Health Canada Santé Canada

REPORT C

EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY

Canada

REPORT ON BIOAVAILABILITY OF ORAL DOSAGE FORMULATIONS OF DRUGS USED FOR SYSTEMIC EFFECTS

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

EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY

HEALTH PROTECTION BRANCH

DECEMBER 1992

REPORT C

This report was prepared by the Expert Advisory Committee on Bioavailability to the Drugs Directorate, Health Protection Branch, Health and Welfare Canada.

The committee chairman is Dr. John Ruedy, Dean, Faculty Medicine, Dalhousie University, Halifax, Nova Scotia.

The views and recommendations contained herein represent the consensus of the committee and do not necessarily constitute endorsement by the Department of Health and Welfare. Examples, data and calculations presented in the reports are for illustrative purposes only.

December 1992

NAMES AND AFFILIATION OF MEMBERS OF THE EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY (REPORT C)

CHAIRMAN

John R. Ruedy, M.D., F.R.C.P.	Dean, Faculty Medicine Dalhousie University Sir Charles Tupper Building HALIFAX, Nova Scotia B3H 4H7

MEMBERS

James E. Axelson, Ph.D.	Faculty of Pharmaceutical Sciences Division of Biopharmaceutics University of British Columbia 2146 East Mall VANCOUVER, B.C. V6T 1Z3
George Carruthers, M.D.	Professor and Head of Medicine Victoria General Hospital 442 Bethune HALIFAX, Nova Scotia B3H 2Y9
Jean Cusson, M.D., Ph.D. (February 1989 - December 1992)	Centre de Recherche Hotel-Dieu de Montreal Pavillon Marie de la Ferre 3850, rue Saint-Urbain Montreal, Quebec H2W 1T8
Daniel Sitar, Ph.D.	Geriatric Clinical Pharmacology Department of Pharmacology and Therapeutics University of Manitoba 770 Bannatyne Avenue WINNIPEG, Manitoba R3E 0W3
Michael Spino, Pharm. D (May 1986 - April 1991)	Associate Professor Faculty of Pharmacy University of Toronto Hospital for Sick Children 555 University Avenue Toronto, Ontario M5G 1X8
Jake J. Thiessen, Ph.D. (appointed July 1991)	University of Toronto Faculty of Pharmacy 19 Russell Street Toronto, Ontario M5S 2S2

SECRETARY

Keith Bailey, Ph.D., F.C.I.C.
(May 1986 - November 1991)

Director
Bureau of Drug Research
Drugs Directorate
Health Protection Branch
Banting Research Centre
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

D.W.Hughes, Ph.D., F.C.I.C.
(appointed November 1991)

Special Project Officer
Bureau of Drug Research
Drugs Directorate
Health Protection Branch
Banting Research Centre
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

INTRODUCTION

Earlier Reports (A and B) presented proposed guidelines for bioavailability testing and standards for bioequivalence of drugs with uncomplicated or non-variable pharmacokinetics, marketed as modified (Report B) or unmodified (Report A) formulations.

This Report presents similar guidelines for "complicated" drugs marketed as unmodified formulations. The following categories have been identified and are discussed:

1. Drugs for which pharmacodynamic studies are appropriate alternatives to bioavailability and bioequivalence studies of oral dosage formulations

2. Highly toxic drugs

3. Drugs with non-linear kinetics

4. Drugs products with an effective half-life >12 hrs

5. Drugs for which an early time of onset or rapid rate of absorption is important

6. Drugs with a narrow therapeutic range

7. Combination drug products

The recommendations are often additional to those for "uncomplicated" drugs and hence this Report must not be used in isolation from Reports A and B. In particular the glossaries of terms in Reports A and B are applicable to this Report; other definitions are given in each chapter of this Report as necessary.

1. DRUGS FOR WHICH PHARMACODYNAMIC STUDIES ARE APPROPRIATE ALTERNATIVES TO BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES OF ORAL DOSAGE FORMULATIONS.

Studies to measure bioavailability or establish bioequivalence are dependent upon quantitative analysis of the drug and/or metabolite(s) in plasma (or blood or serum) or urine. If such measurements cannot be made with sufficient accuracy and sensitivity, pharmacodynamic studies can be used as a substitute. It is recognized that for oral dosage formulations this has become increasingly unusual because of developments in drug analysis.

Parameters for Assessment and Methodology:

If pharmacodynamic studies are to be used, they must be no less exacting than bioavailability studies; this applies to measures of both efficacy and toxicity (see Reports A and B). If pharmacodynamic data only are provided, the sponsor should give an outline of other methods which have been tried and the reasons why they were unsuitable, or why other methods could not be used. Several requirements must be recognized in the design of such studies including:

1. The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy.

2. The methodology must be validated for precision, accuracy and reproducibility.

3. Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects. Dose ranging may be a necessary part of the design.

4. The response should be measured quantitatively under double blind conditions, and be recordable in a machine-produced or machine-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. In those instances where such measurements are not possible, recording on visual analog scales may be used. In other instances where the data are limited to qualitative (categorized) measurements special statistical analysis will be required.

5. Non-responders should be excluded from the study by prior screening. The criteria by which responders *vs* non-responders are identified must be provided.

6. In instances where an important placebo effect can occur, comparison between products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved with a placebo cross-over phase in the pharmacodynamic study.

7. The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.

8. A cross-over design should be used. Where this is not appropriate, a parallel study will be required.

Standards:

The requirements of a pharmacodynamic study should be comparable to those of standard bioavailability or bioequivalence studies, including measures of the magnitude, onset and duration of response. For approval under such circumstances, criteria similar to those defined for bioavailability and bioequivalence studies that use drug concentration measurements must be derived; e.g., AUC of measured pharmacodynamic response and maximum response. In addition, similar standards should be met in these criteria to establish bioavailability and bioequivalence.

2. HIGHLY TOXIC DRUGS

A highly toxic drug is one whose therapeutic use may result in dose-or concentration-dependent adverse effects, which are persistent, irreversible or slowly-reversible, or life-threatening. Examples include those listed in the appendix.

Parameters for Assessment:

The parameters to be determined for bioavailability and bioequivalence are the same as those described in Reports A and B, "Guidelines and Standards for Bioavailability of Oral Dosage Formulations of Drugs used for Systemic Effects".

Methodology:

Due to the nature of these drugs, usually it will be necessary to conduct studies in patients rather than in healthy subjects. Studies in both the fasting and fed states will be required except where there are specific reasons for not doing such studies.

The variability of the disease states in patients in whom the studies are performed will be an important consideration in deciding the size of cohort which will have to be investigated in order to satisfy the standards. It is highly recommended that the study group be as homogeneous as possible with respect to predictable sources of variation in drug disposition.

Where the drug is being administered chronically, it may be possible to study bioavailability only during a dose interval at steady-state. The test drug product would be required to replace a single dose of the reference drug product during a usual dose interval at steady-state. Standardization of the study conditions is essential, particularly with respect to the time of day of drug administration and posture of the subject.

A three-period cross-over study (reference drug fasting, test drug fasting, test drug after food) may be adequate to establish bioavailability. However, two two-period cross-overs (or one four- period cross-over) may be found necessary, and, except where ethical considerations dictate otherwise, are mandatory in studies to establish bioequivalence. Ethical considerations may dictate that these studies be conducted in parallel groups rather than by a crossover design.

Standards:

The following standards in a comparative bioavailability study will be used to determine bioequivalence:

1. The 95% confidence interval of the relative mean AUC of the test to reference formulation should be within 80 to 125%; the relevant AUC or AUCs as described in Reports A and B are to be determined.

2. The 95% confidence interval of the relative mean measured C_{max} of the test to reference formulation should be between 80 and 125%. However, where it has been demonstrated that the toxicity is not related to maximum concentration, the relative mean measured C_{max} should be between 80 and 125%.

3. These requirements are to be met in both the fasted and fed states except where there are specific reasons for not doing such studies.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

3. DRUGS WITH NON-LINEAR KINETICS

Non-linear pharmacokinetics occur when a change in dose results in a disproportional change in the concentration of the drug in the blood.

Such non-linearity may be caused by differences in absorption, distribution and/or metabolism and elimination. Capacity-limited metabolism is commonly considered to be a major reason for nonlinear kinetics (e.g., with phenytoin). Capacity-limited renal excretion may also occur, as is observed with high doses of organic acids (e.g., with penicillins). In addition, concentration-dependent plasma protein binding can result in non-linear kinetics (e.g., with disopyramide). Drugs may also induce their own metabolizing enzyme systems which may be a factor in non-linearity when multiple dosing is required. In some cases more than one non-linear kinetics process may be in effect. The appropriate study design, as well as standards and criteria, for bioavailability and bioequivalence studies may differ depending on the nature of the non-linear process(es) operative for that compound.

The following are important considerations in study design and in the establishment of criteria and standards for studies on drugs with non-linear kinetics. In considering these issues, it is important to recall that both absorption and first-pass metabolism contribute to the assessment of the extent of absorption in bioavailability studies.

1. The rate of delivery of the drug to the metabolizing organ may be a determinant of the AUC, not just the C_{max}. For some drugs, such as phenytoin, where the Michaelis-Menten constant (K_m) is usually within the therapeutic range, small differences in the rate of absorption could potentially have substantial effects on the extent of absorption and therefore the AUC.

2. These requirements must be met in both the fasting and fed states except where it has been demonstrated that food does not modify bioavailability at doses within the range of strengths to be marketed.

Parameters for Assessment:

The following pharmacokinetic parameters should be calculated from single dose studies: AUC_X, AUC_I, C_{max} and, where possible, λ. The following parameters should be calculated from steady state studies: AUC_τ, C_{max}, C_{pd}, and C_{min}.

Methodology:

In general, the same methodology may be used, as that described in "Guidelines and Standards for Bioavailabililty of Oral Dosage Formulations of Drugs used for Systemic Effects", but with the following considerations:

1. The bioavailability of at least the lowest and highest dosage strengths should be studied.

2. For those drugs which demonstrate non-linear kinetics at any clinically-relevant dose, chronic dose studies may be required.

Standards:

Single Dose

Standards for bioavailability and bioequivalence are those described in Report A: "Bioavailability of Oral Dosage Formulations of Drugs Used for Systemic Effects".

Chronic Dose

For drugs requiring chronic dose studies the following bioavailability and bioequivalence standards are required:

1. The 90% confidence interval of the relative mean $AUC_{\tau*}$ of the test to reference formulation should be within 80 to 125%.

2. The relative mean measured C_{max} of the test to reference formulation should be within 80 to 125%.

3. The relative mean measured C_{min} of the test to reference formulation should be within 80 to 125%.

*$AUC_{\tau*}$ is defined as the area under the plasma concentration- time curve after several doses indicating "pseudo" steady state. Because of the non-linearity, steady state may be difficult to discern.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

4. DRUG PRODUCTS WITH AN EFFECTIVE HALF-LIFE >12 hrs

A drug in this category is one in which the effective half-life is greater than 12 hours. The effective half-life is that which is determined by the disposition rate constant which predominantly affects the dosing regimen.

Parameters for Assessment:

The parameters to be determined for bioavailability and bioequivalence are the same as those described in Reports A and B, with the exception of AUC parameter. For these drugs, $AUC_{0\text{-}72\ hrs}$ will be employed.

Methodology:

In general, the methodology described in Report A will be used with the following considerations:

1. $AUC_{0\text{-}72}$ is employed, assuming absorption is completed in most subjects within 72 hours. Sampling will therefore be needed up to 72 hours after drug administration.

2. Designs

The cross-over design is the preferred design for comparative bioavailability studies. However, a cross-over design necessitates a sufficiently long wash-out period to minimize the risk of a carry-over effect (ordinarily at least 9-10 times as long as the disposition half-life, and ordinarily less than 4 weeks). When the effective half-life is >72 hours, a wash-out period of less than 4 weeks is not sufficient to eliminate the risk of carry-over effects, but a longer wash-out period means an increased risk of other problems (concurrent disease, seasonal effects etc...).

Consideration should then be given to other study designs such as:

- Parallel studies
- Steady-state studies in volunteers or patients
- Use of stable isotopes

Standards for bioavailability and bioequivalence are those normally required for each product as described in Report A using $AUC_{0\text{-}72}$ for the extent parameter. Statistical analysis will be done according to the specific design used.

In the case of steady state studies in volunteers or patients:

1. The 90% confidence interval of the relative mean AUC_{τ} of the test to reference formulation should be within 80 to 125%.

2. The relative mean measured C_{max} of the test to reference formulation should be within 80 to 125%.

3. The relative mean measured C_{min} of the test to reference formulation should be within 80 to 125%.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

5. DRUGS FOR WHICH AN EARLY TIME OF ONSET OR RAPID RATE OF ABSORPTION IS IMPORTANT

A drug in this category is one in which the time of onset of effect is important because of therapeutic or toxic effects. An example of such a drug is an analgesic for rapid relief of pain.

Parameters for Assessment:

The parameters to be determined for bioavailability and bioequivalence include those described in Report A and B, "Guidelines and Standards for Bioavailability of Oral Dosage Formulations of Drugs used for Systemic Effects". In addition, for comparative bioavailability studies, the area under the curve to t_{max} ($AUCt_{max}$) must be determined. In comparative studies with a marketed product, the area under the curve to the t_{max} of the marketed reference product ($AUC_{Reftmax}$) must be determined.

Methodology:

It is recommended that a minimum of six samples at different times up to t_{max} of the reference product be included to increase the reliability of the estimate of $AUC_{Reftmax}$.

Standards:

The following standards in a comparative bioavailability study will be used to determine bioequivalence:

1. The 90% confidence interval of the relative mean AUC of the test to reference formulation should be within 80 to 125%; the relevant AUC and AUCs as described in Reports A and B are to be determined.

2. The 90% confidence interval of the relative mean measured C_{max} of the test to reference formulation should be between 80% and 125%.

3. The relative mean $AUC_{Reftmax}$ of the test to reference formulation should be within 80 to 125%.

$AUC_{Reftmax}$ 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.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

6. DRUGS WITH A NARROW THERAPEUTIC RANGE

A drug with a narrow therapeutic range is one which commonly exhibits adverse effects which limit the therapeutic use in doses close to those required for the therapeutic effect. When there is a known relationship of plasma concentrations to therapeutic and toxic effects, the ratio of the lowest concentration at which clinical toxicity commonly occurs (toxic) to the median concentration providing a therapeutic effect (therapeutic) would not be greater than 2. An example of such a drug is theophylline, toxic : therapeutic concentration (molar) :: 110:70 (i.e., ratio = 1.6).

Parameters for Assessment:

The parameters to be determined for bioavailability and bioequivalence are the same as those described in Reports A and B, "Guidelines and Standards for Bioavailability of Oral Dosage Formulations of Drugs used for Systemic Effects".

Methodology:

These drugs are usually studied in healthy normal volunteers. Studies in both the fasting and fed states will be required except where there are specific reasons for not doing such studies. It is highly recommended that the study group be as homogeneous as possible with respect to predictable sources of variation in drug disposition. A three-period cross-over design (reference drug fasting, test drug fasting, test drug after food) may be adequate to establish bioavailability. However, two two-period cross-overs (or one four-period cross-over) may be found necessary, and are mandatory in studies to establish bioequivalence.

Standards:

The following standards in a comparative bioavailability study will be used to determine bioequivalence:

1. The 95% confidence interval of the relative mean AUC of the test to reference formulation should be within 80 to 125%; the relevant AUC or AUCs as described in Reports A and B are to be determined.

2. The 95% confidence interval of the relative mean measured C_{max} of the test to reference formulation should be between 80 and 125%. However, where it has been demonstrated that the toxicity is not related to maximum concentration, the relative mean measured C_{max} should be between 80 and 125%.

3. These requirements are to be met in both the fasted and fed states except where there are specific reasons for not doing such studies.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

7. COMBINATION DRUG PRODUCTS

A combination drug product contains two or more active ingredients.

There are two main types of combination products:

1. Each drug in the product is chosen to elicit a desired effect. The effects of each ingredient are not known to depend on predetermined ratios of concentrations of the drugs in the serum.

2. The amount of each drug in the product is chosen to elicit a synergistic effect dependent upon predetermined ratios of concentrations of the drugs in the serum.

Parameters for Assessment and Standards for Bioequivalence:

Type 1

The pharmacokinetic parameters to be reported and assessed are those which would normally be required of each drug if it were in the formulation as a single entity, as described in "Guidelines and Standards for Bioavailability of Oral Dosage Formulations of Drugs used for Systemic Effects".

The following standards obtained in single dose cross-over comparative bioavailability studies determine bioequivalence:

1. The 90% confidence interval of the relative mean AUC of each drug of the test to reference formulation should be within 80 to 125%; the relevant AUC or AUCs as described in Reports A and B, "Bioavailability of Oral Dosage Formulations of Drugs Used for Systemic Effects", are to be determined.

2. The relative mean measured C_{max} of each drug of the test to reference formulation should be between 80% and 125%.

These standards must be met on parameters calculated from both the measured data and data corrected for measured drug content.

Type 2

The preceding parameters must be reported and assessed and the following additional parameters reported for each subject:

1. The ratios of the concentrations of each drug and/or metabolites at the t_{max} as determined for each drug.

2. The ratios of the concentrations of the drugs at the last time point of the most commonly used dosing interval (i.e., at t_X);

3. The ratios of the $AUCt_X$ of the drugs and/or metabolites.

The mean (± SD) value for each of these 3 parameters must be reported for each product.

A figure illustrating the mean ratios of the concentrations of each drug at each time point must be provided for both the test and reference products.

Where the mean concentration ratios at t_{max} and t_X or the ratios of AUC_T do not correspond to the predetermined accepted range of ratios of the reference product, the manufacturer may be required to provide additional information.

Appendix (Report C)

EXAMPLES OF DRUGS FOR ORAL ADMINISTRATION

HIGHLY TOXIC DRUGS

Examples:

Amiodarone

Most oral antineoplastics including:
- Busulfan
- Chlorambucil
- Cyclophosphamide
- Estramustine
- Etoposide
- Flucytosine
- Hydroxyurea
- Lomustine
- Melphalan
- 6-Mercaptopurine
- Methotrexate
- Mitotane
- Thioguanine

Immunomodulators:
- Chloroquine
- Hydroxychloroquine

Retinoids, analogs of Vitamin A including:
- Etretinate
- Isotretinoin

DRUGS WITH NON-LINEAR KINETICS

Examples:

Acetylsalicylic Acid
Acyclovir
Carbamazepine
Cephalosporins
Disopyramide
Fluorouracil
Glucocorticosteroids
Griseofulvin
Levodopa
Phenytoin

Propranolol
Rifampin
Valproic acid
Verapamil

DRUGS WITH AN EFFECTIVE HALF-LIFE > 12 HRS

Examples:

Amiodarone
Amlodipine
Digitoxin
Digoxin
Chloroquine
Tamoxifen

DRUGS FOR WHICH AN EARLY TIME OF ONSET OR RAPID RATE OF ABSORPTION IS IMPORTANT

Examples:

Acetaminophen
Acetylsalicylic acid
Dimenhydrinate
Ibuprofen (and other NSAIDs approved for acute pain relief)
Nitroglycerin
Salbutamol
Short-acting benzodiazepines (e.g., midazolam)

DRUGS WITH A NARROW THERAPEUTIC RANGE

Examples:

Antiarrhythmics
- Disopyramide
- Flecainide
- Mexiletine
- Procainamide
- Propafenone
- Quinidine
- Tocainide

Anticholinergics
- Atropine
- Bethanechol
- Propantheline
- Trihexyphenidyl

Anticoagulants
- Coumarins

Anticonvulsants
- Carbamazepine
- Hydantoin derivatives
- Valproic acid

Antivirals
- Dideoxyinosine
- Zidovudine

Drugs with a narrow therapeutic range

Examples:

Immunomodulator:
- Cyclosporin

Glycosides
- Digitoxin
- Digoxin

Psychotropics:
- Lithium
- Ethchlorvynol
- Glutethimide
- Methyprylon
- Clozapine

Theophylline and derivatives
- Aminophylline
- Choline theophyllinate
- Diprophylline
- Theophylline