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

March 13 & 14, 2003

Committee Members Present: Dr. J. Thiessen (Chair), Dr. J.G. Besner, Dr. A. Donner (March 14 only), Dr. R. Herman, Dr. F. Jamali, Dr. M. Kara (March 13 only), Dr. R. Nair, Dr. W. Racz (March 13 only), Dr. K. Renton, Dr. D. Sitar, Dr. F. Varin, Mr. S. Walker,

Regrets: Dr. J.N. McMullen, Dr. E. Palylyk-Colwell

Health Canada (HC) Participants: L. Cockell (DBE*), G. Condran(BPS*), L.N. Cui (DBE), M. Davis (EAC Secretariat Officer, PB*), C. Ficker (DBE), S. Ghani (BPS) (March 13 only), K. Kourad (BGTD*)(March 13 only), C. Lourenco (BGTD), A. Makinde (DBE), A. Melnyk (DBE), A. Naperstkow (BPS) (March 14 only), E. Ormsby (PB), C. Pereira (EAC-BB Coordinator, PB), R. Peterson (DG-TPD*)(March 13 only), P. Roufail (BMORS*), C. Simon (DBE), A. Tam (DBE)

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

BGTD	=	Biologics and Genetic Therapies Directorate
BMORS	=	Bureau of Metabolism, Oncology and Reproductive Sciences
BPS	=	Bureau of Pharmaceutical Sciences
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
DG-TPD	=	Director General, Therapeutic Products Directorate
PB	=	Policy Bureau
BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence
EAC - BB	=	Expert Advisory Committee on Bioavailability & Bioequivalence

➤ **ITEM 1 - Opening Remarks & Welcome, Conflict of Interest** (R. Peterson)

The Director General (DG) welcomed the members and delivered a short outline of the meeting expectations. He stated that HC would like to finalize BB guidance documents with very decisive, substantive statements that can be supported by scientific data. He stressed the need for a clear definition of non-linear drugs, and fed study requirements, which would also demonstrate a valid basis as to why we would have different requirements from other regulatory authorities.

The DG elaborated that since broad consultation has been ongoing for over a decade on BB requirements, it is now time to move documents out of draft form to final guidance, in an effort to shorten the submission review time. HC is constantly being challenged and the non-linear document should help to make evaluations more straight forward. This final draft document crafted from these discussions would go out for consultation, then be published as a guidance document.

He also asked that the committee give a decisive recommendation for the Clarithromycin issue at this time. He concluded by thanking the members in advance for their time.

➤ **ITEM 2 - Roundtable Conflict of Interest (COI) Declarations** (C. Pereira)

A short presentation was made requesting all members to declare verbally any situations which they felt might place them in either a perceived, potential, or real COI, specifically keeping the agenda for this meeting in mind. On behalf of Health Canada, the Committee Coordinator went around the table and each member was given an opportunity to briefly outline any pertinent issues, if applicable. Most had no conflict to declare. Upon completion of the declarations, it was unanimously agreed that all members could participate fully in the meeting.

➤ **ITEM 3 - Chair's address, Review & Adjustment of Agenda** (J. Thiessen)

The Chair made a brief comment stressing that he would very much like to finalize the non-linear agenda issues in particular during this meeting. He asked members to recall discussions from the last workshop/meeting in November 2002, which points to the generic companies preferences to challenge/drop these requirements.

The DG interjected that the discussions should not be driven by the expectations of industry, but that their concerns should be taken into consideration. The EAC's recommendations, which will form the basis of requirements in Canada, need to be based on good science.

➤ **ITEM 4 - Approval of November 2002 Record of Proceedings** (J. Thiessen)

The Chair thanked those who made comments and worked on the finalization of the record, and opened the floor for final comments.

There was discussion of one point found under item 14 & 16, Critical Dose Drugs, EAC Recommendation #6. The modified text will read:

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 at a later date.

With this change, the record of proceedings was approved.

➤ **ITEM 5 - Presentation: Current requirements for non-linear drugs in other jurisdictions; HC concerns** (C. Pereira)

International regulatory requirements in bioequivalence studies involving non-linear drugs including the need for a food study were summarized from several guidance documents. The documents surveyed were:

a) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (US Food and Drug Administration (FDA), October 2000)
b) Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (US FDA, December 2002)
c) Note for Guidance on the Investigation of Bioavailability and Bioequivalence (European Agency for the Evaluation of Medicinal Products (EMEA) 26 July 2001. Note: The Therapeutic Goods Administration (TGA), Australia has adopted this guidance)
d) Guideline for Bioequivalence Studies of Generic Products (The National Institute of Health Sciences (NIHS), Japan 1997)

The US and Japan do not have any special bioequivalence requirements for non-linear drugs. The EU may require steady-state studies in some cases. The strength to be used in the bioequivalence study should be the one with largest sensitivity to identify differences between the test and reference products.

Some HC concerns with respect to previous recommendations were summarized. These included:

a) Definition of non-linearity: Data to define degree of non-linearity is often unavailable or unclear.
b) Which dose should be studied (high dose *versus* high strength): Although use of the highest common safe initial dose may be logical it may not always be practical.
c) When and why do we need fed studies: Need to have clearly stated reasons.

In order to facilitate finalization of requirements in bioequivalence studies involving drugs that exhibit non-linear pharmacokinetics, recommendations with respect to the following issues were sought:

a) Definition of "non-linear" i.e., what degree of non-linearity would be considered significant and how should that be calculated? Alternatively, the existing practice could be continued i.e., if the literature indicates kinetic non-linearity within the usual dosage range, regardless of the degree of non-linearity, the drug would be considered to exhibit non-linear kinetics. Also, should we have special requirements only when the non-linearity is absorption-related or should we also include non-linearity due to a liver-related process?

b) Dose to be used. For drugs that show more than proportional increase in AUC with increases in dose, either the highest safe common initial dose or alternatively, continue the present practice of using the dose provided by a single unit of the highest strength the sponsor wishes to market.

c) Need for study under fed conditions particularly for immediate-release dosage forms.

Aside from general recommendations, the committee was also asked for recommendations specific to clarithromycin which is considered to exhibit non-linear pharmacokinetics (more than proportional increase in AUC with increase in dose) within the usual dosage range. The following question was posed:

d) For the purpose of bioequivalence assessment, should a study under fed conditions be required, in addition to a study under fasted conditions, for clarithromycin 250 mg and 500 mg immediate-release formulations?

➤ **ITEM 6 - Presentation: Effects of food on Bioequivalence assessment: products containing drugs exhibiting non-linear pharmacokinetics** (J. Thiessen)

The presentation summarized some of the issues surrounding food effects in bioequivalence assessment including the issue of variability. Questions raised during the presentation included:

a) Why is food effect not examined as a factor for "Part A" drugs?

b) Why is food effect to be examined as a factor for "Part B" drugs?

c) What is unique about non-linear drugs ("Report C")?

A general discussion ensued. No consensus opinion was reached at this stage on the issues surrounding the need for food effect studies in bioequivalence determination.

➤ **ITEMS 8 & 10 - Discussion Non-Linear Drugs** (EAC Members)

The discussion covered a variety of issues, such as:

- variability due to food
- the relevant kinetic parameter to examine for non-linearity (AUC versus C_{max})
- requirement for administration with or without food in approved labelling
- likelihood of food matrix interaction with an immediate-release product
- do all types of non-linearity necessitate a food study?
- statistical test to apply to determine whether 25% difference in dose normalized AUC was significant (e.g. t-test, alpha = 0.05, beta = 0.2)
- what dose to study?
- safety of dose in healthy volunteers
- need for phenotyping volunteers
- consider indication for use of drug when considering relevant dose range
- requirements for combination products when one ingredient is non-linear

This list is by no means exhaustive and is intended only to give a sense of the type of issues discussed.

➤ **ITEM 12 -Final recommendations**

By consensus, the following final recommendations were provided with respect to bioequivalence requirements for drugs exhibiting non-linear pharmacokinetics:

(Requirement for food effect study)

Food and fasted ARE required for all non-linear drugs, with the following exceptions:

> ***-non-linearity occurs after the drug enters the systemic circulation unless there is evidence that a product exhibits a food effect;***
>
> ***-if a condition (fasted/fed) for product ingestion is contraindicated, that condition may be waived in a bioequivalence trial.***

(Definition of non-linear)

AUC is the most reliable metric, whether following a single dose or steady state dosing because it reflects both input and clearance. (Therefore AUC will be considered in the decision on whether or not a drug exhibits non-linear kinetics rather than C_{max})

A drug is considered to exhibit non-linear pharmacokinetics when a change in dose results in a disproportional change in the single dose or steady state concentrations in the blood. For

the purpose of this discussion paper, a drug will be considered to exhibit non-linear pharmacokinetics if this is indicated in the peer-reviewed scientific literature or the approved labelling for the drug. However, the drug may be treated in the same way as those exhibiting linear pharmacokinetics, if evidence is provided to show that the dose-normalized concentrations deviate (increase or decrease) by less than 25% over the labeled dose range for the proposed indication.

(Dose to be used in bioequivalence studies)

For bioequivalence testing the fasting and fed doses shall be the same. Where non-linearity arises from capacity limited absorption, the test dose shall be a single unit of the lowest strength.

Where non-linearity arises from capacity limited clearance, the highest strength for the proposed indications shall be tested.

In the latter instance, if single doses do not fall within the non-linear range, then multiple units of the highest formulation strength or steady state studies in the non-linear range may be required.

In all situations, safety in dosing shall be considered.

➤ **ITEM 13 - Discussion on Clarithromycin** (J. Thiessen)

The committee having previously reviewed background information on clarithromycin provided by Health Canada, including an expert scientific report prepared by Drs. J. Thiessen, W. Racz and R. Nair, discussed the question posed by Health Canada, i.e., for the purpose of bioequivalence assessment, should a study under fed conditions be required, in addition to a study under fasted conditions, for clarithromycin 250 mg and 500 mg immediate-release formulations?

By unanimous consensus, the expert opinion provided was that ***a food study is required for clarithromycin.***

The committee stated that the studies should be conducted using a 500 mg dose (single tablet).

The committee also provided a consensus statement on why a food effect study was necessary. They stated that for non-linear drugs, ***food effects may amplify the differences between formulations with respect to the rate and extent of absorption***.

➤ **ITEMS 15, 16, 18 - Bioequivalence criteria for levothyroxine tablets and food requirements for critical drugs**

There was insufficient time for agenda items 15, 16 and 18. Discussion of these items was deferred.

➤ **ITEM 20 - Future Agenda Item Proposals** (C. Pereira)

It is the intention of HC to draft a series of updates to Guideline A, consult electronically and then publish the resulting changes to Guideline A. The topics currently being considered include:

- Fifteen percent random replicate analysis
- Use of metabolite data
- Long half-life drugs
- Combination products
- Rapid onset

In addition, several discussion papers are being developed under external contract. These papers will serve as starting points for discussion and consultation. Topics include:

- Highly variable drugs
- Endogenous compounds
- Critical dose drugs (list)
- Outliers
- Add-on studies
- Use of urine data

HC is planning on having a stakeholder workshop and EAC meeting in June. This is conditional on timely completion of work under certain external contracts. Tentative topics for the June meeting are:

- Highly variable drugs
- Use of metabolite data
- Fed BE studies

➤ **ITEM 21 - Scheduling of next meeting and adjournment** (J. Thiessen)

Meeting adjourned: 2:00 PM
Tentative teleconference proposed for March 27 or 28, 2003 to deal with Levothyroxine
Next proposed meeting: June 26 & 27, 2003

Prepared by: M. Davis and C. Pereira