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To: Stakeholders

**Re: Therapeutic Comparative Advertising:
Directive and Guidance Document**

The Therapeutic Products Directorate (TPD) has completed the review of the Guidance Document: *Data Requirements to Support Comparative Claims Related to Therapeutic Aspects of Nonprescription Drugs Used in Consumer-Directed Advertising and Labelling*.

This Guidance Document is a complement to the initial Directive on the *Principles for Comparative Claims Related to the Therapeutic Aspects of Drugs*, issued on May 23, 1997. The TPD has now combined the Directive and the Guidance Document to become one new document: *Therapeutic Comparative Advertising: Directive and Guidance Document*. This will facilitate access to all TPD information in this area.

PART I includes the 1997 Directive which incorporates revisions to the Sections on Roles and Responsibilities and effective date. By merging the Directive and Guidance document into one document, it became redundant to repeat the Roles and Responsibilities in the two documents. Furthermore, this section is applicable to advertising and labelling for all drugs for human use regardless of the intended audience.

PART II consists of the Guidance Document detailing the data requirements to support comparative claims related to the therapeutic aspects of nonprescription drugs used in consumer-directed advertising and labelling. It was subject to extensive internal and external consultation in 1999 and 2000. These data requirements outline the standards adopted by the TPD for use by independent advertising preclearance agencies and sponsors. Clear standards are set to avoid any potential disagreement concerning the level of evidence required to support comparative therapeutic claims and to allow for consistency in advertising review.

The Guidance Document is effective upon the date of publication for the review of product labelling. With respect to product advertising, implementation will take effect upon the finalization of operational guidelines by the independent advertising preclearance agencies endorsed by the TPD.

The TPD greatly appreciates the input received from industry, health professional and industry associations, independent advertising preclearance agencies and various individuals on this issue. The TPD believes that this framework provides the standards of supporting evidence and presentation of therapeutic comparative claims in drug advertising such that these claims will not be false, misleading or deceptive to the intended audience.

Any comments that relate to interpretational issues or clarity should be forwarded to:

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Yours sincerely,

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Enclosure

THERAPEUTIC COMPARATIVE ADVERTISING

DIRECTIVE AND GUIDANCE DOCUMENT

MARCH 2001

Administrative Update : OCTOBER 2005

Advertising Issues Working Group
Health Products and Food Branch

PREFACE

For ease of reference, this document combines Health Canada's Comparative Advertising Directive and Guidance Document relating to therapeutic attributes of drugs.

The broad principles are outlined in Part I of the Directive - *Principles for Comparative Claims Related to the Therapeutic Aspects of Drugs*. This directive is applicable to all drugs for human use regardless of the intended audience (health professionals, consumers). The Directive is basically the same as when it was initially issued on May 23, 1997. However, this revised version now includes the roles and responsibilities of the different players, that is the independent advertising preclearance agencies, Health Canada and the advertising sponsors.

Part II consists of the Guidance Document - *Data Requirements to Support Comparative Claims Related to the Therapeutic Aspects of Nonprescription Drugs Used in Consumer-Directed Advertising and Labelling*. This guidance outlines the data requirements to support consumer-directed nonprescription drug comparative advertising and labelling.

Advertising preclearance agencies such as the Pharmaceutical Advertising Advisory Board and Advertising Standards Canada provide additional guidance through their respective codes of advertising acceptance.

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PART II - GUIDANCE DOCUMENT

Data Requirements to Support Comparative Claims Related to Therapeutic Aspects of Nonprescription Drugs Used in Consumer-Directed Advertising and Labelling

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Health Products and Food Branch

Issued: May 23, 1997
Administrative Update: October 2005

PART I - DIRECTIVE
Principles for Comparative Claims Related
to the Therapeutic Aspects of Drugs

A. Purpose

To provide a framework for the standards of supporting evidence and presentation of comparative claims in drug advertising such that these claims will not be false, misleading or deceptive to the intended audience.

B. Background

Section 9(1) of the *Food and Drugs Act* prohibits advertising and labelling for any drug that is "*false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety*". This legislative provision is intended to help minimize the risk associated with selection and use of drug products. To meet this condition, comparative claims must be based on conclusive evidence that is based on sound scientific principles.

In accordance with the requirements of the *Food and Drugs Act* and *Regulations*, pharmaceutical manufacturers are required to file a submission containing information and material to establish the safety and efficacy of a drug product prior to marketing, and to be in receipt of marketing authorization in the form of a Notice of Compliance (NOC) and/or a Drug Identification Number (DIN).

A drug submission in support of a request for issuance of a NOC or a DIN is required to establish the safety and efficacy of the product on its own merits. Apart from bioequivalence studies for second entry new drugs, a premarket drug submission is not generally **required** to include comparative data that would support a comparative claim. Although, some drug submissions do, in fact, include comparative data in support of clinical efficacy (e.g., where use of a placebo control would be inappropriate /unethical) comparative advertising claims are generally supported by evidence that was not submitted for premarket review.

It is Health Canada's responsibility to provide interpretation of regulatory provisions, and to set minimum standards for data requirements that would support market authorization **and** advertising claims. Consistent standards that are published for the reference of all stakeholders are essential to consistent regulatory, and preclearance review decisions and to a transparent, equitable regulatory system. In the absence of adequate standards, there

can be no assurance that comparative advertising claims will not be misleading, and that they will support the appropriate selection and use of drug products.

In a preliminary round of consultation on this issue in June 1996, stakeholders indicated that standards for comparative claims should ensure that the claim:

- is evidence-based and balanced,
- does not compromise health and safety,
- promotes informed choice,
- supports the selection of appropriate therapies that will lead to improved health outcomes
- is subject to independent review prior to dissemination,
- is not unfairly disparaging of competing products or drugs, and that
- the standards consider the differing needs of the various target audiences.

The *Competition Act* which applies to all marketing practices in Canada, also prohibits misleading or deceptive representations in advertising and requires that performance or efficacy claims be based on "adequate and proper" tests. Related interpretative guidelines state, inter alia, that these tests must be "concluded before the representation is made"; that "the results must not only be significant but must be meaningful"; and that "the reliability of the data resulting from a test is conditional upon achievement of similar results from a repetition of the test".

It is also pertinent to note that the U.S. Food and Drug Administration, in a 1994 letter to the pharmaceutical industry, indicated that comparability or superiority claims made on behalf of drug products are "subject to the same standards for review as for efficacy and safety claims in a product's approved labelling", and that comparative efficacy claims "generally must be based on at least two adequate and well controlled studies".

The principles expressed by stakeholders in the June 1996 consultation and the requirements of other regulatory authorities mentioned above were used as a guide in the development of this Directive. In turn, the principles expressed in this Directive are intended to guide the development by the independent advertising review agencies of more detailed standards for evidence and presentation of comparative claims related to therapeutic aspects of drugs.

C. Scope

This Directive applies to comparative claims, relating to therapeutic attributes, that are made in advertising for all drugs for human use, regardless of the intended audience or the medium of dissemination¹. The policy provisions also apply to such claims made in product labelling.

This Directive does **not** apply to comparison of nontherapeutic aspects of drug advertising, e.g., taste, flavour, colour, packaging, market position, or to claims of cost effectiveness or quality of life; neither does the policy refer to comparison with non-drug therapies.

The comparison relates to drug products/ingredients that have been authorized for sale in Canada.

D. Definitions

For the purposes of this Directive, the following terms are defined:

Comparative claim is a statement that compares an identified attribute of one drug product/ingredient to that of another/other drug product(s)/ingredient(s) in terms of comparability or superiority².

Terms of market authorization are comprised of information in the Product Monograph and the document that assigns a Drug Identification Number (DIN) (including related product labelling material and prescribing information) authorized by Health Canada upon issuance of the DIN.

Indication(s) for use is(are) the therapeutic/diagnostic/prophylactic use(s) defined in the authorized product information, and may include limitations to the drug product's use, such as the applicability to a specific population, (e.g., pediatric), or other special conditions (e.g., in combination with other therapies).

¹ Not applicable to direct-to-consumer advertising of prescription drugs which is restricted by regulation (Section C.01.044 of the *Food and Drugs Regulations*) to name, price and quantity.

² Claims such as "non-drowsy", "acts in half an hour" , "low incidence of side effect ..." that do not refer directly (more effective than product B) or by implication (e.g., more effective, faster) to other drug products/ingredients do not fall within the scope of this policy, but nevertheless must be supported by evidence based on sound scientific principles.

Conditions of use include the circumstances under which the product is used for the authorized indication(s), e.g., with adjunctive therapies, in-patient vs outpatient, daytime vs nighttime use.

Clinical relevance refers to the practical value of the claim itself in assisting prescribers and consumers to select an appropriate therapy, and to the practical value of a statistically significant effect when one treatment is compared to another.

Ingredient refers to the active ingredient(s) unless otherwise qualified.

E. Policy

Consistent with the provisions of Section 9(1) of the Food and Drugs Act, pharmaceutical manufacturers are required to observe the following principles in making claims that compare the therapeutic aspects of drugs:

1. the compared drugs/products have an authorized indication for use in common, and the comparison is related to that use; or, in addition to the common indication for use, a second authorized indication is claimed as an added benefit of the advertised drug; and
2. the comparison is drawn between drugs under the same conditions of use, e.g., at equivalent part(s) of their authorized dose ranges (e.g., maximum vs. maximum dosage), in a similar population; and
3. the claim does not conflict with the terms of market authorization of the compared products³, and
4. the claim is of clinical relevance in humans, i.e., relevant to treatment selection, and, where this is not readily apparent, its clinical relevance can be justified by the sponsor, and
5. the evidence generated to substantiate the claim is conclusive and based on:

³ For drugs subject to Division 8, Part C of the *Regulations*, Health Canada Policy: *Changes to Marketed Drugs* provides guidance on product information changes that require the filing of a Supplemental New Drug Submission, Notifiable Change etc. For drug products assigned a DIN but not subject to Division 8, Part C of the *Regulations*, Section C.01.014.4 of the *Regulations* identifies the product information changes that require a new DIN application, provided the new information does not render the product subject to Division 8, Part C of the *Regulations*.

- (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 data⁴.
6. the claim and its presentation should:
- (i) identify the compared entities⁵, and
 - (ii) the medicinal use related to the claim where this is not readily apparent⁶, and
 - (iii) not obscure the therapeutic use of the advertised product/ingredient⁷, and
 - (iv) not attack the compared drug product(s)/ingredient(s) in an unreasonable manner, and
 - (v) be expressed in terms, language and graphics that can be understood by the intended audience.

F. Roles and Responsibilities

Health Canada has currently endorsed two independent advertising preclearance agencies, the Pharmaceutical Advertising Advisory Board and Advertising Standards Canada. Additional information on the roles and responsibilities of these agencies and Health Canada may be located in these distinct policies:

⁴ extrapolation beyond the actual conditions of the supporting studies is not acceptable.

⁵ i.e., hanging comparisons such as "better", "faster acting" are unacceptable, as are vague statements such as "compared to the leading brand...."

⁶ where the advertised entity has more than one indication for use, it should be clear to which use the claim refers.

⁷ i.e., the comparative claim should be afforded no more prominence than the therapeutic use.

PAAB and Health Canada Roles and Consultation Related to Advertising Review.

Advertising Standards Canada and Health Canada Roles and Consultation Related to Advertising Review and Complaint Adjudication.

The independent advertising preclearance agencies are responsible for the evaluation of comparative claims in accordance with the principles and standards outlined in this Directive and Guidance Document. Additional clarification of their roles with respect to comparative advertising is provided below.

1. Responsibilities of Independent Advertising Preclearance Agencies

- a) Develop and publish explicit, detailed Standard Operating Procedures for review of comparative therapeutic claims to ensure that the same standards and criteria contained in the “Directive” and “Guidance Document” are applied to all such evaluations (internal agency consistency and inter-agency consistency to ensure expected outcomes) and that they are in accordance with those exercised by Health Canada when granting market authorization.
- b) Function as the first level for lodging drug advertising complaints from any source (trade competitors, health professionals, associations, consumers).
- c) Ensure that the comparative claim does not compromise consumer safety or consumer protection against false or misleading advertising by:
 - (i) declining misleading advertising (e.g., those that contain an incomplete message);
 - (ii) obtaining from the advertiser all the information required by the Guidance Document necessary to draw valid conclusions and a balanced view;
 - (iii) reviewing comparative claims in the context of the available body of scientific evidence with respect to the comparator drugs;
 - (iv) requesting labelling that is current and consistent with the terms of market authorization and any promotional materials relevant to the proposed claim and campaign; and
 - (v) consulting with Health Canada on any perceived new indications,

unclear safety issues, etc.

2. Responsibilities of Health Canada

- a) Retain ultimate responsibility for decisions regarding product safety.(e.g., Health Canada takes direct action if advertising claims lead to potential health safety hazards).
- b) Evaluate comparative therapeutic claims submitted to Health Canada in the context of a submission (DINA, NDS, SNDS).
- c) Establish effective liaison with independent advertising preclearance agencies by making publicly available distinct Policies and Standard Operating Procedures outlining the roles and consultation processes for complaints adjudication between Health Canada and advertising preclearance agencies. Provide relevant information within the constraints of maintaining confidentiality.
- d) Inform and seek input from independent advertising preclearance agencies and advertising sponsors of new processes, procedures, policies and guidelines in development related to the review of therapeutic comparative claims in labelling and advertising.
- e) Review and determine the acceptability of new therapeutic claims and/or conditions of use should the comparison fall outside the scope of the parameters under which market authorization was granted. This will be undertaken pursuant to the filing of the appropriate submission to Health Canada.
- f) Ensure transparency in its decision making and documentation of the data upon which market authorization was based, subject to existing parameters of confidentiality.
- g) Upon request, advise the independent advertising preclearance agencies on unclear safety issues, new indications, etc., within the constraints of maintaining confidentiality.
- h) Review and approve all comparative therapeutic claims to be included in the labelling (as opposed to advertising) of drugs.
- i) If required, audit the independent advertising preclearance agencies to ensure compliance with the terms of the agreement between Health

Canada and the independent advertising preclearance agency.

- j) Function as the next level of appeal, when all appeal mechanisms of the advertising preclearance agencies have been utilized without a resolution of the appeal for advertising complaints.

3. Responsibilities of Advertising Sponsor

- a) Submit to Health Canada the comparative claims which represent conditions of use that exceed the parameters under which marketing authorization was granted (e.g., new dose, indications, population), in the context of a drug submission.
- b) Observe the advertising regulatory provisions outlined in the *Food and Drugs Act and its Regulations* and all applicable codes, guidelines, guidances and policies.
- c) Demonstrate to independent advertising preclearance agencies that the comparative therapeutic claim has not been extrapolated beyond the actual conditions and study populations of the supporting comparative clinical trials unless a sound, scientific justification has been provided for doing so.
- d) Provide to independent advertising preclearance agencies sound scientific evidence in support of the comparative therapeutic claims that is in accordance with the requirements outlined in the "Directive" and "Guidance Document".
- e) Provide to independent advertising preclearance agencies copies of labelling that is current and consistent with the terms of market authorization (most recent Health Canada-approved Product Monograph, Labelling Standard, Prescribing Information, Patient/Consumer Package Insert, or label, as the case may be) and any promotional materials relevant to the proposed claim and campaign.
- f) Provide authorization for independent advertising preclearance agencies to access the data upon which Health Canada market approval was based.
- g) Ensure the continuing validity of the comparative claims by reassessing the supportive evidence and amending the claim(s) to remain consistent with emerging new data or information.

G. Effective Date

With respect to the review of product labelling, this Directive became effective upon the date of first publication, May 23, 1997.

With respect to product advertising, this Directive is effective upon the date of publication and will be put into operation upon finalization of implementation guidelines by independent advertising preclearance agencies such as the Pharmaceutical Advertising Advisory Board (PAAB) and Advertising Standards Canada (ASC).

The PAAB, has incorporated the *Health Canada Directive: Principles for Comparative Claims Related to the Therapeutic Aspects of Drugs* in Section 5 and 11 of their Code of Advertising Acceptance on January 1, 1999. These Sections provide guidance for the preclearance of comparative therapeutic claims for use in advertising of prescription and nonprescription drugs directed to health professionals.

Implementation guidelines for the preclearance of comparative therapeutic claims for use in advertising of nonprescription drugs directed to consumers, pursuant to Part II of this document, remain to be finalized.

Health Products and Food Branch

Issued: March 2001
Administrative Update: October 2005

PART II - GUIDANCE DOCUMENT

Data Requirements to Support Comparative Claims Related to Therapeutic Aspects of Nonprescription Drugs Used in Consumer-Directed Advertising and Labelling

A. Purpose

To provide data requirements to support the inclusion of comparative therapeutic claims for use in consumer-directed nonprescription drug advertising and labelling. This Guidance Document complements the Directive, *Principles for Comparative Claims Related to the Therapeutic Aspects of Drugs* issued by Health Canada on May 23, 1997, revised in March 2001 and updated in October 2005.

B. Background

These data requirements have been developed after extensive consultation with industry, associations, independent advertising preclearance agencies and Health Canada. They set the minimum standards for data requirements that would support the inclusion of comparative therapeutic claims for use in **consumer-directed nonprescription drug advertising and labelling**. This Guidance Document outlines the standards adopted by Health Canada for use by independent advertising preclearance agencies and sponsors. Clear standards are set to avoid any potential disagreement concerning the level of evidence required to support comparative claims.

C. Definitions

For the purpose of this guidance document, the following terms are defined:

Comparative Therapeutic Claim: A statement that compares an identified therapeutic attribute of one drug product/ingredient to that of another /other drug product(s)/ingredient(s) in terms of equivalence, parity or superiority.

Types of Comparative Claims: Superiority - Product claims performance better than another product (Brand A works better than Brand B at relieving heartburn).

Equivalence - Product claims equal or identical performance to another product. (Brand A works as

well as Brand B at relieving heartburn).

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.)

Product:	Refers to the Brand Name of a particular drug which may be composed of one or more active ingredients.
Ingredient:	Refers to the active ingredient(s) unless otherwise qualified.
Brand Name:	Means, with reference to a drug, the name, whether or not including the name of any manufacturer, corporation, partnership or individual, in English or French, that is assigned to the drug by its manufacturer, under which the drug is sold or advertised, and that is used to distinguish the drug.
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..
Systematic Review ¹ :	A summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies.

¹ Definition from: Sackett DL, Strauss SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*; New York; Churchill Livingstone; Second Ed.:2000. The appraisal of individual studies submitted by the sponsor includes the review of the data submitted.

D. Data Requirements

Evidence to support comparative therapeutic claims of nonprescription drugs must be conclusive, definite, validated and must possess the highest level of evidence.

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

However, the review Bureau 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 Health Canada on a case by case basis. Also, the study must be designed in the very beginning to show superiority. This type of study design is quite different from that normally used for ordinary clinical trials to show safety and efficacy. Ordinary clinical trials which may have accidentally shown some potential superiority after the trial was completed, normally are not of an adequate design and power to conclusively demonstrate product superiority.

However 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 the 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 Health Canada on a case by case basis.

1. Comparative efficacy

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. This 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.

1-1 Standard of evidence

- a) For drugs that are subject to the requirements of Division 8 of the *Food and Drug Regulations*, the efficacy parameters measured in 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 presented. 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.

- b) Product to product (brand name A to brand name B) comparison
- (i) Statements that make an **equivalence, parity, or a superior** efficacy claim must be supported by at **least two independent**², well-designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards (see Section 1-3(a)). 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
 - (ii) Sponsors should provide an attestation that the results of supporting studies reflect the "body of available evidence"³ and have not been superseded by contradictory findings⁴; or, a justification for any difference should be provided for consideration.
or
 - (iii) If conditions i) and ii) are not presented then data reported in the public domain (e.g., articles in peer reviewed, 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 (such data are also subject to the standards cited in Section 1-1 b) (i) and (ii)⁵.

² The term 'independent' is not meant to exclude company-sponsored clinical trials.

³ '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'.

⁴ Intended to ensure that the results are viewed in the context of all available information.

⁵ Peer review of published articles is not all conducted to the same standard.

c) Ingredient to ingredient or product to ingredient comparisons

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).

(i) 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 meet the standards cited in Section 1-1 (b)(i) and (ii).

(ii) The systematic review should adhere as closely as possible to the following methodological guidelines⁶:

- the research plan should be documented *a priori*, and should include:
 - . the question(s) to be addressed by the review;
 - . a reproducible and robust method for finding all relevant studies for review⁷, with search parameters stated;
 - . a reproducible method for selecting studies, from those retrieved, for detailed review (inclusion and exclusion criteria, with a list of excluded studies);
 - . a reproducible method for evaluating the scientific quality of studies;
 - . a reproducible method for extracting evidence from studies;
 - . identification of proposed subgroup analyses;

⁶ Consistent with the principles expressed in: Cook DJ, Sackett DL and Spitzer WO. Methodologic Guidelines for Systematic Reviews of Randomized Control Trials in Health Care from the Potsdam Consultation on Meta-analysis. *J. Clin. Epidemiol.*1995;48:167-171.

⁷ 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.

- a documented justification to support any changes in the predetermined plans for data retrieval and subgroup analyses;
 - labelling of all subgroup analyses according to whether they are *a priori* or *a posteriori*;
 - 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;
 - the results of the systematic review and meta-analysis should be provided.
- (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.
- d) Product/ingredient to **all** other Canadian products/ingredients for the same indication
- (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 Section 1-1(b) and (c).

1-2 Test and reference products

- a) For product vs. product comparisons, the actual products cited in the comparison should be used in the supporting comparative clinical trials.
- 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:

- (i) the sponsor's Canadian product is identical⁸ to, or has no major change(s)⁹ from the corresponding non-Canadian product used in the **original** studies and this has been verified by the manufacturer; **and**
- (ii) the compared product complies with Health Canada Policy: *Canadian Reference Product*; **or**
- (iii) the compared product is a product which would not be subject to a bioequivalence study for premarket approval in accordance with Health Canada Guideline *Preparation of Drug Identification Number Submissions* and meets the criteria in Appendix II;
- (iv) the Canadian and non-Canadian comparator products are shown to be bioequivalent¹⁰.

Where these criteria are not met, clinical studies using the Canadian versions of the compared products are required.

1-3 Clinical study design/methodology/analysis

- 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;

⁸ Identical master formula and manufacturing process

⁹ Major change(s) as defined by a Level 1 or Level 2 change in Health Canada Policy on *Changes to Marketed New Drugs*.

¹⁰ If the comparator product, in accordance with current Health Canada Guidelines and Policies (see Appendix I), 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.

- (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.

1-4 Interpretation

- a) The minimum acceptable level of statistical significance of the measured difference between treatments is $p < 0.05$; the 95% confidence intervals should also be stated;
- b) Evidence of clinical relevance should be presented in order to assist the consumer in selecting an appropriate therapy;
- 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 equivalence¹¹;
- 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

¹¹ 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;3:345-353.

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.*

2. Onset or duration of action

Comparison may be made between drug products/ingredients regarding the onset or duration of action where this measurement is of clinical relevance¹² in humans, provided the general provisions of the directive, the guidance document and this section are met. This comparison should be based on existing Health Canada approved product information, since new information on onset of action is subject to Health Canada review.

2-1 Standard of evidence

- 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.
- b) Product to product (brand name A vs. brand name B) comparison
 - (i) Two clinical trials, as outlined in Section 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.
 - (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

¹² As defined in the Definitions of this Guidance document. Refers to the practical value of the claim itself in assisting consumers to select an appropriate therapy.

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

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.

(iii) Sponsors should provide an attestation that the results of supporting studies reflect the "body of available evidence"³ and have not been superseded by contradictory findings; alternatively, a justification for any difference should be provided for consideration;

c) Ingredient to ingredient and product to ingredient comparisons

(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.

d) Product/ ingredient to **all** other Canadian products/ingredients for the same indication

(i) Evidence and data generated to support equivalence, parity, or superiority 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.

2-2 Test and Reference products

a) For product vs. product comparisons, the actual products cited in the comparison should be used in the supporting comparative clinical trials.

b) Data generated to support a **product to product comparison** from clinical

³ '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'.

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:

- i) the sponsor's Canadian product is identical⁸ to, or has no major change(s)⁹ from the corresponding non-Canadian product used in the **original** studies and this has been verified by the manufacturer;
and
- (ii) the compared product complies with Health Canada Policy: *Canadian Reference Product*;
or
- (iii) the compared product is a product which would not be subject to a bioequivalence study for premarket approval in accordance with Health Canada Guideline *Preparation of Drug Identification Number Submissions* and meets the criteria in Appendix II;
- (iv) the Canadian and non-Canadian comparator products are shown to be bioequivalent¹⁰.

Where these criteria are not met, clinical studies using the Canadian versions of the compared products are required.

2-3 Interpretation

- a) The minimum acceptable level of statistical significance of the measured difference between treatments is $p < 0.05$; the 95% confidence interval should also be stated.
- b) Evidence of clinical relevance should be presented in order to assist the consumer in selecting an appropriate therapy.

⁸ Identical master formula and manufacturing process.

⁹ Major change(s) as defined by a Level 1 or Level 2 change in Health Canada Policy on *Changes to Marketed New Drugs*.

¹⁰ If the comparator product, in accordance with current Health Canada Guidelines and Policies (see Appendix I), 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.

- 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 equivalence¹¹.

3. Comparison of side effect profiles and other safety parameters

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

3-1 A comparison of side effects and other safety parameters may be done if the following conditions (where applicable) are met:

- a) the approved indications are disclosed in the advertisement;
- b) the side effect is self-limiting, self-recognizable, understandable and of clinical relevance to the consumer (e.g., dizziness, drowsiness, dry mouth);
- c) given the broad spectrum of nonprescription drugs, all comparisons for products that have complex side effect/safety profiles must present the benefits and the risks of each drug to provide an accurate, balanced and fair representation;
- d) as the complexity or seriousness of adverse effects and safety concerns increase, the access to easily understandable patient information for the sponsor's drug must increase and be readily available for consumers;
- e) sponsors should always provide easy access to the complete patient information on proper drug use, (e.g., patient package insert, Product Monograph) which may include simultaneous dissemination to targeted audiences in various mediums such as print, 1-800 information lines, broadcast, Internet etc. (the amount of information made available would increase especially as complexity of comparisons increase);
- f) comparisons that require medical/scientific knowledge to accurately interpret the results are to be avoided in consumer directed advertising;

¹¹ 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;3:345-353.

- g) the advertisement should not impact negatively on patient compliance, nor deter or cause delay from seeking appropriate treatment. Provisions should be included to refer consumers to a qualified health care professional (pharmacist, nurse, physician etc) if consumers require additional information or if symptoms persist;
- h) the advertisement does not attack the compared drug product(s)/ingredients(s) in an unreasonable, disparaging manner;

Comparison of drug interactions, complex adverse reactions, contraindications, precautions, risks and other safety factors are difficult to present to consumers without being potentially misleading or deceptive. This is especially difficult to achieve in most advertising media which are limited in time and length. Furthermore, generalizations concerning comparisons of product effects may not always be applicable to each individual because other confounding factors such as the individual's medical conditions, use of multiple drug therapies etc., may directly impact on the selection of appropriate drug therapy. It is considered misleading to focus on a comparison of one particular side effect or safety parameter of a drug product to show a benefit, when in fact the product may show other side effects or safety concerns that compare unfavourably with the comparator product.

In most cases, a fair and balanced presentation of comparable effects can only be carried out when a complete comparison of the benefits and risks of two drugs is done. The overall safety of a drug depends on many factors and to highlight only one aspect provides an incomplete picture of the product merit and may be inherently misleading. Even in such a complete comparison, caution is required because the message may still be confusing if an evaluation of that material requires medical/scientific knowledge to accurately interpret that information.

Claims based on differences that are subtle or require the disclosure of study parameters in order to accurately interpret the results, obviously should not be advertised to the public but only to the health professional who has the expertise to understand the scientific complexities and nuances. Therefore, if such comparisons are targeted to the public, they must be considered with caution as the amount of information required to provide a fair and balanced view of the relative safety may exceed the amount of information that can reasonably be provided to and/or understood by the consumer in most consumer advertising messages.

3-2 Standard of evidence

- a) The side effects and safety parameters compared must be limited to those that are cited in Health Canada approved terms of market authorization and/or labelling of the products compared (for a product vs. product comparison), or of those currently required to be referenced in Health Canada approved PM or labelling of products containing only those ingredients compared (for an ingredient vs. ingredient comparison)
- b) Product to product (brand name A vs. brand name B) comparison
- (i) To support product to product comparison of side effect and safety profiles, the evidence based on clinical or other studies must be supported by at least two independent², well designed, adequately controlled, blinded, randomized clinical studies that have been conducted to current scientific standards, which meet the conditions outlined in Section 1-1(b), 1-2, 1-3(a) and 1-4(c).
- (ii) Sponsors must provide an attestation that the results of supporting studies reflect the "body of available evidence"³ in the public domain and have not been superseded by contradictory findings, or an explanation/ justification for any difference should be provided for consideration. The "attestation" must contain the results of either a meta-analysis or a systematic review to show that the two studies reflect the body of medical evidence, provided the conditions in Section 1-2 are met for International data.
- (iii) Comparison of the authorized product information may be used to support comparison of the side effect and safety profile of the advertised product in contrast to the compared product, provided that:
- effects unique to differences in formulation and route of administration have been accounted for;
 - the study populations, methodologies, dosing and measurement criteria are comparable;
 - the side-by-side presentation of adverse events and safety data

² The term 'independent' is not meant to exclude company-sponsored clinical trials.

³ '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'.

are comparable.

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

- c) Ingredient to ingredient and product to ingredient comparisons

In addition to the criteria outlined in Section 3-2 (a) and (b):

- (i) Statements that compare the side effect and safety profiles of drug ingredients in terms of their presence or absence¹² should be based on evidence obtained through a systematic review¹³ of the available evidence relating to the compared ingredients.
- (ii) With respect to a comparison of the incidence of side effects of ingredients, the method of quantifying the incidence must be identical for all compared entities, and the data and method of calculation must be provided.

- d) Product/ingredient to **all** other Canadian products/ingredients for the same indication

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

3-3 Test and reference products

Refer to Sections 1-2 and 2-2.

3-4 Interpretation

- a) The minimum acceptable level of statistical significance of the measured difference between treatments is $p < 0.05$; the 95% confidence intervals

¹²

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

¹³

It is recognized that it may not be possible to include a quantitative analysis.

should also be stated.

- b) Evidence of clinical relevance should be presented in order to assist the consumer in selecting an appropriate therapy.¹⁴
- 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.¹¹

E. Effective Date

With respect to the review of product labelling, this guidance document is effective upon the date of publication.

With respect to product advertising, this Guidance Document is effective upon the date of publication and will be put into operation upon finalization of implementation guidelines by the independent advertising preclearance agencies endorsed by Health Canada.

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

¹¹ 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;3:345-353.

Appendix I

PREPARATION OF DRUG SUBMISSIONS INVOLVING COMPARATIVE BIOAVAILABILITY STUDIES AND BIOEQUIVALENCE

Health Canada has published numerous guidelines and policies to assist manufacturers in filing drug submissions. The following provides a list of contacts and Web site addresses for those guidelines and policies which may be of particular interest to sponsors of Abbreviated New Drug Submissions (ANDS); New Drug Submissions (NDS) which involve comparative bioavailability studies related to bioequivalence; and supplements to such submissions. This list is NOT INCLUSIVE, and one must appreciate that the Web site is subject to continual update and improvement, but this list should be helpful in accessing the more relevant guidances.

Health Products and Food Branch (HPFB) Web site address:

http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/index_e.html

Guidances related to Bioavailability and Bioequivalence Studies

Draft Guidance for Industry - Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format - May 18th, 2004

Notice

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ctdbe_notice_avis_e.html

Draft Guidance Document

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/draft_ebauche_ctdbe_e.html

Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations used for Systemic Effects 1992

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/bio-a_e.html

Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations - July 23, 1997

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/bio-b_e.html

Canadian Reference Product - December 5, 1995

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/crp_prc_pol_e.html

Bioequivalence of Proportional Formulations: Solid Oral Dosage - March 7, 1996

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/pol/bioprop_pol_e.html

Guidance for Industry : Pharmaceutical Quality of Aqueous Solutions - February 15th, 2005

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/aqueous_aqueuses_e.html

Bioequivalence Requirements: Drugs Exhibiting Non-linear Pharmacokinetics -DRAFT - July 3rd, 2003

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/pol/nonlin_pol_e.html

Related Guidances

Guidance to Industry; Management of Drug Submissions Health Canada Policy; Appeals Procedures for Drug Submissions - April 4, 2003

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/pol/appe_pol_e.html

Guideline on Preparation of Drug Identification Number (DIN) Submissions - February 22, 1995

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/din/pre_din_ind_e.html

Stereochemical Issues in Chiral Drug Development - February 14, 2000

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/stereo_e.html

Letter to Associations - Comprehensive Summary - Chemistry and Manufacturing (CS(CM-rDNA)) and Certified Product Information Document (CPID) April 1, 1996

http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demanded/guides/qualit/prod/lett-cmr dna-cfadnr/cscm-sgc_f_let_e.html

Generic Parenteral Drugs, Submissions for - March 1, 1990

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/pol/gen_subm_pres_pol_e.html

Submissions for Topical Non-Steroidal Anti-inflammatory Drugs (Topical NSAIDs) -
July 22, 1998

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/topnsaids_ainstop_pol_e.html

Guidance for Clinical Trial Sponsors : Clinical Trial Applications

Notice

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdctanotice_ctddecavis_e.html

Guidance Document

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec_e.html

Modification to Good Manufacturing Practices (GMP) Guidelines 2002 Edition, May 23,
2002

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/guide-ld-2002/index_e.html

Appendix II

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 Canada Guidelines and Policies.
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.
3. Labelling for the foreign comparator drug product and the comparator drug product marketed in Canada must be submitted and shown to be comparable.
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 (e.g. 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.