Interchangeable Drug Products - Additional Criteria

Principle:

Decisions respecting interchangeability and drug lists remain in the domain of the institution responsible for the costs of the product which includes hospitals, provincial governments and other third party payers (*6/9/95 Canada Gazette Part ll, Vol. 129, No. 18)*

Preface:

The *Alberta Health and Wellness Drug Benefit List (AHWDBL*) contains designations of interchangeability for approved multisource drug products. The Expert Committee on Drug Evaluation and Therapeutics makes recommendations on interchangeability to Alberta Health and Wellness through the Executive Director, Pharmaceutical Funding and Guidance Branch, Health Policy and Service Standards Division. The Minister of Health and Wellness makes the final decisions on interchangeability after reviewing the recommendations of the Expert Committee and/or Alberta Health and Wellness.

Definitions:

(Note: additional definitions in the applicable Appendices may apply)

Interchangeable Drug Product: An interchangeable drug product is a drug product that has been designated as interchangeable by the Minister of Health and Wellness after reviewing the recommendations of the Expert Committee or Alberta Health and Wellness. Recommendations regarding interchangeability are made taking into consideration the scientific, therapeutic, clinical and socio-economic merits of drug products in accordance with the published criteria. Drug products designated as interchangeable are expected to be safe when interchanged with other drug products in the interchangeable grouping, and to have the same therapeutic effectiveness when administered to patients under the conditions specified in the labeling. The designation of interchangeability is made only for the purpose of funding of drug benefits covered under the Alberta government-sponsored drug benefit programs and is not to be used as a scientific reference or prescribing guide.

Multisource Drug Product: Drug products are considered to be multisource drug products when they are manufactured and/or distributed by more than one manufacturer.

Pharmaceutical Alternative: Drug products may be considered to be pharmaceutical alternatives if they use the same route of administration and contain the same active therapeutic ingredient(s) but are different salts, esters or complexes of that moiety, or are different dosage forms or strengths.

Pharmaceutical Equivalent: Drug products are considered to be pharmaceutical equivalents if they contain the same active therapeutic ingredient(s), are of comparable dosage form(s), route of administration and are identical in strength or concentration.

Pseudo-Generic Drug Product: A pseudo-generic drug product is a drug product that is manufactured under the identical master formulae and manufacturing and quality control specifications as a) the innovator brand of the drug; or b) any drug product that is currently listed on the *AHWDBL* within the submission product's interchangeable grouping.

TPD Reports - refers collectively to the following Health Canada Therapeutic Products Directorate (TPD) guidance publications as of December 31, 2009:

- *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects, and Part B: Oral Modified Release Formulations*; (which may be referred to in the *List* as "**TPD Part A**", and "**TPD Part B**"); and
- *Report C: Report on Bioavailability of Oral Dosage Formations, Not in Modified Release Form, of Drugs used for System Effects, Having Complicated or Variable Pharmacokinetics (*which may be referred to in the List as "**TPD Report C**"); and
- *Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State*.

Interchangeable Reviews:

A. The Expert Committee and/or Alberta Health and Wellness and/or the Minister may, in addition to considering the *Interchangeable Drug Products* criteria, also consider any other criteria in the AHWDBL, including but not limited to the *Criteria for Listing Drug Products*.

B. Recommendations regarding interchangeability are made taking into consideration the scientific, therapeutic, clinical and socio-economic merits of drug products in accordance with the published criteria. Drug products designated as interchangeable are expected to be safe when interchanged with other drug products in the interchangeable grouping, and to have the same therapeutic effect when administered to patients under the conditions specified in the labeling.

C. Issuance of a Notice of Compliance by the TPD which includes a Declaration of Equivalence does <u>not</u> mean the drug product will automatically be designated as interchangeable.

<u>Expedited Reviews</u>

1. Multisource drug products seeking a listing designation as interchangeable may be eligible for an expedited review if:

   a. The drug product submission complies with the submission requirements.

   b. The drug product does **NOT** fall into any of the categories of drug products that require a Full Review (below), unless the drug product is a Pseudo-Generic Drug Product.

   c. The drug product is not a subsequent entry biologic (subsequent entry biologics are not eligible for review as interchangeable products).

d. The drug product has been granted a Notice of Compliance by Health Canada that includes a declaration of bioequivalence with a Canadian brand/innovator reference product that is listed (or at the sole discretion of Alberta Health and Wellness and/or the Minister, has been previously listed) on the *Alberta Health and Wellness Drug Benefit List*.

e. The drug product must be a pharmaceutical equivalent to the Canadian innovator reference product.

f. The proposed price in Alberta provided in the manufacturer's submission complies with the Price Policy.

g. Even if the drug submission review is expedited, Alberta Health and Wellness and/or the Minister may refuse to list a drug product, or the listing of the drug product may be delayed, if the manufacturer has failed
   (A) to provide a Price Confirmation,
   (B) to provide a Price Confirmation or Confirmed Price in accordance with the Price Policy and/or the applicable APC Terms and Conditions; or
   (C) to comply with the terms and conditions of an applicable APC.

Full Reviews

Multisource drug products seeking a listing designation as interchangeable that fall within the categories listed below are required to undergo a Full Review by the Expert Committee. The following additional interchangeability criteria will apply to Full Reviews:

1. The drug product must be a
   a. pharmaceutical equivalent; or
   b. pharmaceutical alternative,
   as determined at the sole discretion of the Expert Committee.

2. The drug product is not a subsequent entry biologic (subsequent entry biologics are not eligible for review as interchangeable products).

3. The proposed price in Alberta contained in the manufacturer's submission complies with the Price Policy.

4. The drug product has been demonstrated to be bioequivalent, or has provided evidence of comparative therapeutic efficacy, with the reference drug product as outlined below;

   a. For drug products in the following categories, for which bioequivalence studies CAN be conducted:

      i. For Critical Dose Drug Products, the drug product must meet the criteria in the *Critical Dose Drug Product Appendix*.

      ii. For Non-Linear Drug Products, the drug product must meet the criteria in the *Non-Linear Drug Product Appendix*.

iii. For Rapid Onset Drug Products, the drug product must meet the criteria in the *Rapid Onset Drug Product Appendix*.

iv. For Drug Products for which Bioequivalence is Supported by Metabolite Data, the drug product must meet the criteria in the *Drug Products with Metabolite Data Appendix.*

v. For Drug Products for which Bioequivalence is Supported by Measurement of the Drug in a Matrix other than Plasma or Serum (e.g., Whole Blood, Urine, Tissue), the drug product must meet the criteria in the *Drug Product with Alternate Matrix Measurement Appendix*.

vi. For Old Drug Products, the product must meet the criteria in the *Old Drug Product Appendix*.

vii. For Drug products which possess complex delivery systems, the product must meet the criteria in the *Complex Delivery System Drug Product Appendix*.

b. For drug products in the above categories for which bioequivalence studies CANNOT be conducted:

i) Evidence of comparative therapeutic efficacy of the submitted product with the reference product via:

(A) a therapeutic equivalence study; or

(B) Studies that meet the requirements and standards for pharmacodynamic studies outlined in TPD Report C;

and

ii) Sufficient rationale for why a bioequivalence study cannot be conducted**.**

c. For drug product submissions using a Non-Canadian Reference Product (NCRP):

i) An NCRP may only be used when it meets the *Criteria for use of a Non-Canadian Reference Product* as set out in Health Canada's *Drugs Directorate Policy regarding the use of a Non- Canadian Reference Product under the provisions of Section C.08.002.1(c) of the* Food and Drug Regulations (the "NCRP Criteria"). See also *Interpretation Notice #1*.

ii) If the NCRP Criteria is met, the drug product must demonstrate bioequivalence to the NCRP through studies that meet the requirements and standards of the applicable TPD Reports.

5. The drug product must meet all other criteria outlined in the applicable Appendix.

6. In addition, the Expert Committee may also consider any other factor that may affect the interchangeability of a drug product, including but not limited to:

    - characteristics of the drug product (e.g. shape, scoring, configuration, packaging, labelling);
    - excipients and non-medicinal ingredient(s) (e.g. sugar, sodium);
    - expiration times;
    - storage conditions.

Interchangeable Drug Products - Additional Criteria APPENDICES

Critical Dose Drug Product Appendix

Critical Dose Drug: Is a drug where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent disability or incapacity, or death.

Critical dose drugs include:

a) Any drug listed in *Appendix I - List of Critical Dose Drugs* of Health Canada's Guidance for Industry entitled *Bioequivalence Requirements: Critical Dose Drugs*; and
b) Any other drug that the Expert Committee determines meets the above definition, which determination may include consideration of any other matter that may affect the interchangeability of a product containing a critical dose drug.

Criteria: Bioequivalence studies must meet the requirements and standards in the TPD Reports, with the exception that the following standards will be used:

1. The 90% confidence interval of the relative mean AUC of the test to reference formulation should be within 90.0 to 112.0%; the relevant AUC or AUCs as described in TPD Reports A and B are to be determined.
2. The 90% confidence interval of the relative mean measured Cmax of the test to reference formulation should be between 80.0 and 125.0%.
3. These requirements are to be met in both the fasted and fed states.
4. These standards should be met on log transformed parameters calculated from the measured data and from data corrected for measured drug content (percent potency of label claim).
5. If a steady-state study is required, the 90% confidence interval of the relative mean measured Cmin of the test to reference formulation should also be between 80.0 and 125.0%.

Non-Linear Drug Product Appendix

Non-Linear Drug: A drug is considered to be a Non-Linear Drug if the Health Canada approved product monograph for the Canadian innovator drug product states that it is a non-linear drug.

Criteria:

1. Bioequivalence studies must meet the requirements and standards in the TPD *Reports*, and these requirements and standards should be met in single dose studies in both the fasted and fed states, with the following exceptions:

a) if non-linearity occurs after the drug enters the systemic circulation, a fed study may be waived unless there is sufficient evidence, at the Expert Committee's sole discretion, that a product exhibits a food effect; or

b) if a condition (fasted or fed) for product ingestion is contraindicated, that condition may be waived in a bioequivalence trial. For bioequivalence testing the fasting and fed doses should be the same.

2. At the sole discretion of the Expert Committee, it may be acceptable to conduct bioequivalence studies at either the highest or lowest strength of a range of proportionally formulated strengths as outlined below:

a) For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in **greater than proportional increases in AUC** with increasing dose, the bioequivalence studies should be conducted on at least the **highest** strength. That is, where non-linearity arises from capacity-limited clearance, the highest strength for the proposed indications should be tested. For drugs where the non-linear concentration range is reached only after multiple doses within the approved dosing regimen, studies utilizing multiple units of the highest formulation strength or steady-state studies in the non-linear range may be required. Where steady-state studies are conducted, single dose studies will not be required. In all situations, safety in dosing should be considered.

b) For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in **less than proportional increases in AUC** with increasing dose, the bioequivalence studies should be conducted on at least the **lowest** strength (single dose unit). That is, where non-linearity arises from capacity-limited absorption, the test dose should be a single unit of the lowest strength.

Rapid Onset Drug Product Appendix

Rapid Onset Drugs: Are as defined in TPD Report C.

Criteria: Bioequivalence studies must meet the requirements and standards in the TPD *Reports*, except that the relative mean $AUC_{Reftmax}$ of the test to reference formulation should be within 80 to 125%, where $AUC_{Reftmax}$ for a test product is defined as the area under the curve to the time of the maximum concentration of the reference product, calculated for each study subject.

Drug Product with Metabolite Data Appendix

For drug product submissions for which evidence of bioequivalence is supported by metabolite, rather than the parent drug, data.

Criteria:

1. Bioequivalence studies must meet the requirements and standards in the TPD Reports.

2. If the parent drug is not detectable due to rapid biotransformation or limitations in available assay methodology, the use of metabolite data may be acceptable.

3. The measured metabolite must be a primary (first step) measureable by a validated assay, and there must be sufficient scientific justification for a waiver of the measurement of the parent drug and the use of metabolite data.

4. The choice of using the metabolite instead of the parent drug is to be clearly stated, *a priori*, in the objective of the study in the study protocol.

5. The use of metabolite concentrations in urine is not acceptable.

Drug Product with Alternate Matrix Measurement Appendix

For drug product submissions for which bioequivalence data is supported by measurement of the drug in a matrix other than plasma or serum (e.g., whole blood, urine, extravascular tissue).

Criteria:

- Bioequivalence studies must meet the requirements and standards in the TPD *Reports.*
- The assay used for measurement of the drug (or metabolite) must be validated for the alternate matrix of measurement.
- Sufficient rationale for why the use of an alternate matrix measurement study is appropriate.

Old Drug Product Appendix

Old Drugs: Are drug products where the active therapeutic ingredient(s) is designated as an "old drug" by Health Canada and the drug product is approved on the basis of a DIN application (i.e. an NOC is not issued by Health Canada).

Criteria:

1. Bioequivalence studies must meet the requirements and standards in the TPD *Reports.*
2. For old drug products for which bioequivalence studies CANNOT be conducted, the submission must include:

    i) Evidence of comparative therapeutic efficacy of the submitted product with the reference product via:

        (A) a therapeutic equivalence study; or

        (B) studies that meet the requirements and standards for pharmacodynamic studies outlined in TPD Report C; or

        (C) surrogate comparisons using *in vivo* or *in vitro* test methods.

    and

    ii) Sufficient rationale for why a bioequivalence study cannot be conducted**.**

Complex Delivery System Drug Product Appendix

Complex Delivery System Drugs: Are drug products that possess complex drug release characteristics in the pharmaceutical dosage form that are intended to:

(1) deliver the drug at a rate that is independent of time and the concentration of the drug (i.e. zero order process), or

(2) deliver the drug to a specific physiological site (i.e. site-specific release).

Criteria:

1. Bioequivalence studies must meet the requirements and standards in the TPD Reports.
2. A detailed description of the pharmaceutical dosage forms and specific drug release characteristics of the submitted drug product and reference drug product must be provided to permit evaluation of the similarity of drug release of the respective formulations.