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SCIENTIFIC 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

June 3 & 4, 2004

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. K. Renton, Mr. S. Walker

Regrets: Dr. D. Sitar

Presenters: Mr. J.S. Brunet (Algorithme-Pharma), Dr. B. Davit (US Food & Drug Administration), Dr. L. Endrenyi (University of Toronto), Dr. M. Lefebvre (Algorithme-Pharma), Dr. B. Malhotra (Pfizer), Dr. I. McGilveray (University of Ottawa), Ms. D. Potvin (MDS Pharma Services), Dr. Y.C. Tsang (Apotex)

HC staff: M. Cardinal (PB), M. Chaine (PB*), L. Cockell (DBE*), L-N Cui (DBE), M. Davis (SAC Secretariat Officer, PB*), C. Ficker (DBE), J. Gordon (DBE), R. Li (PB), A. Makinde (DBE), A. Melnyk (DBE), Mr. A. Naperstkow (BPS), Dr. C. Njue (BGTD), E. Ormsby (PB), C. Pereira (SAC-BB Coordinator, PB), J. Rose (PB), F. Shi (PB), C. Simon (DBE), S. Stojdl (DBE), S. Sultan (PB), A. Tam (DBE), M. Walsh (BGTD), P. Wielowieyski (DBE), Y. Yu (PB)

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

BGTD	=	Biologics and Genetic Therapies Directorate
BPS	=	Bureau of Pharmaceutical Sciences
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
HC	=	Health Canada
PB	=	Policy Bureau
TPD	=	Therapeutic Products Directorate

BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence
PK	=	Pharmacokinetics
SAC - BB	=	Scientific Advisory Committee on Bioavailability & Bioequivalence

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. Questions to ponder on 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 presenters and stakeholders made a series of short presentations on the first issue (outliers.) An open discussion followed, moderated by the Facilitator, who allowed SAC-BB members, invited presenters, observers and members of the audience to provide input. The same process was repeated for the second topic (add-on studies).

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

DAY ONE - June 3, 2004

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

➤ **Opening remarks & adjustment of agenda** (Mr. E. Ormsby)

The workshop was opened by the Facilitator who outlined the process and intended outcome for this two-day meeting.

➤ **ITEM 2 - Welcome**, **Chair's address** (Dr. J. Thiessen)

The Chair welcomed all registrants and introduced the Scientific Advisory Committee (SAC) members. He stressed that this was the time for all to offer views and information, and ask any pertinent questions.

➤ **Progress since last workshop** (Mr. E. Ormsby)

It was announced that three guidances were posted to Health Canada's (HC) web-site on the topics of combination products, metabolites, and fed studies.

There has been much interest in the progress made concerning Critical Dose Drugs. To date, the guidance document has been drafted and the original list of drugs attached has been reduced significantly. This document will be posted for consultation and stakeholders will need to submit a rationale and comprehensive evidence why other substances are to be on the list.

In the future, Guidelines A & B will be reworked, but some statistical issues must be re-evaluated first.

➤ **Presentation: Statistical issues in bioequivalence: Outliers and inadequate profiles** (Mr. E. Ormsby) ******

The Facilitator set the stage for the presentations on this topic by outlining the three main issues:

1. Regulatory Concerns
2. Causes
3. Accounting for outliers

➤ **Presentation: Why drug product failure is an unlikely source for an outlier result in a bioequivalence study** (Mr. A. Naperstkow) ******

➤ **Presentation: Outlier detection in bioavailability/bioequivalence studies** (Dr. S. Sultan) ******

➤ **Presentation: Impact of missing values in the concentration-time curve on the assessment of bioequivalence** (Dr. A. Donner) *** ***

➤ **Presentation: Outliers and inadequate profiles: The FDA perspective** (Dr. B. Davit) ******

➤ **Stakeholder Presentations: Outliers and inadequate profiles**

Additional 10-minute presentations were made on this topic by the following stakeholders:

- **Ms. D. Potvin** (MDS Pharma)
  Detection of outliers during the pharmacokinetic data assessment ******

- **Mr. J.S. Brunet** (Algorithme Pharma)
  The impact of statistical outliers on the assessment of bioequivalence: A review of more than 400 crossover studies ******

- **Dr. Y.C. Tsang** (Apotex, representing CGPA)
  The presence of outliers impairs the assessment of bioequivalence ******

- **Dr. B. Malhotra** (Pfizer)
  Adequate pharmacokinetic profiles and outlier data points: diagnosis, decision to include vs. exclude, and impact of study validity ******

➤ **Open discussion (outliers and inadequate profiles)**

A limited number of topic specific questions were allowed after each presentation. At this point, the Facilitator initiated general discussion on the issue, with a focus on the three following points:

1. Retesting
2. Use of Metabolites
3. Other statistical methods, i.e.: non-parametric, robust methods

➤ **Presentation: Combining studies** (Mr. E. Ormsby) ******

The Facilitator set the stage for the presentations on this topic by outlining the three main issues:

1. Use of add-on studies
2. Use of sequential designs
3. How to combine studies

➤ **Presentation: Statistical strategies to deal with combining information from studies to establish bioequivalence** (Dr. R. Nair) ******

➤ **Presentation: Group sequential design** (Ms. J. Rose) ******

➤ **Presentation: Add-on studies: The FDA perspective** (Dr. B. Davit) ******

➤ **Stakeholder Presentations: Add-on studies**

Additional 10-minute presentations were made on this topic by the following stakeholders:

- **Ms. D. Potvin** (MDS Pharma)
  Should add-on group(s) be allowed in BA/BE studies and how? ******

- **Dr. M. Lefebvre** (Algorithme Pharma)
  *Add-on studies: Scientific or regulatory purposes?***

- **Dr. I. McGilveray** (McGilveray Pharmacon Inc)
  *Add-on studies: An opinion***

- **Dr. L. Endrenyi** (University of Toronto)
  Interim analysis of results: Group-sequential and add-on designs **

➤ **Open discussion (add-on studies)**

A limited number of topic specific questions were allowed after each presentation. At this point, the Facilitator asked if there were any more general questions on this subject.

➤ **Open discussion on other BB topics**

The following topics were listed as possible future issues of interest:

- Develop guidelines for PK studies for new drugs;
  what information needs to go in the product monographs?
  area of non-linearity;
  well run food studies;
  Critical Dose Drugs, what criteria do generic drugs need?
- Report C to be finished;
- Draft rewrite of Guideline A;
  e.g. 15% replicates, half-life, rapid onset, etc.;
- Endogenous substances;
- Guidance for urine data;
- Intra-subject variation;
- Highly variable drugs (HVD): Do they need a special category?
- Canadian Reference Product, review foreign reference product guidelines;
- Metabolites, (see draft guidance just posted on web);
- Reference list for dosages with high adverse event profiles drugs;
  the FDA has such a list for adverse event drugs (orange book) and keeps it updated by changing recommendations as necessary.

➤ **Adjournment of day 1**

The Chair closed the workshop by thanking all presenters, the FDA and HC staff for the day.

Adjourned at 4:05 PM

DAY TWO - June 27, 2003

➤ Outline of expected outcome for day 2

The Facilitator described the process for the day and outlined the expected outcome. The meeting was turned over to the Chair. Below will follow a list of issues discussed and conclusions drawn from the discussions.

➤ Outliers and inadequate profiles

OUTLIERS

‣ *Issue discussed*: The likelihood that an extreme observation in one or more subjects was due to a product failure, i.e., a failure of one dosage unit to perform similarly to others from the same batch.
A presentation was made by Health Canada on the quality (chemistry and manufacturing) data requirements for drug products.
‣ *Conclusion*: There was general agreement that while it is not possible to definitively rule out product failure as an explanation for an extreme observation, this is unlikely to be the cause, given current product quality requirements.

‣ *Issue discussed*: What is an outlier?
‣ *Conclusion*: Various statistical screening methods were discussed, to flag observations as possibly being from a population other than the one of interest. However it was agreed that statistical tests alone were not enough to designate an observation as being a true outlier and therefore cannot be the sole basis for elimination of that observation.

‣ *Issue discussed*: What is the potential reason for the outlying observation?
‣ *Conclusion*: If there was a valid, documented clinical explanation, that was specified *a priori* in the protocol, for screening possible outlying observations, (e.g., the subject vomited after taking the dose) then the subject's data may be dropped. If there is no clear documented reason for the observation, the observation cannot be deleted without further investigation.

‣ *Issue discussed*: Practical strategies for dealing with outliers.
‣ *Conclusion*: The strategy of retesting subjects was discussed in this context. The committee was split on this issue and no clear consensus was reached.

Nine members were willing to consider re-testing subjects who were outliers. However, other "control" subjects from the same group (for example 20%) should be re-tested as well. If the results on re-testing the outlying subject were within the range of the others in the original sample, the original results for that subject could be considered to be anomalous and dropped. If the results were similar to the original results for that subject, the subject's original data should be retained. No consensus was reached on how similar the results should be. Nevertheless, in no case should the re-test data be included in the analysis for a bioequivalence decision. Criteria for choosing subjects to be re-tested must be specified *a priori*.

Three members did not agree that re-testing subjects was a valid option as it was perceived to introduce unacceptable bias. One of the three members suggested that the original study should be discarded if the bioequivalence standards were not met and a new study should be conducted.

There was no consensus however on how the results of the original study should be handled if a second study is conducted. It was suggested that a study could not simply be eliminated and the results of the two studies should be combined. However, it would be difficult to pass current consistency tests for combining studies in the presence of an outlier. Alternate methods for combining results are available which may overcome this difficulty.

‣ *Issue discussed*: If re-testing is permitted, should it be done for all subjects identified as potential outliers whether or not the study passes bioequivalence standards?
‣ *Conclusion*: Strictly speaking this should be done, i.e., any rules for outliers should be applicable and uniformly applied before the analysis of bioequivalence is done. In the long run if only the outliers from "failed" studies are retested this will introduce bias. However it may not be practical to require re-testing of outliers when a study passes the bioequivalence criteria.

‣ *Issue discussed*: Alternate statistical methods, e.g., non-parametric, robust methods
‣ *Conclusion*: Use of non-parametric methods of statistical analysis would be acceptable only if this was explicitly stated and justified *a priori*. It is not acceptable to choose such methods only when an outlier may be causing the study to fail the bioequivalence criteria.

INADEQUATE PROFILES

‣ *Issue discussed*: What is an inadequate concentration versus time profile?
‣ *Conclusion:* If there are no measurable concentrations or just one concentration, that profile is not adequate. If two consecutive measurable concentrations are observed and the second is lower than the first, it is possible to compute a C_{max} and $AUC_{T.}$ Although these estimates of C_{max} and AUC_T may be somewhat inadequate, the profile should nevertheless be included in the analysis.
No consensus was reached on treatment of inadequate profiles, i.e., on whether these profiles may be simply dropped from the analysis.

➤ **Add-on studies**

‣ *Issue discussed*: As presently practiced, the so-called consumer risk, as defined statistically, is slightly higher than 5% when an add-on study is conducted (and combined with the original study).
‣ *Conclusion*: The consistency tests currently do not appear to provide sufficient protection. To offer consistency, the overall *p*-value needs to be maintained at 0.05. Various methods to achieve this were discussed. Add-on studies should be permitted provided this is pre-specified in the protocol, and that a suitable statistical penalty is adopted for multiple looks at the data.

‣ *Issue discussed*: Could the first study be discarded if the second study passed the bioequivalence criteria on its own?
‣ *Conclusion*: Only one member was willing to discard the results of the first study.

‣ *Issue discussed*: Use of group sequential design in bioequivalence studies.
‣ *Conclusion*: Group sequential design would be acceptable if justified and specified *a priori*. However, this study strategy was felt not to offer sponsors a significant advantage over add-on studies.

Given that final recommendations were not made on any of the above issues, Health Canada proposed to draft position documents and consult with the SAC-BB again.

➤ **Future agenda item proposals**

The list of topics which was generated on day 1 was reviewed and no new items were added.

➤ **ITEM 32 - Administrative details / Closing remarks / Adjournment**

A tentative date of November 2004 was put forward.

Meeting adjourned: 2:30 PM

Prepared by: M. Davis & C. Pereira