Coordinator: Dr. Conrad Pereira, Therapeutic Products Directorate (613) 957-6445
Alternate: Ms. Marilyn Davis, Therapeutic Products Directorate (613) 957-6260

EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

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

RECORD of PROCEEDINGS

November 28 & 29, 2002

Committee Members Present: Dr. J. Thiessen (Chair), Dr. J.G. Besner, Dr. A. Donner, Dr. R. Herman, Dr. F. Jamali, Dr. M. Kara, Dr. E. Palylyk-Colwell, Dr. K. Renton, Dr. D. Sitar

Regrets: Dr. J.N. McMullen

***Ad hoc* Members Present:** Dr. R. Nair, Dr. F. Varin, Mr. S. Walker

Stake-holder Presenters: M. Ducharme (MDS Pharma), S. Gavura (Ontario Ministry of Health and Longterm Care), G. Levy (Toronto General Hospital), E. Masson (Anapharm), I. McGilveray (University of Ottawa), K. Midha (Pharmalytics) M. Spino (Apotex), C. Toal (Bayer Inc.), U. Wiegand (Hoffmann-LaRoche)

Health Canada (HC) Expert Advisory Committee Working Group Members:
L. Carter (CTSAP*), L. Cockell (DBE*), G. Condran(BPS*), M. Davis (EAC Secretariat Officer, PB*), D. Hoffman (BGTD*), K Kourad (BGTD), A. Naperstkow (BPS), E. Ormsby (PB), C. Pereira (EAC-BB Coordinator, PB), P. Roufail (BMORS), 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. Qureshi (BPS), S. Stojdl (DBE), A. Tam (DBE), S. Wagner (BP), P. Wielowieyski (DBE)

*Abbreviations for Health Canada Bureaux/Divisions and other terms used in this record:

BGTD	=	Biologics and Genetic Therapies Directorate
BLPA	=	Bureau of Licensed Product Assessment
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)
HC	=	Health Canada
PB	=	Policy Bureau
TPD	=	Therapeutic Products Directorate

EAC - BB	=	Expert Advisory Committee on Bioavailability & Bioequivalence
BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence

The structure of this new 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 the morning of day 1, invited stakeholders made a series of 10-minute presentations on the first issue (critical dose drugs.) A panel discussion moderated by the Chair of the EAC-BB followed which was restricted to the EAC-BB members and invited presenters. These discussions were however open for all to hear/observe, and were followed by an open discussion, permitting observers and members of the audience to provide input. The same process was repeated for the second topic (drugs exhibiting non-linear pharmacokinetics).

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

DAY ONE - November 28, 2002

****<u>PowerPoint presentations are available upon request for all presentations indicated by double asterisk.</u>****

➤ **ITEM 1 - Opening Remarks & Welcome** (Dr. C. Pereira)

➤ **ITEM 2 - Chair's address, Historical Overview** (Dr. J. Thiessen)
Bioavailability and Bioequivalence: A Historical Overview ******

➤ **ITEM 3 - Critical Dose Drugs Presentations**

A series of 10 minute presentations was made on this topic, beginning with an introduction to the subject by HC, followed by stakeholder presentations.

- **Dr. C. Pereira** (HC)
  Bioequivalence requirements: Critical Dose Drugs ******

- **Dr. M. Ducharme** (MDS Pharma Services)
  Bioequivalence Requirements for Critical Dose Drugs: Recommendations from a Global Contract Research Organization to the TPD ******

- **Mr. S. Gavura** (Ontario Ministry of Health & Longterm Care)
  Critical Dose Drugs ******

- **Dr. G. Levy** (University of Toronto)
  *Critical Dose Drugs in Transplantation: What Do We Need to Know? What Do We Need to Do?*******

- **Dr. E. Masson** (Anapharm)
  Proper dose selection for Bioavailability/Bioequivalence Studies ******

- **Dr. I. McGilveray** (McGilveray Pharmacon Inc & U of Ottawa)
  Exploring The Challenges of Bioequivalence with Narrow Therapeutic Range (NTR), Highly Toxic or Critical Dose Drugs ******

- **Dr. K. Midha** (Pharmalytics Research Institute)
  Critical Dose Drugs ******

- **Dr. M. Spino** (Apotex)
  Critical Dose Drugs: A Pragmatic Perspective ******

- **Dr. Cory Toal** (Bayer)
  Is Pharmacokinetics without Pharmacodynamics always enough to Determine

*Bioeqivalence and Therapeutic Interchangeability?***

- **Dr. U. Wiegand** (F. Hoffmann- La Roche Ltd.)
  *Bioequivalence Requirements for Critical Dose Drugs: Do we need a subgroup for teratogenic drugs?***

➤ ITEM 5 - Panel Discussion (Critical Dose Drugs)

The Chair initiated general discussion on bioequivalence requirements for critical dose drugs. Some of the questions considered were:

i) Should narrow therapeutic range (NTR) & highly toxic drugs be grouped into a single category?
ii) How should this category be defined or characterized?
iii) What are the criteria to be used for AUC, C_{max}, and CI?
iv) Can we come up with examples we can all agree to? (List?)
v) Are fed & fasted studies both required?

➤ ITEM 8 - Non-Linear Drugs Presentations

A series of 10 minute presentations was made on this topic, beginning with an introduction to the subject by HC, followed by stakeholder presentations.

- **Dr. C. Pereira** (HC)
  Bioequivalence requirements: Drugs exhibiting non-linear pharmacokinetics **

- **Dr. M. Ducharme** (MDS Pharma Services)
  Bioequivalence Requirements for non-Linear PK drugs: Recommendations from a Global Contract Research Organization to the TPD **

- **Mr. S. Gavura** (Ontario Ministry of Health & Longterm Care)
  Non-linear kinetics **

- **Dr. K. Midha** (Pharmalityics Research Institute)
  Non-Linear Kinetics **

- **Dr. M. Spino** (Apotex)
  Non-Linear Drugs: A Pragmatic Perspective **

➤ ITEM 10 - Panel Discussion Non-Linear Drugs

There was general discussion on bioequivalence requirements for these drugs. Some of the issues considered were:

i) 25% deviation from linearity
ii) which dose should be tested?
iii) criteria for AUC and C_{max}?
iv) do non-linear drugs require food effect testing?

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

The Chair invited the stakeholders to give their impressions of which BB items from our list posted on the website should be discussed at the next meeting in March. The items mentioned, in no specific order, were:
-US Food and Drug Administration (US FDA) Biopharmaceutics Classification System (BCS) guidelines should be studied
-inhaled steroids (nasal & oral)
-fed & fasted studies should be addressed
-highly variable drugs
-use of metabolite data
-long half life
-in vitro & in vivo correlations
-aqueous solutions
-pharmacodynamic studies
-drugs with a critical time of onset

Idea proposed: For future meetings with stakeholders, tackle one difficult issue and one fairly simple issue.

➤ **ITEM 13 - Adjournment of day 1**

The Chair thanked all presenters and stakeholders for participating; he polled the audience as to whether they found this new format to their satisfaction and there appeared to be complete agreement from the participants. Polling once again to see how many would attend another similar meeting, the participants gave a nearly unanimous show of hands.

The meeting was adjourned.

DAY TWO - November 29, 2002

Committee Members Present: Dr. J. Thiessen (Chair), Dr. J.G. Besner, Dr. A. Donner, Dr. R. Herman, Dr. F. Jamali, Dr. M. Kara, Dr. E. Palylyk-Colwell, Dr. K. Renton, Dr. D. Sitar

Regrets: Dr. J.N. McMullen, Dr. R. Nair

***Ad hoc* Members Present:** Dr. F. Varin, Mr. S. Walker

Health Canada (HC) Expert Advisory Committee Working Group Members:
L. Cockell (DBE), G. Condran(BPS), M. Davis (EAC Secretariat Officer, PB), D. Hoffman (BGTD), K Kourad (BGTD), A. Naperstkow (BPS), E. Ormsby (PB), C. Pereira (EAC-BB Coordinator, PB), P. Roufail (BMORS), 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. Qureshi (BPS), S. Stojdl (DBE), A. Tam (DBE), P. Wielowieski (DBE)

➤ ITEM 22 - Workshop Format

The chair opened the session with a brief introduction of the EAC core and new *ad hoc* members. He also welcomed Dr. Sylvia Storpirtis from the Brazilian Sanitary Surveillance Agency, who was present as a special observer.

This was followed by an informal evaluation of the format of the previous day's workshop. The Chair first asked each EAC member for input, and then opened the floor to comments from HC staff.

In general, the EAC members were of the opinion that the workshop was a good exercise and they were satisfied with the outcome. It was useful for information gathering and gave all stakeholders an opportunity to understand the range of views on each issue. There were some excellent presentations, although having abstracts for all presentations ahead of time would have been helpful.

Health Canada staff agreed that the format was useful and meetings of this type should be repeated. It was suggested that the US FDA could be invited to participate in these meetings. While there was representation from the different industry sectors, contract research organizations and the Provinces, the public was not adequately represented. Having abstracts ahead of time was also supported; it was hoped that there might be more input from the audience at future meetings.

➤ ITEM 14 & 16 - Critical Dose Drugs

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

-Is it necessary to have a special category? If so, is the definition adequate, or should the category be

split, e.g., back into narrow therapeutic range and highly toxic drugs?
-Are the factors to be considered adequate?
-Are both a definition and a list of drugs needed?
-Goal posts need to be defined. What are the consequences of Type 1 and Type 2 error with this type of drug?
-Should highly variable drugs be addressed separately?
-Are both fasted and fed studies needed?
- Other issues, such as sample size.

EAC Recommendations:

1. It was reiterated that the previous recommendation that a special category, critical dose drugs, was necessary for the purpose of bioequivalence assessment.
2. The previously recommended definition, as stated in the discussion paper was supported. This definition is as follows:

   "Critical dose drugs" are defined as those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events.

3. The previously recommended list of factors to consider, as stated in the discussion paper was also supported; body surface area should be added to factor iv). The list of factors is as follows:

   Some factors to consider when including drugs in a list of Critical Dose Drugs:

   i) serious dose-dependent adverse effects exist close to the dosing range
   ii) narrow therapeutic range or narrow tolerance range
   iii) requirement for blood level monitoring to control and individualize treatment; this is the standard of care or normal condition of use
   iv) dosing based on body weight, *body surface area*, or other highly individualized dosing requirements
   v) serious clinical consequences of overdosing (toxicity) or under-dosing (lack of effect)
   vi) steep dose response relationship for efficacy and/or toxicity

4. It was reiterated that a definition and a list of factors to consider are required in order to characterize new drugs that would not yet be included in a list of critical dose drugs.

5. A list of drugs, which takes into account the proposed definition and list of factors, should be drafted by Health Canada (potentially under external contract) and then widely circulated for comment.

6. With respect to creation of the list, the issue of high intra-subject variability exhibited by some drugs was discussed. No consensus was reached and the issue will be re-visited a later meeting.

7. It was re-iterated that tightening the 90% CI standard for AUC for critical dose drugs was done in recognition of the fact that the risk of making a Type I error (i.e., concluding two products are bioequivalent when they are truly not) is greater for critical dose drugs. The larger sample size of subjects (n) required for bioequivalence studies is not considered to be unreasonable and will serve to reduce the probability of both a Type I and Type II error. With regard to the proposed standard for C_{max}, the 90% CI requirement actually represents a relaxation of the previous Report C standard (95% CI)

8. Studies under both fasting and fed conditions should be required, unless the approved labelling of the drug specifically states that the drug should only be taken in the fasted or fed state for safety reasons. This ordinarily pertains to immediate (regular) release products only.

9. In general, multiple-dose studies are not required.

10. BE studies for critical dose drugs can, if appropriate, be conducted in healthy volunteers.

➤ ITEM 18 & 20 - Non-Linear Drugs

The Committee discussed issues related to bioequivalence requirements for drugs which exhibit non-linear pharmacokinetics, including issues raised at the previous day's stakeholder meeting. Some of the issues discussed were:

-Is it necessary to have a special category? If so, is the definition adequate?
-How should non-linearity be defined?
-What data should this classification be based on?
-What dose should be studied to demonstrate BE?
-What dose should be studied in a comparative bioavailability study? For example, the dose provided by the highest strength proposed for marketing or the highest common initial dose?
-Are both fasted and fed studies required?
-If non-linearity is due to binding, or due to a process that is post-absorption, is a fed study necessary?
-Are there some drugs that should be addressed with a unique guidance e.g. phenytoin?

Discussion Notes:

1. There appeared to be general agreement that a special category, drugs exhibiting non-linear pharmacokinetics, was necessary for the purpose of bioequivalence assessment. However, consensus was not reached on exactly how drugs should be classified as having non-linear kinetics for the purpose of bioequivalence assessment. For example, would a 25% deviation in

AUC from the expected value trigger special requirements? If so, how should that deviation be calculated, based on what data and using what range of doses?

2. A view presented was that the use of the highest common initial dose recommended in the approved labelling would be expected to be safe in the study subjects (e.g., healthy volunteers). In addition to the possibility of toxicity to healthy volunteers, the discussion of this issue took into consideration the possibility that the high dose may not be in the non-linear range. It was suggested that in that case a relevant dose should be used.

3. There appeared to be general agreement that fed studies should not be required if non-linearity was due to a post-liver process and that fed studies should be required if the non-linearity was due to any process that occurred in or before the liver.

4. The possibility of developing specific drug guidances for selected drugs (e.g. phenytoin) was raised.

EAC Recommendation: *Without a consensus on the bioequivalence requirements for drugs exhibiting non-linear pharmacokinetics, it was recommended that the topic be revisited at the next EAC meeting.*

➤ ITEM 21 - Future Agenda Item Proposals/Administrative Details/Closing remarks

The members were polled for their suggestions of priority issues that could be addressed at future meetings. Issues mentioned were:

- Phenytoin
- use of metabolite data
- need for fed and fasted studies
- highly variable drugs
- pharmacodynamic studies
- long half life (minor topic)
- non-linear (revisited)
- standards when endogenous compounds are present
- in-vivo/in-vitro correlation
- review aqueous solutions
- topical effect for nasal delivery
- inhaled steroids

➤ ITEM 23 - Scheduling of next meeting and adjournment

Meeting adjourned. 3:40 pm
Next proposed meeting: June 26 & 27, 2003
Prepared by: M. Davis and C.Pereira