NOVA SCOTIA CRITERIA FOR INTERCHANGEABILITY

The Nova Scotia Department of Health through Pharmaceutical Services (PS) approves a schedule of commonly prescribed, interchangeable pharmaceutical products in accord with Chapter 36 of the Acts of 2001, the Pharmacy Act.

The Drugs and Therapeutics Committee, representing the professions of Medicine, Dentistry and Pharmacy, is responsible for determining interchangeability among pharmaceutical products and for recommending to the Department of Health those products which will appear as interchangeable in the Nova Scotia Formulary.

Composition of the Drugs and Therapeutics Committee:

Chairperson, (PS Appointment)

Secretary, (PS Appointment)

PS Liaison

Medical Society of Nova Scotia - 2 representatives

College of Pharmacy, Dalhousie University - 1 representative

Nova Scotia College of Pharmacists (Community Practice) - 2 representatives

Nova Scotia College of Pharmacists (Hospital Practice) - 1 representative

Nova Scotia Dental Association - 1 representative

Department of Pharmacology, Faculty of Medicine, Dalhousie University - 1 representative

Clinical Department of the Faculty of Medicine, Dalhousie University - 1 representative

Nova Scotia Provincial Drug Purchasing Program, (PS Appointment) - 1 representative

INCLUSION CRITERIA

Pharmaceutical products are considered for interchangeability only when they are the subject of a formal submission which complies with the Nova Scotia Criteria for Interchangeability, Guidelines for Manufacturers (page 3).

Pharmaceutical products are recommended for interchangeability when, following assessment by the Drugs and Therapeutics Committee, they satisfactorily meet interchangeability requirements.

EXCLUSIONS

The following categories are excluded:

- nonprescription analgesics, vitamins, mouth preparations, throat preparations, nasal preparations, laxatives, antacids, and cough and cold products,
- artificial sweetening agents, dietary supplements
- soaps, cleaners and shampoos

GUIDELINES FOR INTERCHANGEABILITY

The determination of "interchangeability" among pharmaceutical products which are sold in Nova Scotia by more than one manufacturer is solely the responsibility of the Department of Health upon the recommendation of the Drugs and Therapeutics Committee.

1. To be considered for interchangeability, the drug product must be the pharmaceutical equivalent of the comparator brand and must
   - contain the same amount(s) of the same active ingredient(s)
   - have the same route(s) of administration

2. The manufacturer's methods, facilities and documentation must be acceptable to the Drugs and Therapeutics Committee. The drug product must be formulated and produced in accordance with Good Manufacturing Practices.

3. Comparative data pertaining to both the sponsor's product and the originating manufacturer's product will form the basis of the interchangeability assessment. A product currently approved for market in Canada is the comparator. In exceptional circumstances, an alternate comparator may be considered, following an independent review by the Drugs and Therapeutics Committee.

4. The Committee utilizes standards for bioequivalence, for example: Health Canada's Conduct and Analysis of Bioavailability and Bioequivalence Studies: Part A: Oral Dosage Formulations Used for Systemic Effects, and Part B: Oral Modified Release Formulations.

5. The Committee may defer a decision until such time that recognized study design requirements and standards acceptable to the Committee become available, for drugs with the following characteristics:
   - drugs for which pharmacodynamic studies are appropriate alternatives to bioavailability and bioequivalence studies of oral dosage formulations
   - highly toxic drugs
   - drugs with non-linear kinetics
   - drugs for which an early time of onset or rapid rate of absorption is important
   - drugs with a narrow therapeutic range
   - combination drug products

6. If the drug product utilizes a specialized dosage form, the Committee may defer a decision until specific study design requirements and standards for bioequivalence are established.

7. The Committee will also consider factors or issues which could affect patient safety, acceptance and compliance including, but not limited to:
   - product identification features
   - nonmedicinal ingredients
   - integrity and stability of the dosage form
   - product packaging
   - labeling (the Committee may consider voluntary standards and guidelines: Labeling of Drug Ampoules, Vials, and Prefilled Syringes (CAN/CSA Z264.2-99). Toronto: CSA International (formerly the Canadian Standards Association).; Guidelines for Drug Packaging and Labeling for Manufacturers, 2001. Official Publications 2003/2004. Ottawa: Canadian Society of Hospital Pharmacists)
   - product name which may cause confusion for the prescriber or dispenser
   - palatability (palatability studies may be required on some products)
   - size, shape and scoring of the dosage unit

8. Other considerations:
   - comparable tablet and capsule formulations of a chemical substance may be considered interchangeable, following an independent review by the Drugs and Therapeutics Committee
   - different salts and esters of a chemical substance may be considered interchangeable, following an independent review by the Drugs and Therapeutics Committee
   - products with different delivery systems are generally not considered interchangeable
   - colors of solid or liquid dosage forms or shape will not affect interchangeability
   - in general, excipients do not affect interchangeability unless the Committee determines there is a particular reason for concern (e.g. allergies with tartrazine)

GUIDELINES FOR MANUFACTURERS

Please note that for any submission, the Committee reserves the right to request any further information that the Committee feels is necessary to make an informed decision and to ensure that no public harm comes from interchanging drug products.

Section I: Core Requirements

1. Notice of Compliance (NOC) or Drug Notification Form for drugs without NOCs

2. A letter authorizing unrestricted communication regarding the drug product between Nova Scotia and
   - other federal, provincial and territorial (F/P/T) drug programs
   - F/P/T health authorities and related facilities
   - Health Canada
   - Patented Medicine Prices Review Board (PMPRB)
   - Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

3. Health Canada approved Product Monograph

4. Sample of finished product and packaging as it will appear on the market. Market ready packaging and labeling may be provided for narcotic and controlled drugs.

5. Letter indicating the product is available in sufficient quantity to meet demand and pricing information (lowest price at which each package size is sold to wholesaler and pharmacies in Canada).

6. Comparative dissolution data with innovator product

7. (a) Evidence of bioequivalence (including an executive summary)
   Manufacturers must provide two additional copies of the executive summary under separate cover.

   (b) The executive summary will include:
   - date(s) and place(s) of clinical and analytical studies
   - declaration of the source and master formula for the sponsor's product used in the biostudies; and the Canadian source of the innovator's, or originating manufacturer's product, used as the comparator for each study included in the submission
   - summary of approved protocol and amendments
   - summary of protocol violations
   - summary of analytical methods, including validation of the assay method, limit of quantification
   - summary of interday and intraday variation, and summary of findings of reassay report
   - summary of demographic data
   - tabulated adverse events
   - summary of potency corrected values
   - completed pharmacokinetic/statistical worksheet (a template is provided on page 8)
   - statistical summary for each pharmacokinetic parameter including determination of power of the test for each parameter
   - graph of mean plasma concentrations comparing the two products (regular and semi-log) including an estimate of the variability at each time point
   - the Pre-Clinical and Clinical Evaluation Report, Health Canada

8. Chemistry, manufacturing and quality control data: Health Canada approved Certified Product Information Document (CPID). In lieu of the CPID, a Master Formula and Final Product Specifications must be provided.

9. If the product does not have a NOC (i.e. DIN product) then the manufacturer's Good Manufacturing Practices (GMP) report must be provided.

10. The product must not be subject to a cross-licensing agreement (i.e. cross-referenced submission). See Ultrageneric Products and Cross-Referenced Products submissions.

11. Upon declaration of interchangeability in the Nova Scotia Formulary, the Committee requires that the drug sponsor provide written notification of any change made in future to the product formulation, site of manufacture, or any other significant product change which could be considered by the Nova Scotia Drugs and Therapeutics Committee to affect bioequivalence, or interchangeability due to patient safety, acceptance or compliance. The Committee may, at its discretion, request additional information to support continued declaration of interchangeability in the Nova Scotia Formulary.

Section II: Exemptions to Core Requirements

For any submission, the Committee reserves the right to request that a manufacturer provide the full list of core requirements, and any other information the Committee feels is necessary to make an informed decision and to ensure that no public harm comes from interchanging drug products. However, manufacturers of products which fall into the following categories may provide the information listed to initiate a review.

Submissions with Health Canada Assigned Canadian Reference Product (CRP)

Where Health Canada has declared bioequivalence with a Canadian Reference Product, and the product does not have a characteristic described in Guidelines, item 5, page 2; the submission review will be initiated if the following information is provided:

1. NOC indicating the Canadian Reference Product

2. A letter authorizing unrestricted communication regarding the drug product between Nova Scotia and
   - other federal, provincial and territorial (F/P/T) drug programs
   - F/P/T health authorities and related facilities
   - Health Canada
   - Patented Medicine Prices Review Board (PMPRB)
   - Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

3. Product monograph

4. Sample of finished product and packaging as it will appear on the market. Market ready packaging and labelling may be provided for narcotic and controlled drugs.

5. Letter indicating the product is available in sufficient quantity to meet demand and pricing information (lowest price at which each package size is sold to wholesaler and pharmacies in Canada)

6. Products which are subject to a cross-licensing agreement (i.e. cross-referenced submission) must be declared and submitted according to the requirements for Ultrageneric Products and Cross-Referenced Products.

7. Upon declaration of interchangeability in the Nova Scotia Formulary, the Committee requires that the drug sponsor provide written notification of any future Level One or Two changes made to the product. The Committee may, at its discretion, request additional information to support continued declaration of interchangeability in the Nova Scotia Formulary.

Ultrageneric Products and Cross-Referenced Products (when the Cross-Referenced Product is deemed interchangeable in Nova Scotia):

This section applies only in cases where the submitted product is identical to the cross-referenced/ cross-licensed product in all aspects including:

- strength and dosage form
- formulation including both active and inactive ingredients and their quantities
- raw materials and finished product specifications
- manufacturing processes
- manufacturing site
- basic packaging (excluding embossing and labels)

In these cases, the review will be initiated if the following information is provided:

1. NOC or Drug Notification Form for drugs without NOCs

2. A letter authorizing unrestricted communication regarding the drug product between Nova Scotia and
   - other federal, provincial and territorial (F/P/T) drug programs
   - F/P/T health authorities and related facilities
   - Health Canada
   - Patented Medicine Prices Review Board (PMPRB)
   - Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

3. Product Monograph

4. Sample of finished product and packaging as it will appear on the market. Market ready packaging and labeling may be provided for narcotic and controlled drugs.

5. Letter indicating the product is available in sufficient quantity to meet demand and pricing information (lowest price at which each package size is sold to wholesaler and pharmacies in Canada).

6. Letter from manufacturer of the cross-referenced product indicating that the product being reviewed is identical to the cross-referenced product in all aspects, the identity of the manufacturer of both products, and the location of the manufacturing facility (i.e. identical site of manufacture) for both products.

7. Upon declaration of interchangeability in the Nova Scotia Formulary, the Committee requires that the drug sponsor provide written notification of any future Level One or Two changes made to the product. The Committee may, at its discretion, request additional information to support continued declaration of interchangeability in the Nova Scotia Formulary.

Other considerations:

For some products such as solutions for parenteral use, oral solutions including simple solutions, elixirs and syrups, topical products, the Committee may accept comparative physiochemical properties, pharmacodynamic studies etc as evidence of bioequivalence.

Bioequivalence studies may not be required for each strength of a drug product if the manufacturer provides appropriate bioequivalence studies and can then provide evidence of proportionality to support bioequivalence of the other strengths being marketed. The master formula and comparative dissolution data must be provided for all strengths of the drug being reviewed.

Section III: Submission Process

Manufacturers are requested to provide submission materials according to the following specifications:
- provide a cover letter describing the submission stating the formulations and strengths submitted for consideration of interchangeability, and the identity of the comparator product(s)
- provide a cross-indexed checklist of submission requirements with the cover letter
- use clearly labelled, sturdy binders with identification provided on both the spine and cover
- provide a table of contents for each binder, and identify contents with large labelled tabs
- provide pagination for the complete submission

All correspondence and submissions should be addressed to:

Pharmacist Consultant
Nova Scotia Pharmacare Programs
P. O. Box 500
Halifax, NS B3J 2S1

or

Pharmacist Consultant
Nova Scotia Pharmacare Programs
7 Spectacle Lake Drive
Dartmouth, NS B3B 1X7

Notification:

Manufacturers will be notified in writing that their submission has been received and whether a product sample was also received. This notification does not confirm that all submission requirements have been met.

Manufacturers will receive written notification of the outcome of the submission review.

Pharmacists will be notified via a Pharmacare Bulletin of products determined to be interchangeable. On the effective date noted, the pharmacist may dispense the product as interchangeable.

The Nova Scotia Formulary is updated approximately four times a year and, at this time, any interchangeable products approved since the last Formulary update will be added.

Deadline for Submission:

In general, complete submissions are reviewed in order of receipt. Market ready samples, or labelling when indicated, are required to complete each submission. Specific deadlines for submission to the Committee are not provided.

INCOMPLETE SUBMISSIONS WILL BE REJECTED

LEGISLATION

The Legislation pertinent to product selection found in the Pharmacy Act, Chapter 36 of the Acts of 2001 is as follows:

28 (1) Every person who dispenses a prescription, unless expressly prohibited in the prescription by the prescriber, may select and dispense an interchangeable pharmaceutical product other than the one prescribed if the interchangeable pharmaceutical product is listed as interchangeable in a formulary of interchangeable drugs approved or issued by the Province or a department or agency of the Province.

(2) When a drug is prescribed by its common, generic, chemical or proper name, the person who dispenses the prescription shall select and dispense a pharmaceutical product listed as interchangeable in a formulary of interchangeable drugs approved or issued by the Province or a department or agency of the Province.

NOVA SCOTIA DRUGS AND THERAPEUTICS COMMITTEE

PHARMACOKINETIC / STATISTICAL WORK SHEET (W1)

Name of Drug Product/Metabolite: _____ Date Completed: _____

Name of Original Product: _____ Strength/Dosage Form: _____

Section 1

AUC (0-T)	**Test Product** (name/strength/dosage form)	**Reference Product** (name/strength/dosage form)
Mean		
Standard Deviation		
Coefficient of Variation		
Ratio of Means		
Mean of Ratios		
90% Confidence Interval (potency corrected)		
ANOVA [S/NS]	Subject [ ] Treatment [ ] Sequence [ ]	

	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
Distribution of individual ratios (# subjects test vs. ref.)							

Section 2

AUC (0-∞)	**Test Product** (name/strength/dosage form)	**Reference Product** (name/strength/dosage form)
Mean		
Standard Deviation		
Coefficient of Variation		
Ratio of Means		
Mean of Ratios		
90% Confidence Interval (potency corrected)		
ANOVA [S/NS]	Subject [ ] Treatment [ ] Sequence [ ]	

	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
Distribution of individual ratios (# subjects test vs. ref.)							

PHARMACOKINETIC / STATISTICAL WORK SHEET (W2)

Name of Drug Product/Metabolite: _____ Date Completed: _____

Name of Original Product: _____ Strength/Dosage Form: _____

Section 3

Cmax	**Test Product** (name/strength/dosage form)	**Reference Product** (name/strength/dosage form)
Mean		
Standard Deviation		
Coefficient of Variation		
Ratio of Means		
Mean of Ratios		
90% Confidence Interval (potency corrected)		
ANOVA [S/NS]	Subject [ ] Treatment [ ] Sequence [ ]	

	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
Distribution of individual ratios (# subjects test vs. ref.)							

Section 4

Tmax	**Test Product** (name/strength/dosage form)	**Reference Product** (name/strength/dosage form)
Mean		
Standard Deviation		
Coefficient of Variation		

Adapted from:
Ontario Guidelines for Drug Submission and Evaluation. Ontario: Ministry of Health and Longterm Care, 2000.