# DISCUSSION PAPER

## Bioequivalence Requirements: Drugs Exhibiting Non-Linear Pharmacokinetics

This discussion paper, which is based upon the recommendations from the Health Products and Food Branch (HPFB) Expert Advisory Committee on Bioavailability and Bioequivalence (EAC-BB), is intended for discussion at the November 28-29, 2002 workshop and meeting

This discussion paper is not intended to be interpreted as HPFB policy.

Please note that while the EAC-BB makes recommendations to the Director General, Therapeutic Products Directorate (TPD), decision-making responsibility remains with the TPD.

**Therapeutic Products Directorate Website**: www.hc-sc.gc.ca/hpb-dgps/therapeut

*September 2002 DRAFT*

Canada

## PURPOSE

The purpose of this discussion paper is to present to stakeholders the most current position of the EAC-BB on drugs that exhibit non-linear pharmacokenetics. It will also act as the basis for discussion at the November 28 meeting of the EAC, stakeholders and HPFB. The results of that discussion will determine the need and input for a policy on this issue. It is not intended to be interpreted as HPFB policy.

## 1. BACKGROUND

In 1992, the Health Protection Branch Expert Advisory Committee (EAC) on Bioavailability recommended, in Report C[1], that drugs which exhibit non-linear pharmacokinetic characteristics be subject to special requirements with respect to comparative bioavailability studies. Current HPFB bioequivalence requirements for drugs exhibiting non-linear pharmacokinetics are based on Report C recommendations.

In 1997, a draft policy concerning bioequivalence requirements for drugs exhibiting non-linear pharmacokinetics was circulated for comment. This policy took the 1992 EAC recommendations into account. Comments received were analysed and, where appropriate, were incorporated into a discussion paper.

In 2001, the Health Products and Food Branch EAC on Bioavailability and Bioequivalence gave preliminary consideration to this paper and made some initial recommendations. The requirements below take the most recent recommendations into consideration.

## 2. SCOPE

A drug is considered to exhibit non-linear pharmacokinetics when a change in dose results in a disproportional change in the concentration of the drug in the blood. For the purpose of this discussion paper, a drug will be considered to exhibit non-linear pharmacokinetics if this is indicated in the peer-reviewed scientific literature or the approved labelling for the drug. However, the drug may be treated in the same way as those exhibiting linear pharmacokinetics, if evidence is provided to show that dose-normalized AUC values deviate (increase or decrease) by less than 25% over the practical clinically recommended single dose range.

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[1]Expert Advisory Committee On Bioavailability Report C: Report On Bioavailability Of Oral Dosage Formulations, Not In Modified Release Form, Of Drugs Used For Systemic Effects, Having Complicated Or Variable Pharmacokinetics. December 1992.

This discussion paper may not cover all situations for drugs which exhibit non-linear pharmacokinetics. Therefore, the submission sponsor should provide an acceptable scientific justification as to why the submitted studies were performed only at the chosen dosage level(s).

Drugs which exhibit time-dependent non-linear pharmacokinetics are not necessarily covered under this discussion paper and therefore will be considered on a case-by-case basis.

All drugs included in the scope of this discussion paper should also meet the requirements and standards of all applicable TPD guidelines and policies. For example, a drug with non-linear pharmacokinetics that is also considered to be a critical dose drug should also meet any additional requirements for that particular category. Of the standards set out in these policies, the most stringent combination will apply.

## 3. REQUIREMENTS

Drugs which exhibit non-linear pharmacokinetic characteristics with single doses of approved strengths should meet standards for bioequivalence as outlined in the TPD Guideline on the *Conduct and Analysis of Bioavailability and Bioequivalence Studies: Part A* or *Part B*[2], as applicable. These requirements should be met in single dose studies in both the fasted and fed states. The requirement for studies under fed conditions may be waived if scientific evidence is provided to show that the non-linearity is not related to a capacity-limited process such as absorption or pre-systemic metabolism.

While each drug is treated on its own merit, in general, it may be acceptable to conduct comparative bioavailability studies at either the highest or lowest strength of a range of proportionally formulated strengths as outlined below:

i) 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 comparative bioavailability studies should be conducted on at least the **highest** strength.

ii) 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 comparative bioavailability studies should be conducted on at least the **lowest** strength (single dose unit).

[2]Conduct and Analysis of Bioavailability and Bioequivalence Studies Part A: Oral Dosage formulations used for Systemic Effect (1992), Part B: Oral Modified Release Formulations (1996).