

# Advertising Standards Canada Consumer Drug Section Therapeutic Comparative Advertising SOP

## Part I: Directive & Part II, Section 2: Onset or Duration of Action

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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<sup>1</sup> for each of the compared drugs/ingredients. Advertisers must submit new therapeutic claims to HPFB for review and approval.

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<sup>1</sup> 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:

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#### 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:

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Authorized Indication(s) for Advertised drug/ingredient:

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Name of Comparator drug/ingredient:

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Authorized Indication(s) for Comparator drug/ingredient:

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#### 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\*

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\* 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:

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Authorized Conditions of Use of Advertised drug/ingredient:

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**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:

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Authorized Conditions of Use of Comparator drug/ingredient:

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**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:

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**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:

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**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<sup>2</sup>, **and**

**Assessment:**

How Advertised drug/ingredient is identified in ad:

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Other products in Advertised drug/ingredient product line:

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How Comparator drug/ingredient is identified in ad:

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Other products in Comparator drug/ingredient product line:

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**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\*

<sup>2</sup> 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<sup>3</sup>; **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<sup>4</sup>, **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.

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<sup>3</sup> Where the advertised entity has more than one indication for use, it should be clear to which use the claim refers  
<sup>4</sup> 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 2: Onset or Duration of Action

**Note:** For Onset or Duration of Action 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:**

*Comparison may be made between drug products/ingredients regarding the onset or duration of action where this measurement is of clinical relevance<sup>5</sup> in humans, provided the general provisions of the **Directive**, the **Guidance Document** and this **Section** are met. This comparison should be based on existing HPFB approved product information, since new information on onset of action is subject to HPFB review.*

#### SECTION 2-1 STANDARD OF EVIDENCE

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

The onset or duration of action should be determined through measurement of the same parameters used to establish efficacy in the context of premarket submission review and market authorization, or justification provided where this is not the case.

**Assessment:**

Complete assessment as per Section 1-1(a).

**Review Decision:**

Are the efficacy parameters that were measured in the comparative studies the same as those that were evaluated in the context of premarket submission review and upon which market review was based?

**Yes:** Proceed with review

- For Product to Product (Brand Name A to Brand Name B) comparisons, go to 2-1(b)
- For Ingredient to Ingredient and Product to Ingredient comparisons, go to 2-1(c)
- For Product/Ingredient to All Other Canadian Products/Ingredients for the Same Indication, go to 2-1(d)

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<sup>5</sup> HPFB Definition: "Clinical Relevance": Refers to the practical value of the claim itself in assisting consumers to select an appropriate therapy.

- No:** If No, has the Advertiser provided adequate justification as to why this is not the case?
- Yes:** Proceed with review.
- For Product to Product (Brand Name A to Brand Name B) comparisons, go to 2-1(b)
  - For Ingredient to Ingredient and Product to Ingredient comparisons, go to 2-1(c)
  - For Product/Ingredient to All Other Canadian Products/Ingredients for the Same Indication, go to 2-1(d)
- No:** Resubmit/Reject Submission\*

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

**Section 2-1(b)**  
**Product to Product (Brand Name A vs. Brand Name B) Comparison**

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

Two clinical trials, as outlined in Sections 1-1(b),

**Assessment:**

Complete assessment as per 1-1(b).

**Review Decision:**

Do the supporting data meet the standards set out in Section 1-1(b)?

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

**No:** Go to Section 2-1(b)(ii)

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

Two clinical trials, as outlined in Sections 1-1(b), 1-2 (...) are required to support a comparison of the onset or duration of action of two products.

**Assessment:**

Complete assessment as per 1-2.

**Review Decision:**

Do the supporting data meet the standards set out in Section 1-2?

**Yes:** Proceed with review. Go to 2-1(b)(i) (3).

**No:** Go to Section 2-1(b)(ii)

**HPFB Guidance Document Requirement 2-1(b)(i) (3):**

Two clinical trials, as outlined in Sections 1-1(b), 1-2, 1-3(a) (...) are required to support a comparison of the onset or duration of action of two products.

**Assessment:**

Complete assessment as per 1-3(a).

**Review Decision:**

Do the supporting data meet the standards set out in Section 1-3(a)?

**Yes:** Proceed with review. Go to 2-1(b)(i) (4).

**No:** Go to Section 2-1(b)(ii)

**HPFB Guidance Document Requirement 2-1(b)(i) (4):**

Two clinical trials, as outlined in Sections 1-1(b), 1-2, 1-3(a) and 1-4(c) are required to support a comparison of the onset or duration of action of two products.

**Assessment:**

Complete assessment as per 1-4(c).

**Review Decision:**

Do the supporting data meet the standards set out in Section 1-4(c)?

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

**No:** Go to Section 2-1(b)(ii)

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

Alternatively, sponsors should justify and provide information on alternative methods used and data generated to support the comparison.

For example, comparative pharmacokinetic/pharmacodynamic studies may be appropriate in this context, provided that a strong correlation can be established between the measured endpoint and the onset or duration of the therapeutic effect of the compared products, e.g., where the rate of absorption is a direct measure of the onset of symptom relief; or where differences in duration of action can be attributed to modification of the dosage form of the advertised product, as supported by comparison of the authorized Product Monographs/product labelling.

In no circumstances would extrapolation of the claim beyond the actual conditions of the supporting studies be acceptable.

**Assessment:**

Has the Advertiser supported the claim with alternate methods?

**No:** Proceed with Review. Go to 2-1(b)(iii).

**Yes:** If yes, evaluate the Advertiser's justification and rationale for the alternate methods used and data generated to support the comparison.

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

**Review Decision:**

Do the methods and data generated to support a comparison of onset and/or duration of action claim adequately support (e.g., sound scientific methods, robust statistical analysis, appropriate interpretation of data) the claim?

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

**No:** Resubmit/Reject Submission\*

**Review Decision:**

Does the therapeutic comparative claim extrapolate the data beyond the actual conditions of the supporting studies?

- Yes:** Resubmit/Reject Submission\*
- No:** Proceed with review. Go to 2-1(b)(iii).

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

Sponsors should provide an attestation that the results of supporting studies reflect the “body of available evidence”<sup>6</sup> and have not been superseded by contradictory findings; alternatively, a justification for any difference should be provided for consideration;

**Assessment:**

Assessment completed under 2-1(b)(i) (1) above.

**Review Decision:**

Based on previously completed assessment, has 2-1(b)(iii) been met?

- Yes:** Proceed with review. Go to Section 2-2.
- No:** Resubmit/Reject Submission\*

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<sup>6</sup> ‘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’.

**Section 2-1(c)**  
**Ingredient to Ingredient and Product to Ingredient Comparisons**

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

Comparisons may be drawn with respect to onset and/or duration of action provided sponsors adequately justify the method(s) used, and the data generated, to support the comparative claim relating to onset or duration of action.

**Health Canada Note:**

*“An ‘adequate justification’ encompasses the HPFB definition of the expression ‘Body of available evidence’<sup>7</sup>. Therefore, requirement 2-1(c)(i) could be read as follows: “Comparisons may be drawn with respect to onset and/or duration of action provided sponsors’ methods used and data generated reflect the ‘body of available evidence’ to support the comparative claim relating to onset or duration of action. ‘Adequately justify’ also is meant to be conducted according to appropriate scientific standards such as two double blinded randomized clinical studies, reproducible, claims not to be extrapolated beyond the actual conditions and study populations, similar endpoints, appropriate scientific methodologies etc.”*

**Assessment:**

Evaluate the Advertiser’s justification and rationale for the methods used and data generated to support the comparison.

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

**Review Decision:**

Do the methods and data generated to support a comparison of onset and/or duration of action claim adequately support (e.g., sound scientific methods, robust statistical analysis, appropriate interpretation of data) the claim?

**Yes:** Proceed with review. Go to Section 2-3.

**No:** Resubmit/Reject Submission\*

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<sup>7</sup> 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’.

**Section 2-1(d)**  
**Product/Ingredient to All Other Canadian Products/Ingredients**  
**for the Same Indication**

**HPFB Guidance Document Requirement 2-1(d)(i):**

Evidence and data generated to support equivalence<sup>8</sup>, parity<sup>9</sup>, or superiority<sup>10</sup> claims of one product/ingredient over all others for the same indication with respect to onset/duration of action should be consistent with the requirements for individual comparisons and subject to the standards cited in Section 2-1.

**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 product/ingredient listed above against the standards cited in 2-1:

**Assessment and Review Decision:**

Do the data for the Advertised product/ingredient vs. each of the Canadian Comparator products/ingredients meet the criteria in 2-1?

**Yes:** Proceed with review. Depending of type of comparison, go to one or more of the following:

- For Product to Product (Brand Name A to Brand Name B) comparisons, go to 2-1(b)(i) and next Review Decision.
- For Ingredient to Ingredient and Product to Ingredient comparisons, go to 2-1(c) and next Review Decision.

**No:** Resubmit/Reject Submission\*

<sup>8</sup> HPFB Definition: "Equivalence": Product claims equal or identical performance to another product (Brand A works as well as Brand B at relieving heartburn).

<sup>9</sup> HPFB Definition: "Parity": Product claims show no proven superiority in any given parameter, i.e., that the available products have equal efficacy (Nothing has been shown to relieve heartburn better than Brand A).

<sup>10</sup> HPFB Definition: "Superiority": Product claims performance better than another product (Brand A works better than Brand B at relieving heartburn).

**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 of 2-1(b)?

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

**No:** Resubmit/Reject Submission\*

**- For Ingredient to Ingredient and Product to Ingredient comparisons:**

Do the data for the Advertised product/ingredient vs. each of the Canadian Comparator products/ingredients meet the criteria of 2-1(c)?

**Yes:** Proceed with review. Go to 2-3.

**No:** Resubmit/Reject Submission\*

**Section 2-2  
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 2-2) are not met, clinical studies using the Canadian versions of the compared products are required.*

**HPFB Guidance Document Requirement 2-2(a):**  
For product vs. product comparisons, 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 2-2(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 2-2(b).
- No:** Request data
  - If data available: Go to 2-2(b)
  - If data not available: Reject Submission\*

**HPFB Guidance Document Requirement 2-2(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 2-2(b)(i)
- No:** Go to section 2-3

**HPFB Guidance Document Requirement 2-2(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, may be used to support comparison of the **equivalent Canadian products** provided it can be demonstrated that:

**2-2(b)(i):** the **sponsor's Canadian product** is identical<sup>11\*</sup> to, or has no major changes(s)<sup>12\*</sup> 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.*

**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 2-2(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 2-2(b)(ii).
  - No:** Reject Submission\*

<sup>11</sup> Identical master formula and manufacturing process

<sup>12</sup> 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 and the Changes to Marketed New Drugs 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 2-2(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, may be used to support comparison of the **equivalent Canadian products** provided it can be demonstrated that:

**2-2(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 2-3.

**No:** Go to 2-2(b)(iii) (1).

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

**2-2(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 2-2(b)(iii) (2).

**No:** Go to 2-2(b)(iv)

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

**2-2(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 is met?

**Yes:** Proceed with review. Go to Appendix II Criteria 2.

**No:** Go to 2-2(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 is met?

**Yes:** Proceed with review. Go to Appendix II Criteria 3.

**No:** Go to 2-2(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:

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Terms of Market Authorization for foreign Comparator drug product:

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**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 2-2(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:**

<b>Attribute</b>	<b>Canadian Comparator drug</b>	<b>Foreign Comparator Drug</b>
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 2-3.
- 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 2-3.
  - No:** Go to 2-2(b)(iv)

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

The Canadian and non-Canadian comparator products are shown to be bioequivalent<sup>13</sup>.

**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 2-3.

**No:** Resubmit/Reject Submission\*

**Guidance Document Excerpt:**

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

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<sup>13</sup> 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.

## Section 2-3 Interpretation

### HPFB Guidance Document Requirements 2-3(a):

**2-3(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:

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

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#### 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 2-3(a) 2.

**No:** Resubmit/Reject Submission\*

### HPFB Guidance Document Requirement 2-3(a):

**2-3(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 2-3(b).

**No:** Resubmit/Reject Submission\*

### HPFB Guidance Document Requirement 2-3(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 2-3(c).

**No:** Resubmit/Reject Submission\*

**HPFB Guidance Document Requirement 2-3(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 equivalence<sup>14</sup>.

**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 review procedures.
- No:** Resubmit/Reject Submission\* (equivalence may not be claimed)

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<sup>14</sup> E.g., Section 3.2.2, ICH E9 document on Statistical Principles for Clinical Trials; Dunnett CW, Gent M. *Biometrics* 1977;33:509-602. Blackwelder WC. *Clin Trials* 1982;3:345-353.