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SCIENTIFIC ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

RECORD of PROCEEDINGS

Teleconference

January 29, 2004

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. A. Donner, Dr. R. Herman, Dr. F. Jamali, Dr. E. Palylyk-Colwell, Dr. W. Racz, Dr. K. Renton, Dr. W. Riggs, Dr. F. Varin, Mr. S. Walker

Regrets: Dr. R. Nair, Dr. D. Sitar (Comments sent by e-mail before the teleconference)

Health Canada (HC) Expert 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)

HC Observers: L-N Cui (DBE), C. Ficker (DBE), J. Gordon (DBE), A. Makinde (DBE), A. Melnyk (DBE), S. Stojdl (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
CDD	=	Critical Dose Drugs
CTSAP	=	Clinical Trials & Special Access Programme
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
EAC	=	Expert Advisory Committee
HC	=	Health Canada
HPFB	=	Health Products and Food Branch
PB	=	Policy Bureau
SAC	=	Scientific Advisory Committee
TPD	=	Therapeutic Products Directorate

This teleconference was called as a result of comments received from the SAC-BB on TPD's draft Critical Dose Drugs (CDD) policy, including the draft list of examples of CDDs. TPD posed eight questions to be considered for this meeting. All questions are listed, but there was only time to discuss the first three as listed below. This record summarizes the final outcome of the meeting.

- **Item 1 - Roll Call, review agenda, COI** - Dr. J. Thiessen

- **Item 2 - Discussion of issues/Deliberation of questions & finalization of recommendations** - Dr. J. Thiessen

i. *Is amiloride a highly toxic or narrow therapeutic range drug as defined in Report C of the EAC-BB (1992)?*

There was consensus, among the committee members in attendance, that amiloride should not be considered a highly toxic or a narrow therapeutic range drug, for the purpose of bioequivalence assessment. Altering potassium or magnesium levels, e.g., as occurs with use of some diuretics, does not necessarily imply high toxicity. The adverse effects are easily treated, are not persistent, not irreversible and not slowly reversible.

One absent member indicated, in correspondence circulated to all members prior to the teleconference, that in his opinion amiloride should not be considered a highly toxic drug.

The other absent member, in correspondence prior to the teleconference, declined to comment on amiloride.

ii. *Is sotalol a highly toxic or narrow therapeutic range drug as defined in Report C of the EAC-BB (1992)?*

The majority of SAC-BB members in attendance (six of ten) indicated that sotalol HCl meets the Report C definition of a highly toxic drug for the purpose of bioequivalence assessment. Use of sotalol can cause torsades de pointe which can be a very serious adverse event. Although the relationship between sotalol concentration and adverse events is not clear, one should err on the side of patient safety.

Three of the members present recommended that sotalol should not be considered a highly toxic or a narrow therapeutic range drug. Adverse effects are reversible. A prolonged QT interval or the occurrence of torsades does not necessarily imply that the drug is highly toxic. The definition in Report C should be considered in the context of switchability, i.e., if a patient is stable on one sotalol product, switching to another sotalol product is unlikely to cause different adverse effects.

One absent member indicated, in correspondence circulated to all members prior to the teleconference, that in his opinion sotalol should not be considered a highly toxic drug.

One present member abstained from comment.

The other absent member, in correspondence prior to the teleconference, declined to comment on sotalol.

The Chair concluded that although the committee was split on this issue, if one were to err on the side of patient safety, sotalol should be considered to fit the Report C definition of a highly toxic drug.

iii. *Do we need to adjust the **definition** of a CDD **before** circulating the draft for public comment?*

One member proposed an adjustment to the draft definition of a CDD, to re-focus on the patient risk associated with use of a drug. There was extensive discussion of the proposal. However there was insufficient time to arrive at a recommendation and it was agreed that the discussion should continue by electronic mail.

In response to a question specifically regarding levothyroxine, which the SAC-BB previously concluded was a CDD (on April 16, 2003) , the committee agreed it would provide a statement if perchance any change in the proposed definition of a CDD might lead to a change in the levothyroxine classification.

iv - viii. There was insufficient time to discuss the remaining CDD questions. Discussion will be continued by electronic mail.

iv. a) *Do any of the "factors to consider" conflict with the current definition, or the potential new definition? Yes or No and why?*

b) *Are all factors needed before a drug becomes a CDD? Yes or No and why?*

v. *Changes to the definition will require re-construction of the list of examples. Do we need to re-examine the CDD **list before** circulating the draft for public comment?*

vi. *Do we need to re-examine the CDD **list** anyway **before** circulating the draft for public comment? (In order to ensure that we are applying the definition appropriately, for example focusing on dose and/or concentration dependence and seriousness rather than over-emphasizing the 'factors to consider' independently of the definition?)*

vii. *Is sotalol a CDD? Why or why not?*

viii. *Is amiloride a CDD? Why or why not?*

! **Item 3 - Announcements/updates regarding next meeting** - Mr. E. Ormsby

Members were polled with respect to potential dates for the next SAC-BB meeting in Ottawa. Dates in May and June 2004 were considered.

! **Item 4 - Meeting adjourned** - Dr. J. Thiessen

The meeting was adjourned at 2:30 p.m.

Prepared by C. Pereira & M. Davis
2004-02-26