Health Canada Santé Canada

Contact: Policy_Bureau_Enquiries
Telephone: 613-948-4623
Fax: 613-941-1812

SCIENTIFIC ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

RECORD of PROCEEDINGS

Teleconference

November 6, 2003

Therapeutic Products Directorate Note: Until such time as final recommendations are made and policy is developed and published, current bioequivalence requirements remain unchanged.

Committee Members Present: Dr. J. Thiessen (Chair), Dr. R. Herman, Dr. F. Jamali, Dr. R. Nair, Dr. E. Palylyk-Colwell, Dr. W. Racz, Dr. K. Renton, Dr. W. Riggs, Dr. D. Sitar, Dr. F. Varin, Mr. S. Walker

Regrets: Dr. A. Donner

Health Canada (HC) Scientific Advisory Committee Working Group Members: M.M. Bernard (BMORS), L. Carter (CTSAP), L. Cockell (DBE), M. Davis (SAC Secretariat Officer, PB), E. Ormsby (PB), C. Pereira (SAC-BB Scientific Advisor, PB), C. Simon (DBE)

HC Observers: L-N Cui (DBE), C. Ficker (DBE), J. Gordon (DBE), A. Makinde (DBE), S. Stojdl (DBE), A. Tam (DBE), P. Wielowieyski (DBE)

Abbreviations for Health Canada Directorates, Bureaux, Divisions and other terms used in this record:

BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence
BMORS	=	Bureau of Metabolism, Oncology and Reproductive Sciences
CTSAP	=	Clinical Trials & Special Access Programme
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
HC	=	Health Canada
HPFB	=	Health Products and Food Branch
PB	=	Policy Bureau
SAC	=	Scientific Advisory Committee
TPD	=	Therapeutic Products Directorate

Discussions during this teleconference centered on a draft policy statement on the use of metabolite data in bioequivalence studies and associated questions posed by HC to the SAC members. This record summarizes the final outcome and consensus reached by the members.

! **Item 1 - Opening remarks, (Jake Thiessen)**

! **Item 2 - Presentation of HC questions (Eric Ormsby)**

The draft policy was introduced. It reflects current practice, although we do not have a published policy on the use of metabolite data in bioequivalence studies. Statements in current guidelines are not clear. Several questions remain to be resolved.

! **Item 3 - Deliberation (Jake Thiessen)**

Before addressing the draft policy and specific questions raised by the TPD, the Chair invited general comment on the issue. Some of the comments were:

-With unstable drugs such as acetylsalicylic acid, it may be necessary to measure the metabolite/breakdown product, in this case salicylic acid.
-Parent compound is the best if it can be measured (even if it is a pro-drug)
-Measurement of the parent compound may be a problem when the drug has very short half-life, where concentrations of the parent drug are too low to be measured reliably.
-Use of metabolite data may be acceptable if it reduces variability with highly variable drugs i.e. it may improve the quality of the bioequivalence assessment.
-If the parent drug can be satisfactorily assessed, then it should be the choice

! **Item 4 - Final recommendations (Jake Thiessen)**

I) *What is meant by "reliably measurable"? This question includes the issue of duration, i.e., if the parent drug concentrations can be measured for just 2 hours, is that an adequate length of time?*

No consensus was reached on a definition of "reliable" in this context. It was suggested that if a company claimed that a drug was not reliably measurable they would have to provide an acceptable justification for the claim.

It was suggested that the analytical method used should be able to cover 80% of the AUC_{inf} expected based on literature data.

The method should be able to provide drug concentration versus time profiles that allow valid calculation of the relevant kinetic parameters/bioequivalence metrics.

State-of-the-art technology should be used where possible. Older validated methods could be used if they suited the purpose of bioequivalence assessment.

ii) *How to deal with situations where 'bracketing' studies must be done, i.e., studies on high and low strengths where it may be possible to measure parent drug with the high dose but not with the low dose? Is it acceptable to use the parent in one case and the metabolite in the other?*

It is acceptable to use the parent drug with the high dose and a metabolite with the low dose if the parent cannot be reliably measured after the low dose.

It was reiterated that the analyte to be studied must be established *a priori*

iii) *Under what, if any, circumstances would use of metabolite data be acceptable even though the parent drug concentrations are measurable?*

This question was not specifically addressed. However, from the discussion it may be concluded that an acceptable *a priori* justification for the use of metabolite data instead of parent drug data could be provided even though the parent drug is measurable. For example, the parent drug concentrations may be measurable but too low to allow valid calculation of the relevant kinetic parameters /bioequivalence metrics.

iv) *If metabolite data is to be used, does it have to be an active metabolite? If so, why?*

The metabolite does not have to be an active one. It should be a primary (first step), major metabolite. In addition if there is a choice between two primary metabolites, one being the precursor of an active species and the other not, either metabolite may be used.

v) *If metabolite data is to be used, does it have to be a major metabolite? (If so, what is meant by 'major')? Or can any primary metabolite be used?*

Any primary (first step) metabolite can be used. A major metabolite (one present in the largest quantities) would presumably be easier to measure and would have the highest reliability in testing differences between the products.

vi) *How to deal with submissions where both parent and metabolite data have been provided but the protocol does not specify which moiety is to be used for bioequivalence assessment?*

If the use of metabolite data instead of parent drug data has not been adequately justified *a priori* and stated clearly in the protocol, the parent drug data should be used.

vii) *Are there cases where it would be necessary to base the BE determination on BOTH parent and metabolite data? For example, one author suggests that the parent/metabolite ratio is important in assessment of BE for amiodarone.*

The committee did not have time to discuss this question specifically. However, the discussions did not present any compelling reasons to ever measure both parent and metabolite concentrations in the assessment of bioequivalence.

The committee agreed with the wording of the draft policy statement with the following exception:

In paragraph 3 the sentence

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

should be changed to read:

"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."

! **Item 5 - Announcements/next meeting (Eric Ormsby)**

A stakeholder workshop and SAC meeting are being tentatively arranged for June 2004. The topics for the meeting have not yet been decided.

! **Item 6 - Adjourn (Jake Thiessen)** 3:05 PM

Prepared by: Marilyn Davis & Conrad Pereira (2004-01-28)