredients for the same indication:

Product/ingredient 1: _____

Product/ingredient 2: _____

Product/ingredient 3: _____

Product/ingredient 4: _____

Review Decision:

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

- No:** Resubmit/Reject Submission*
- Yes:** If yes, evaluate the data for each of the above against the standards cited in Sections 1-1(b) and 1-1(c).

Review Decision:

Do the data for the Advertised product vs. each of the Canadian Comparative products meet the criteria in Section 1-1(b)?

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

Review Decision:

Do the data for the Advertised product/ingredient vs. each of the Canadian Comparative ingredients meet the criteria in Section 1-1(c)?

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

**Section 1-2
Test and Reference Products**

Health Canada Note:

This section applies for advertising purposes only and is not meant to be used as the basis of approval or market authorization of therapeutic products.

Guidance Document Excerpt:

Where these criteria (Section 1-2) are not met, clinical studies using the Canadian versions of the compared products are required.

HPFB Guidance Document Requirement 1-2(a)(1):

For product vs. product comparisons...

Assessment and Review Decision:

Is the comparison a product vs. product comparison?

Yes: Proceed with review. Go to 1-2(a)(2).

No: Go to 1-3.

HPFB Guidance Document Requirement 1-2(a)(2):

...the actual products cited in the comparison should be used in the supporting comparative clinical trials.

Health Canada Note:

The “actual products cited in the comparison” means:

- *the claim and supporting studies must both concern the Canadian marketed product (and, where the studies are done with a non-Canadian product section 1-2(b) applies); and,*
- *the supporting studies must have been done with the actual product cited in the claim – for example, a comparative claim about “Antacid Plus” must be supported with studies done with “Antacid Plus” rather than the plain “Antacid” product.*

Assessment:

Products cited in the comparative claim:

Advertised Product: _____

Comparator Product: _____

Study 1:

Test product: _____

Comparator: _____

Study 2:

Test product: _____

Comparator: _____

Review Decision:

For product vs. product comparisons, are the actual products cited in the comparative claim those used in the supporting comparative clinical trials?

- Yes:** Proceed with review. Go to 1-2(b).
- No:** Request data
 - If data available: Go to section 1-2(b)
 - If data not available: Reject Submission*

HPFB Guidance Document Requirement 1-2(b):

Data generated to support a **product to product comparison** from clinical trials conducted in other countries with **non-Canadian versions** of the **products** cited in the comparison,

Assessment and Review Decision:

Were the clinical trials used to support the product-to-product comparison conducted with non-Canadian versions of the products cited in the comparison?

- Yes:** Go to 1-2(b)(i)
- No:** Go to section 1-3

HPFB Guidance Document Requirement 1-2(b)(i):

Data generated to support a **product to product comparison** from clinical trials conducted in other countries with **non-Canadian versions** of the **products** cited in the comparison, may be used to support comparison of the **equivalent Canadian products** provided it can be demonstrated that:

1-2(b)(i): the **sponsor's Canadian product** is identical^{14*} to, or has no major changes(s)^{15*} from the corresponding non-Canadian product used in the original studies and this has been verified by the manufacturer; **and**

Health Canada Note:

The bioavailability and bioequivalence principles that apply to Market Authorization are the same as those that apply to Therapeutic Comparisons in advertising.

¹⁴ Identical master formula and manufacturing process

¹⁵ Major change(s) as defined by a Level 1 or Level 2 change in the Health Products and Food Branch Policy on *Changes to Marketed New Drugs*.

Health Canada Note:

The principles outlined in the Canadian Reference Product Policy are equally applicable to Division 1 and Division 8 drugs, for the purpose of comparative claims, when the comparator is a non-Canadian product. This is necessary to establish the validity of the comparative claims. No major changes – sponsors have to confirm that the non-Canadian product and Canadian product are the same, for example that the claims are meaningful for their own product.

Assessment and Review Decision:

Has the Advertiser provided ASC a written attestation that the Advertiser’s Canadian product is identical to the corresponding non-Canadian product used in the original studies?

- Yes:** Proceed with review. Go to 1-2(b)(ii).
- No:** If no, has the Advertiser provided ASC a written attestation that the Advertiser has verified that, as per the HPFB Policy: *Changes to Marketed New Drugs*, its Canadian product has no major changes from the corresponding non-Canadian product used in the original studies?
 - Yes:** Proceed with review. Go to 1-2(b)(ii).
 - No:** Reject Submission

Health Canada Note:

The principles outlined in the Canadian Reference Product Policy are equally applicable to Division 1 and Division 8 drugs, for the purpose of comparative claims, when the comparator is a non-Canadian product. This is necessary to establish the validity of the comparative claims. No major changes – sponsors have to confirm that the non-Canadian product and Canadian product are the same, for example that the claims are meaningful for their own product.

HPFB Guidance Document Requirement 1-2(b)(ii):

Data generated to support a **product to product comparison** from clinical trials conducted in other countries with **non-Canadian versions** of the **products** cited in the comparison, may be used to support comparison of the **equivalent Canadian products** provided it can be demonstrated that:

1-2(b)(ii): the compared product complies with the Health Products and Food Branch Policy: *Canadian Reference Product* ; **or**

Assessment:

Assess submitted data as per criteria in HPFB Policy *Canadian Reference Product*.
(*Health Canada Note: An attestation is not acceptable for the Compared product*).

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.

Review Decision:

Does the Compared product comply with the HPFB Policy *Canadian Reference Product*?

- Yes:** Proceed with review. Go to 1-3.
- No:** Go to 1-2(b)(iii) (1).

HPFB Guidance Document Requirement 1-2(b)(iii):

1-2(b)(iii) (1): the **compared product** is a product which would not be subject to a bioequivalence study for premarket approval in accordance with the HPFB Guideline: *Preparation of Drug Identification Number Submissions and...*

Health Canada Note:

The HPFB Guideline: Preparation of Drug Identification Number Submissions applies to drug products such as toothpaste and vitamins.

Assessment:

Assess submitted data for Compared product vs. all factors outlined in Appendix E – Factors to be Addressed in Assessing Bioequivalence Requirements of HPFB Guideline: Preparation of Drug Identification Number Submissions, as justification for waiver of bioequivalence requirements.

Review Decision:

Based on the above assessment, has the Advertiser provided sufficient justification for a waiver of bioequivalence requirements, as per Appendix E of HPFB Guideline: Preparation of Drug Identification Number Submissions?

- Yes:** Proceed with review. Go to 1-2(b)(iii) (2).
- No:** Go to 1-2(b)(iv)

HPFB Guidance Document Requirement 1-2(b)(iii):

1-2(b)(iii) (2): (the compared product) meets the criteria in Appendix II.

Assessment of Appendix II criteria:

Appendix II - Criteria 1: It must be documented that the foreign comparator drug product is authorized for marketing by the health authority of a country with drug assessment criteria documented to be comparable to those in Canada as required in the *Food and Drugs Act* and interpreted in Health Products and Food Branch Guidelines and Policies.

Assessment and Review Decision Appendix II Criteria 1:

Do the data provided by the Advertiser support that Appendix II criteria 1 are met?

- Yes:** Proceed with review. Go to Appendix II Criteria 2.
- No:** Go to 1-2(b)(iv)

Appendix II – Criteria 2: It must be documented that the foreign comparator drug product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same medicinal ingredient(s) in the same dosage form in Canada, or that it is marketed in the country of origin through a licensing arrangement with the same company or corporate entity which currently markets the product in Canada.

Assessment and Review Decision Appendix II Criteria 2:

Do the data provided by the Advertiser support that Appendix II criteria 2 are met?

- Yes:** Proceed with review. Go to Appendix II Criteria 3.
- No:** Go to 1-2(b)(iv)

Appendix II – Criteria 3: Labelling for the foreign comparator drug product and the comparator drug product marketed in Canada must be submitted and shown to be comparable.

Assessment Appendix II Criteria 3:

Terms of Market Authorization for Canadian Comparator drug product:

Terms of Market Authorization for foreign Comparator drug product:

Health Canada Note:

“Comparable” foreign labelling does not mean “identical”. The assessment of the material should be based on sound scientific judgement as well as on how the information in the labelling is interpreted.

Review Decision Appendix II Criteria 3:

Is the labelling for the foreign Comparator drug product and the Comparator drug product marketed in Canada comparable?

- Yes:** Proceed with review. Go to Appendix II Criteria 4.
 No: Go to 1-2(b)(iv)

Appendix II - Criteria 4. The foreign comparator drug product must be the same as the comparator drug product marketed in Canada with respect to colour, shape, size, weight, type of coating, flavour, fragrance, etc. The sponsor must justify that differences, if any (flavour, fragrance) between the foreign comparator drug product and the comparator drug product marketed in Canada would not affect the results obtained from the foreign comparative clinical trials.

Assessment:

Attribute	Canadian Comparator drug	Foreign Comparator Drug
Colour		
Shape		
Size		
Weight		
Coating Type		
Flavour		
Fragrance		
Other:		

Review Decision:

Are the foreign Comparator drug and the Canadian Comparator drug the same, based on above evaluation?

- Yes:** Proceed with review. Go to 1-3.
- No:** If no, has the sponsor adequately justified that any differences between the foreign Comparator drug and the Canadian Comparator would not affect the results obtained from the foreign comparative clinical trials?
 - Yes:** Proceed with review. Go to 1-3.
 - No:** Go to 1-2(b)(iv)

HPFB Guidance Document Requirement 1-2(b)(iv):

The Canadian and non-Canadian comparator products are shown to be bioequivalent¹⁶.

Assessment:

Assess submitted data re: bioequivalence between the Canadian and non-Canadian Comparator products, in accordance with current HPFB Bioequivalence Policies and Guidelines (as identified in Appendix I of 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.

Review Decision:

Have the Canadian and non-Canadian Comparator products been shown to be bioequivalent?

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

¹⁶ If the comparator product, in accordance with current HPFB Guidelines and Policies (see Appendix I of Guidance Document) would require a bioequivalence study(ies) for premarket approval, then the Canadian and foreign comparator products must be shown to meet these bioequivalence criteria to allow for the use of the foreign comparative clinical trials.

Guidance Document Excerpt:

Where these criteria (Section 1-2) are not met, clinical studies using the Canadian versions of the compared products are required.

Section 1-3
Clinical Study Design/Methodology/Analysis

HPFB Guidance Document Requirement 1-3(a):

The clinical studies in support of a product to product comparison should be conducted and analysed according to the principles embodied in the guideline of the International Conference on Harmonisation; *Structure and Contents of Clinical Trial Reports* and *Statistical Principles for Clinical Trials*.

For example:

- (i) The clinical studies should be designed to investigate the comparison of interest;
- (ii) The clinical studies should be double blinded (investigator and subjects) or justification provided as to why this could not be accomplished, and what alternative measures have been employed to ensure lack of bias;
- (iii) The study population should be representative of the target population; all subjects assigned to the treatments should be accounted for; the sample size must be based on statistical power analysis.

Assessment and Review Decision:

Has the Advertiser provided to ASC a written attestation that the Advertiser has verified that the clinical studies supporting a product to product comparison were conducted and analysed according to the principles embodied in the ICH Guidelines: *Structure and Contents of Clinical Trial Reports* and *Statistical Principles for Clinical Trials*.

Yes: Proceed with review. Go to 1-4.

No: Resubmit/Reject Submission*

Section 1-4 Interpretation

HPFB Guidance Document Requirement 1-4(a):

1-4(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 1-4(a) 2.
 No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-4(a):

1-4(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 1-4(b).
 No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-4(b):

Evidence of clinical relevance should be presented in order to assist the consumer in selecting an appropriate therapy.

Assessment and Review Decision:

Based on previously completed assessment of clinical relevance (Part I: Directive, HPFB Directive Requirement 4), is the claim relevant to treatment selection?

- Yes:** Proceed with review. Go to 1-4 (c).
 No: Resubmit/Reject Submission*

HPFB Guidance Document Requirement 1-4(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 between the compared treatments. Equivalence can only be established using hypotheses structured for assessing equivalence¹⁷.

Assessment and Review Decision:

Did the clinical studies demonstrate a statistically significant difference in the measured effect?

- Yes:** Proceed with review. Go to 1-4(d).
- No:** Resubmit/Reject Submission* (equivalence may not be claimed)

HPFB Guidance Document Requirement 1-4(d):

The comparative efficacy claim should not be extrapolated beyond the actual conditions and study populations of the supporting comparative clinical trials unless a sound, scientific justification can be provided for doing so.

For example:

- (i) Justification is required for making a comparative claim about benefits to the elderly when the supporting evidence was obtained, for example, from studies in young, healthy adults, or for benefits to smokers when smokers formed a minor proportion of the study population;
- (ii) An extrapolation from data supporting an ingredient-to-ingredient comparison of efficacy (Section 1-1(c) meta-analysis) to a product-to-product comparison of efficacy may be appropriate, e.g., if it can be demonstrated that the measurement of efficacy (endpoint) used in the comparison is independent of formulation or route of administration; *the standards of evidence for this type of extrapolation must be comparable to those needed to obtain product approval in Canada.*

Assessment:

Claimed conditions of use and population:

Study 1: Condition of use and study population:

¹⁷ 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.

Study 2: Condition of use and study population:

Review Decision:

Based on the above assessment, has the comparative efficacy claim been extrapolated beyond the actual conditions and study populations of the supporting studies?

- No:** Proceed with review. Go to standard nonprescription drug advertising review procedures.
- Yes:** If yes, has the Advertiser provided a sound, scientific justification for doing so?
 - Yes:** Proceed with review. Go to standard nonprescription drug advertising review procedures.
 - No:** Resubmit/Reject Submission*