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EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

March 22 - 23, 2001

RECORD of PROCEEDINGS

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

Health Canada (HC) Representatives Present: R. Peterson (DG*, Executive Secretary), E. Ormsby (EAC Coordinator, BPC*), M. Davis (EAC Scientific Support, BPC)

HC Expert Advisory Committee Working Group Members and Presenters:
L. Begin (BPC), J. Gordon (DBE*), D. Hoffman (BBR*), K. Kourad (BBR), S. Mishkin (BPA*), E.J. Northey (Justice Canada), C. Pereira (DBE), N. Pound (DBE), B. Rotter (BPA), C. Simon (DBE), D. Vu (BLPA*)

HC Observers: I. Aldeen (DBE), A. Chow (BPA), L. Cockell (DBE), K. Fitchett (BPA), M. Harczy (BPA), A. Hassen (BPA), T. Mueller (BPA), S. Qureshi (BPC), P. Wielowieyski (DBE), G. Zaror-Behrens (BPA)

- **Director General's Opening Remarks**

The Director General (DG) opened the meeting by welcoming the committee members and thanking them for agreeing to participate in this Expert Advisory Committee (EAC). He outlined the importance of their participation in providing advice to Health Canada (HC).

The DG spoke of the existence of several guidelines on bioavailability and bioequivalence (BB) which now exist in draft form. His hopes are that this EAC will facilitate the move of the drafts forward to a formal status. He stressed the need to settle controversial issues in a definitive manner.

The EAC members were informed that the proceedings of these meetings will be posted to the HC web-site as there is a great deal of interest in this area. The DG described the need for a clear record of decision from the Chair of the committee. He mentioned that the members must remember to exercise caution with regard to confidential documents and issues, and to ensure that they do not represent any comments they might make outside of the committee as anything but their own opinion, and not the view of the committee. Any inquiries from stakeholders, including the press, to the committee members on issues discussed by the committee should be referred to the Chair of the EAC.

The DG briefly addressed the Food and Drugs Act, which is the legislation that governs many of the processes developed by HC and the Therapeutic Products Programme (TPP). Guidelines developed pursuant to this legislation by HC, with the help of EAC members, must be accurate and represent the way in which business is conducted at present. However, once written, they can be updated occasionally to reflect current interpretations of scientific principles and data.

The DG concluded by turning the meeting over to the Chair for introduction of members and a brief outline of their expertise and interest in BB.

- **Roundtable Introductions/Chair's Vision of BB-EAC**

After the members introduced themselves, the Chair gave a brief outline of the Mandate of the EAC and of his personal goals for the operation and results expected. He stated that the EAC should function based on a forum of open dialogue, and he encouraged views from varying perspectives in an effort to form a consensus with authoritative recommendations as an outcome. He commented that members may experience added pressure in accomplishing this task due to the transparency under which this committee must operate.

The Chair likened the impact of bioavailability and bioequivalence to an image of three overlapping circles which represent the chief faces of BB: 1) the elements of science and statistics, 2) the clinical and practical issues influencing product selection and product interchangeability, and 3) the commercial interests which encompass the marketing of competitive products. There might not always be total agreement (overlap) among these three spheres.

In concluding his remarks, he welcomed the challenge of participating in this committee.

- **Review Agenda**

The agenda was reviewed and accepted.

- **Overview of Legislation and Regulation**

L. Begin (BPC) delivered a presentation intended to give EAC members a basic understanding of the authority and responsibility to regulate therapeutic products under the Food and Drug Act and Regulations. Definitions of terms were given and the Decision-Making and Policy Processes were addressed. Members found the presentation informative and requested a copy of the electronic version of the presentation.

Action: HC to send electronic version of presentation to members.

- **Terms of Reference** (TOR)

The Chair reviewed the elements of the TOR with the members and discussed preferences for distribution to committee members of materials and minutes generated from meetings.

The Terms of Reference were accepted as is and the members support their use as a guide for the EAC's activities.

- **Identification of Inadequate Subject Profiles in a Bioequivalence Study**

A presentation of the issue was made by J. Gordon (DBE) and the following question was posed to the committee for deliberation:

What criteria should be used to define an adequately characterized concentration-time profile, and when can subjects with inadequate profiles be removed from the statistical analyses of the study data without negating the validity of the study?

The EAC members agreed on this final answer to the question posed by HC:

> **A concentration versus time profile is ideally characterized when the absorption and elimination phases are adequately captured and AUC_t is 80% of the AUC_i. This usually requires 12-18 points, as stated in Guideline A. Placement of sampling times will depend on inter-subject variability and also upon the drug, formulation and study conditions. The onus is on the sponsor of a study to collect samples at appropriate times that will adequately characterize all potential subject profiles. It is acknowledged that, from time to time, the occasional individual subject data derived from a bioequivalence study may be less than ideal. The theoretical number of points needed to define the three metrics, C_{max}, AUC_t and AUC_i legitimately must be at least two, where the second point must be of a lower concentration. Therefore profiles with zero, one, two points (where the second measured point is of a higher concentration that the first) are not considered to be adequate. It follows that such profiles may legitimately be removed from the statistical analysis when a sound scientific rationale to do so is stated in advance in the study protocol (*a priori* criteria). If the inadequate profiles cannot justifiably be removed then the study itself is invalid and not amenable to further analysis. Likewise, exclusion of adequate profiles is also only justified with a sound scientific rationale. The committee reinforced the statement in Guidelines A and B which states, "It is rarely acceptable to exclude more than 5% of the subjects or more than 10% of the data for a single subject-formulation combination."**

- **Orally Administered Products with Topical Action**

Two of the EAC members declared possible Conflict of Interest (COI) for this issue. A roundtable poll of the remaining members showed a unanimous acceptance and belief that the two individuals could operate free of bias on this topic, and agreed to allow the two members to continue participation in the deliberation.

A presentation of the issue was made by B. Rotter (BPA) and the following questions were posed to the committee for deliberation:

1. For orally administered products with topical/local action (e.g. 5-ASA, Misoprostol) is a properly designed comparative bioavailability study sufficient to establish bioequivalence and hence the safety and efficacy of a second-entry product?

2. If not, what specific circumstances would necessitate clinical studies for orally administered products with topical/local action (e.g. 5-ASA, Misoprostol)?

3. Is there a validated surrogate marker that can be utilized either for 5-ASA or Misoprostol to conduct a pharmacodynamic study (PD)? Should the PD study be carried out in patients or healthy volunteers?

S. Mishkin, (Gastroenterology, Hematology and Oncology Division, BPA) joined the EAC members by teleconference for the discussion of this issue.

The EAC members concluded that each of the two drugs cited in the questions posed by HC (and in general, drugs in this category) should be addressed individually for the following reasons:

<the sites of release and absorption of the drug in the GI tract may be therapeutically important,
<the degree of systemic absorption of the drugs differ,
<the formulations of the drugs differ (i.e. immediate *versus* modified release).

MISOPROSTOL

For Misoprostol, a properly designed comparative bioavailability study is sufficient to establish bioequivalence and hence the safety and efficacy for immediate release products.

If a drug (e.g. Misoprostol) is systemically absorbed comparatively rapidly and completely, then regardless of its site of action, the effect is evident during the systemic absorption phase and continues after the formulation is absorbed. Hence, as long as the two formulations demonstrate comparable rate and extent of absorption, they should be considered bioequivalent.

5-ASA

Aminosalicylate formulations for subsequent marketed Modified Release (MR) products should be considered in the context of Group III drug products as described in Report B "Oral Modified Release Formulations".

The subsequent entry product has to show that the site of release is comparable to the reference product. It is unknown if absorption and action are at the same site. Drugs can have the same absorption profile but different action profiles.

The committee could not reach a consensus on these issues at this time. However, it was stated that concentration/time data is not sufficient to determine bioequivalence. A need for clinical study was identified.

Action Item: EAC members to investigate the feasibility (sensitivity, specificity) of a surrogate pharmacodynamic marker(s) to accurately measure the site of GIT absorption for orally administered, topically acting drugs (eg. ^{51}Cr EDTA, mannitol, etc.)

- **Conflict of Interest and Indemnification with respect to Expert Advisory Committees**

A brief presentation was made by J. Northey, Counsel from Department of Justice Canada to ensure that the members have a common understanding of legal issues associated with Health Canada Expert Advisory Committees (EAC). The presentation touched on Indemnification, Conflict of Interest and Access to Information Policy.

Discussion during and after the presentation centered around "care and control" of confidential documents and member's personal notes. The members requested more information on this subject.

Action: HC to research this issue and send the members an information package on the matter.

- **Adjournment of Day 1**

The Chair discussed the schedule for tomorrow and set mutually agreeable times for certain issues which were not completed in the time frame allowed to be revisited on Day 2.

Meeting adjourned until March 23, 2001, 8:30 am.

- **Welcome and review of Agenda for Day 2**

The timetable was adjusted to allow for the early departure of some members.

For continuity and ease of flow of information, all material discussed on one agenda item will be reported under the one heading in these minutes, even if the topic was discussed on both days.

- **Narrow Therapeutic Range (NTR) Drugs**

A presentation of the issue was made by C. Pereira (DBE) and the following questions were posed to the committee for deliberation:

1. **For regulatory purposes, is it necessary to have a NTR category of drugs/products to which more stringent bioequivalence requirements will apply?** Or are current bioequivalence requirements for 'uncomplicated' drugs (90% CI for AUC_t and relative mean C_{max} between 80 to 125%) adequate for all drugs/products for which in vivo demonstration of bioequivalence is required?

[The following questions assume that the recommendation on the above question is that it is necessary to have a 'NTR' category of drugs.]

2. **What is the definition of 'NTR'?** And should some other drugs be included in this group such as some which may undergo therapeutic drug monitoring (TDM) but which don't fit the definition of NTR drugs in terms of defined effective and toxic concentrations?

3. **What bioequivalence standards should be applied to NTR drugs?** At present, the standard applied is based on 95% CI for both AUC_t and C_{max} between 80 to 125% potency-corrected and un-corrected, in single-dose cross-over studies under both fasted and fed condition. Various suggestions have been made, including narrowing the CI (e.g. 90 to 112%).

4. **Should studies under both fasting and fed conditions be required, or is one condition sufficient?** At the present time, bioequivalence standards must be met under both fasting and fed conditions for drugs deemed to have a NTR. Also, should the same bioequivalence standards be applied to studies under fed conditions as to studies under fasted conditions?

5. **Under what (if any) conditions should studies under steady-state conditions be required?** If such studies are required, what bioequivalence standards should be applied?

The EAC members formulated the following answers to the five questions on this issue:

1. **Conceptually, some drugs may be categorized as "critical drugs"; such drugs require stringent bioequivalence requirements.**

2. **"Critical drugs" can generally be defined as those where:**

   Comparatively small differences in dose or concentration lead to serious therapeutic failures and/or adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events.

3. **For "critical drugs", goal-posts must be narrowed.**

4. **For "critical drugs", both fasting and fed studies are necessary. Bioequivalence criteria need to be the same for fasted and fed conditions:**

   Fasted

AUC_t	**90% CI within 90 to 112%**
C_{max}	**90% CI within 80 to 125%**

   Fed

AUC_t	**90% CI within 90 to 112%**
C_{max}	**90% CI within 80 to 125%**

5. **Steady state studies are not required for "critical drugs" unless warranted by exceptional circumstances.**

Further consultation with the EAC may be necessary to refine the definition/description of the "critical" category of drugs to which the more stringent bioequivalence standards will apply. Further guidance will also be sought with respect to compiling a list of drugs to which these standards will apply.

Action Item: EAC Members to compile criteria and listings of probable drugs to include in this category to be brought forward for discussion at the next EAC meeting.

' **Future Agenda Item Proposals**

N. Pound (DBE) gave a short presentation outlining some issues that the Therapeutic Products Programme (TPP) is currently addressing. Topics from this list may serve as agenda items at upcoming EAC meetings.

<Report C - drugs with complicated kinetics (7 categories)
    -NTR Drugs
    -Non-linear kinetics
    -Highly toxic
    -Long half-life
    -Multiple active ingredients
    -Pharmacodynamic studies
    -Critical time onset or rate of absorption
<Locally topically acting oral drugs
<Exclusion of inadequate profiles
<Topical products for Dermatological, Ophthalmic, Otic and Nasal use
<Nasal solutions for systemic action
<Fed and fasted studies
<International Committee on Harmonization (ICH) Common Technical Document
<Exclusion of "Extreme" values
<Bioanalytical method validation
<*In vivo - In vitro* / Correlation
<*In vitro* bioequivalence
<Canadian Reference Standard

- **Scheduling of next meeting and adjournment of meeting**

The Chair thanked all expert members, HC representatives from different Bureaux, and the Coordinator and Secretariate for the Committee for their time and participation. A tentative date of October, 2001 was proposed for the next meeting, the exact date to be determined.

Meeting adjourned.

Next meeting: November 15 & 16, 2001
Prepared by: M. Davis

*Abbreviations for Health Canada Bureaux/Divisions:

BBR	=	Bureau of Biologics and Radiopharmaceuticals
BLPA	=	Bureau of Licensed Product Assessment
BPA	=	Bureau of Pharmaceutical Assessment
BPC	=	Bureau of Policy and Coordination
DBE	=	Division of Biopharmaceutics Evaluation (BPA)
DG	=	Director General