Health Canada Santé Canada

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EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

RECORD of PROCEEDINGS

June 26 & 27, 2003

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

The structure of this two-day workshop format was intended to allow for more direct stakeholder involvement and greater transparency in policy development. All stakeholders were invited to attend day 1 of this workshop. Only two topics were dealt with in order to give adequate time to fully deliberate and address each issue. Discussion papers, outlining the issues for each topic, were circulated and posted on Health Canada's web site prior to the meeting.

On day 1, invited stakeholders made a series of 10-minute presentations on the first issue. An open discussion, moderated by the Chair of the EAC-BB, which allowed EAC-BB members, invited presenters, observers and members of the audience to provide input. The same process was repeated for the second topic.

On day 2, the EAC-BB deliberated the issues in a closed meeting before making their final recommendations to HC.

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

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

DAY ONE - June 26, 2003

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

Regrets: Dr. A. Donner

Stake-holder Presenters: M. Belisle (Canadian Generic Pharmaceutical Association), W. Curatolo (Pfizer), P. Keown (Vancouver General Hospital), M. Lefebvre (Algorithme-Pharma), I. McGilveray (McGilveray Pharmacon), K. Midha (Pharmalytics), C. Toal (Bayer Inc.)

Health Canada (HC) Expert Advisory Committee Working Group Members:
M.M. Bernard (BMORS), L. Carter (CTSAP), L. Cockell (DBE), M. Davis (EAC Secretariat Officer, PB), Celia Lourenco (BGTD), E. Ormsby (PB), C. Pereira (EAC-BB Coordinator, PB), C. Simon (DBE)

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

****PowerPoint presentations are available upon request for all presentations indicated by double asterisk.**

➤ **ITEM 1 - Opening Remarks & Welcome**, **Chair's address** (Mr. E. Ormsby and Dr. J. Thiessen)

➤ **ITEM 2 - Progress since last workshop** (Dr. C. Pereira)

A draft policy on bioequivalence requirements for non-linear drugs, based on EAC-BB recommendations (March 2003), is to be posted on the TPD website.

HC is still working on a draft list of critical dose drugs. The draft list will be subject to extensive consultation.

➤ **ITEM 3 - Presentation: Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State** (Dr. E. Palylyk-Colwell) ******

Summary of Comments Received (Dr. C. Pereira) ******

➤ **ITEM 4 - Stakeholder Presentations: Requirements for Food Effect Studies**

A series of 10 minute presentations was made on this topic by stakeholders.

- **Dr. W. Curatolo** (Pfizer)
  Mechanistic Studies of the Unusual Dosage Form Dependence of the Azithromycin Negative Food Effect ******

- **Dr. M. Lefebvre** (Algorithme Pharma)
  What Place to Allow to Bioavailability / Bioequivalence Studies in the Fed State for the Comparison of Drug Products ******

- **Dr. I. McGilveray** (McGilveray Pharmacon Inc & U of Ottawa)
  Food Challenge Issues ******

- **Dr. K. Midha** (Pharmalytics Research Institute)
  *The Effects of Food in Bioequivalence Studies*******

- **Dr. Cory Toal** (Bayer)
  Nifedipine Once a Day: Formulations and Food Effects ******

➤ **ITEM 6 - Open Discussion (Requirements for Food Effect Studies)**

The Chair initiated general discussion on bioequivalence requirements for food effect studies. Some of the questions and issues raised were:

i) Should the (US FDA's) Biopharmaceutics Classification System be used when defining risk (to aid in the decision as to which drug products should be subjected to a fed BE study)?
ii) Need to separate formulation issues from biological (patient) issues.
iii) Need to identify components of food that affect absorption, e.g. fat, carbohydrate, fibre.
iv) If the label specifies to be taken with food, then is a fasted study really necessary? Or conversely, if the product is labeled to be taken 1 hour before or 2 hours after food, is a fed study really needed?
v) Linking study requirements to labeling is difficult because labeling may not be clear.
vi) Must differentiate between bioavailability and bioequivalence issues when considering need for heterogenous study population (mixed gender, ethnicity, age, etc.), disease states.
vii) For complicated drugs where a fasted and fed study would normally be required, if the fasted study may be waived due to severe gastric irritation, should a 'minimally fed' study be required instead, in addition to a fed study (high fat, high calorie)?

➤ **ITEM 8 - Presentation: Bioequivalence Requirements: Highly Variable Drugs & Highly Variable Drug Products: Issues & Options** (Dr. K Midha) ******

Summary of Comments Received (Dr. C. Pereira)**

➤ **ITEM 9 - Stakeholder Presentations: Highly Variable Drugs**

A series of 10 minute presentations was made on this topic by stakeholders.

- **Ms. M. Belisle** (Canadian Generic Pharmaceutical Association)
  *Bioequivalence Committee CGPA Position/Opinion***
- **Dr. P Keown** (Vancouver General Hospital)
  Bioequivalence and therapeutic equivalence in organ transplantation **
- **Dr. I. McGilveray** (McGilveray Pharmacon Inc & U of Ottawa)
  *Highly Variable Drugs, HVD – a perspective***
- **Dr. C. Toal** (Bayer)
  Nifedipine Once a Day: Formulations and Variability **

➤ **ITEM 11 - Open Discussion (Highly Variable Drugs)**

There was general discussion on bioequivalence requirements for drugs exhibiting high intra-subject variability. Some of the questions and issues raised were:

i) Need for level playing field, with particular reference to cases where the reference product may not pass bioequivalence standards when compared with itself.
ii) If a generic cannot demonstrate equivalence using plasma concentrations, should equivalence be demonstrated by means of clinical studies?
iii) Impact of scaling on generic to generic substitution.
iv) Use of replicate study designs to distinguish between highly variable drugs and highly variable drug products.
v) Number of subjects required to do studies with highly variable drugs

➤ **ITEM 12 -Open Discussion on other BB topics**

The Chair invited the stakeholders to give their impressions regarding which BB items from our list posted on the website should be discussed at the next meeting in November. The items mentioned, in no specific order, were:

-Use of metabolite data
-Treatment of outliers; retesting of subjects
-How to deal with BE for endogenous compounds, topicals
-Updating Guideline A, e.g., with respect to add-on studies
-Agreement for regulatory process re: product monographs
-Definition for interchangeability, switchability, etc. for BE studies, geared to clinicians
-Reconsider requirement for steady-state studies for modified-release products

➤ **ITEM 13 - Adjournment of day 1**

The Chair thanked all presenters and stakeholders for participating; he polled the participants asking if they liked the day's format. There appeared to be complete agreement from the participants.

The meeting was adjourned.

DAY TWO - June 27, 2003

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

Health Canada (HC) Expert Advisory Committee Working Group Members: M.M. Bernard (BMORS), L. Cockell (DBE), M. Davis (EAC Secretariat Officer, PB), Celia Lourenco (BGTD), E. Ormsby (PB), C. Pereira (EAC-BB Coordinator, PB), C. Simon (DBE)

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

➤ **ITEM 14 - Change of Name from EAC to SAC, Member Issues** (Mr. E. Ormsby)

The change of name from Expert Advisory Committee (EAC) to Scientific Advisory Committee (SAC) was explained. Given the number of different types of expert committees advising Health Canada, it was considered necessary to indicate that the expert advice provided by this committee is scientific in nature.

The TPD hopes to form several new SACs. The TPD will manage the committees, but they are open to all Directorates of the HPFB. The TPD, BGTD, and MHPD are expected to be the biggest clients.

A brief summary of the changes to the Terms of Reference (TOR) was given, and particular attention was given to the appointment of an associate chair and the related duties. One question about the start time for tenure was posed and clarified.

Dan Sitar moved to accept the TOR, Ken Renton seconded. The motion was carried unanimously.

➤ **ITEM 19 & 21 - Highly Variable Drugs (HVD)**

The Committee discussed issues related to bioequivalence requirements for highly variable drugs, including issues raised at the previous day's stakeholder meeting. Some of the questions discussed were:

i) For the purpose of bioequivalence assessment, does the TPD require a separate category called highly variable drugs ?

If so,

ii) What are the most compelling reasons why we would need an HVD category and how should it be defined?

iii) What bioequivalence standards should be applied to such drugs?

SAC Recommendations:

After careful consideration of the need for separate BE requirements for drugs considered to be "highly variable," the SAC concluded that:

1. ***For the purpose of bioequivalence testing, there is no compelling need for a distinct category of "highly variable" drugs, given that there is sufficient permitted flexibility in study design to address exceptional cases;***

2. ***Notwithstanding the potential need for relatively large numbers of subjects in some BE studies, the current requirements do not present an unreasonable barrier to product approval; and***

3. ***The ethical concern surrounding the exposure of a relatively large number of healthy subjects to study drugs does not outweigh the potential risk of exposing the patient population to a bio-inequivalent drug.***

➤ **ITEM 15 & 17 - Requirements for Food Effect Studies**

The Committee discussed issues related to bioequivalence requirements for food effect studies, including issues raised at the previous day's stakeholder meeting. Some of the questions and issues discussed were:

i) Is there a need to increase or decrease the number or type of drugs or drug products requiring a food effect study?
ii) What type of food should be used?
iii) Are there situations where a fed study would suffice (i.e., no fasted study)?
iv) Is there need for a minimal food study in special cases?

SAC Recommendations:

1. ***For uncomplicated drugs in immediate release dosage forms, bioequivalence should be demonstrated in a single-dose study under fasting conditions. However, if there is a documented serious safety risk to subjects from single-dose drug or drug product administration in the absence of food, then an appropriately designed study conducted in the presence of only a sufficient quantity of food to prevent toxicity may be acceptable.***

2. ***For complicated drugs in immediate release dosage form, if there is a documented serious safety risk to subjects from drug or drug product administration, in either the absence or presence of food, then an appropriately designed study conducted in the indicated condition of use (fed or fasted state) may be acceptable for purposes of bioequivalence assessment. For non-linear drugs specifically, the Committee has presented its recommendations at the March 14, 2003 meeting.***

3. ***For drugs in modified-release dosage forms, bioequivalence should be demonstrated under both fasting and fed conditions in keeping with current requirements.***

4. ***The test meal employed in comparative bioavailability studies conducted in the fed state, for purposes of bioequivalence assessment, should be a representative meal in which sufficient food is given to allow potential perturbation of systemic bioavailability of the drug from the drug product. The sponsor should justify the choice of meal and relate the specific components and timing of food administration.***

➤ ITEM 22 - Future Agenda Item Proposals

The members were polled for their suggestions of priority issues that could be addressed at future meetings. Issues mentioned were (with no particular priority):

- Biopharmaceutics Classification System
- Product Monograph (labeling) issues
- Guideline A update
- Add-on studies
- Outliers/Inadequate profiles
- Metabolites
- Pharmacodynamic / Efficacy Trials
- Content uniformity
- Foreign sourced Canadian reference products

➤ ITEM 23 - Workshop Format /Administrative Details/Closing remarks

The Chair thanked all the members, as well as HC staff, for their time and input. It was announced that William Racz has been made a Core member of the Committee.

Comments from the members were solicited regarding this meeting and the Day 1 workshop. There was general support for continuing to have such meetings and for the format. It was noted however that some presentations did not directly address the issues. Also some presentations deviated from copies distributed before the meeting.

➤ ITEM 24 - Scheduling of next meeting and adjournment

Meeting adjourned at 3:30 p.m.
Next proposed meeting: November 2003
Prepared by: M. Davis and C.Pereira (2003/09/18)

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