Insert as a new sub-section in Ontario Guidelines for Drug Submission and Evaluation PART III-B.2.p

PART III-B.2. REQUIREMENTS FOR SPECIFIC CASES (REGULATORY EXEMPTIONS)

p. Non-Systemic Effect Drug Product

6. (6) Clause (1) (h) does not apply to a drug product that has a non-systemic effect where blood concentrations of the product cannot be measured and clinical studies with a pharmacodynamics endpoint are inappropriate or difficult to conduct if all of the following conditions are met:

1. The manufacturer provides in vitro studies that satisfy the executive officer that the product is interchangeable with the original product.
2. The manufacturer satisfies the executive officer that the in vitro studies described in paragraph 1 are scientifically justified, appropriate for the drug class and can demonstrate equal drug product performance.

Subsection 6(1) (h) of Regulation 935 requires that submissions be supported by: *"comparative bioavailability studies on humans, comparative clinical studies on humans, or both, or other in vivo studies that will show the interchangeability of the product with the original product."*

Subsection 6(6) of the DIDFA Regulation exempts certain drug products from the in vivo clinical study requirement in clause 6(1)(h). Subsection 6(6) applies to a drug product for non-systemic effect where Health Canada has not issued a declaration of equivalence (DOE)* to the reference product on the Notice of Compliance (NOC) and where blood concentrations of the product cannot be measured and clinical studies with a pharmacodynamic endpoint are inappropriate to conduct. For these products, the manufacturer must submit in-vitro studies that are scientifically justified, appropriate for the drug class and can demonstrate equal drug product performance. The scientifically justified in-vitro studies must satisfy the executive officer (EO) that the product is interchangeable with the original product. Additional test studies may be required as necessary to designate interchangeability, include providing a clinical trial with a pharmacodynamics endpoint.

*Note: if the generic product has a DOE from Health Canada with the reference product, then the exemption set out in subsection 6(3.1) of the DIDFA Regulation would apply to the generic product.

Submissions under subsection 6(6) of the DIDFA Regulation must be reviewed by the ministry's Committee to Evaluate Drugs (CED). The guidance for Oral products for local effect in the G.I Tract is provided (see below). However for other drug classes, the manufacturers are strongly encouraged to submit their proposed studies for the drug class for review prior to making a formal submission to the ministry for review.

Guidance on the in-vitro test for oral products for local effect in the gastroineternal (G.I) tract:

1. Scientific justification for the proposed in-vitro studies;
2. Evidence that the product formulations are qualitatively and quantitatively the same between the submitted products and the reference products.
3. The reference product(s) is:
    a. identical to the listed original/innovator product, or
    b. a non-Canadian reference product, approved under Health Canada's Non-Canadian Reference Product policy (refer to Part III-B.2.i), or
    c. another listed interchangeable product with which the submitted product would be designated as interchangeable, if the original/innovator product is no longer marketed (Refer to Part II-B.2.k for more information);
4. Standard comparative dissolution profiles between the test and reference products are completed in 3 different media, each of a different pH, ranging between a pH of 1 and 7. Dissolution profile test results must meet f2 condition as per dissolution test standard. That is, at least 12 units should be used for each profile determination. The % coefficient of variation of the assay of the active ingredient at the earlier time point should not be more than 20% and at other time points should not be more than 10% (refer to Health Canada's standard for dissolution profile test); and
5. Evidence of formulation proportionality is required when multiple strengths of drug products are submitted i.e., CPID or master formulation for all strengths.