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EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

November 15 & 16, 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. J.N. McMullen, Dr. E. Palylyk-Colwell, Dr. K. Renton, Dr. D. Sitar

Health Canada (HC) Expert Advisory Committee Working Group Members:
E. Ormsby (EAC Coordinator, BPC*), L. Cockell (DBE*), G. Condran(BPA*), D. Hoffman (BGTD*), C. Pereira (DBE), N. Pound (BPA), P. Roufail (BPA), D. Vu (BLPA*), M. Davis (EAC Scientific Support, BPC)

HC Observers: L-N Cui (DBE), J. Gordon (DBE), A. Hassen (BPA), C. Lourenco (DBE), S. Rau (DBE), C Simon (DBE), P. Wielowieski (DBE)

*Abbreviations for Health Canada Bureaux/Divisions:

BGTD = Biologics and Genetic Therapies Directorate
BLPA = Bureau of Licensed Product Assessment
BPA = Bureau of Pharmaceutical Assessment
BPC = Bureau of Policy and Coordination
DBE = Division of Biopharmaceutics Evaluation (BPA)

An information package was sent out to all members on October 29, 2001. It contained an agenda and information on 11 agenda items. The numbering of the items in this record of proceedings refers to the order in which they were discussed, based on the revised agenda now posted on the HC web site, to accommodate for member schedules. Dr. Donner was present for discussions on November 15 only, and Dr. Herman had to depart around lunch time on November 16 for an early flight. Any mention of TAB # refers to the section of the information binder sent out to the members before the meeting.

- **ITEMS 1 & 2 - Opening Remarks, Review of Agenda**

The Committee Coordinator opened the meeting by welcoming the members and dealing with administrative items. He passed along regrets from the Director General (DG) who was out of the country. Information inserts for agenda items 4 and 9 were updated.

The meeting was turned over to the Chair who greeted the members and outlined the format for this meeting. He suggested that a brief presentation would be made by a HC representative for each topic, followed by debate by the committee members, ending with a commitment to formalize an outcome. The Chair indicated his intention to run this session as a meeting of the collective group, giving HC individuals an opportunity to contribute.

The Chair polled the committee members as to whether any of them had received feedback as a result of being on this Expert Advisory Committee (EAC). One member mentioned an involvement in an issue with a generic company and the member now had a better appreciation for the nuances of drug regulations. The Coordinator stated that several requests to attend this meeting were received from stakeholders and industry, and that this issue should be addressed for future meetings. It was suggested that these representatives may be allowed input, but not complete access to the meetings; perhaps it would be appropriate to give an opportunity to present to the EAC followed by a question/answer period as has been done with prior working groups and committees. The Chair handed out correspondence to the TPD from Drs. Small (McGill) and Keith (McMaster) which outlined the necessity for caution when establishing bioequivalence criteria for nasal products. This information was to be reviewed and included in the discussion of nasal products (Items 16 and 17 on the revised agenda).

The agenda was reviewed and it was agreed that Item 9 on Levothyroxine should be discussed in conjunction with Item 7 Critical Drugs.

- **ITEM 3 - Orally Administered Products with Topical Action**

A presentation was made by P. Roufail, thanking the members for their input and giving an update on this item since it was discussed at the last EAC meeting in March 2001. The guidance obtained has helped in dealing with some products, misoprostol in particular, since it was proposed that only bioequivalence was required in that case.

Feedback was also received from the innovator on 5-ASA.

The next step will be to develop a directive or guidance to give direction to industry. It was discussed that each drug of this type must be considered on its own merit, based on the amount of drug absorbed systemically and sites of absorption, etc. It was stated that under the regulations, bioequivalence could be assessed based on comparative bioavailability data, pharmacodynamic data or clinical data, depending on the individual drug characteristics. The presentation concluded with a reminder that comments would be welcome from committee members, both now and in the future. The committee was directed to the Issue Analysis Summary (IAS) entitled “Orally administered drugs intended for topical/local action- data requirements for subsequent entry products” found in TAB 2 of the information package. A potential typo on page 5 of IAS 20 mcg (IV column) was identified.

A discussion ensued with regards to clinical data being used to establish product bioequivalence and the following comments were made:

<The design of a study must be approved. Clinical studies to establish equivalence require clinical parameters that are capable of discerning significant differences between formulations. These parameters must be clinically important or meaningful, as the choice of measurement will influence what the significant clinical difference is. This may not necessarily be the 20% difference used for bioavailabilty data.
<If drug levels can be measured, they should be as they may be related to toxicity or adverse drug reactions(ADR), even if the concentration in plasma is not therapeutically important.
<Whenever possible, pharmacokinetic (pk) studies should be completed and the customary bioequivalence metrics and criteria used; clinical studies could be conducted to support efficacy and safety.
<Individual guidances are supported for individual drugs due to complex differences in topically acting drugs (i.e. consideration must be given to whether the drug effect is mediated systemically or locally, or if the release of the drug is site-specific.)
<A case by case analysis or guideline is needed.
<Sponsors might look for loopholes if the guidances are too general, they must be specific to each drug.
<There is an inherent problem in defining clinical outcomes vs. pk studies; clinical response is not always as discriminating as pk evidence.

Recommendation: *TPD to develop drug specific recommendations on a case by case basis.*

- **ITEM 4 - Inadequately Characterized Concentration-Time Profiles**

A presentation was made by N. Pound. This issue of defining adequately characterized concentration-time profiles and determining when subjects with inadequate profiles can be removed from the statistical analyses was discussed at the March 2001 meeting. The guidance document entitled "Bioavailability Requirements: Inadequately Characterized Concentration-time Profiles" (TAB 3) was introduced and had been revised to reflect the comments of the EAC. HC now seeks confirmation from the members that this guidance accurately reflects the recommendations made in March.

A discussion ensued, with the following points of interest arising:

<A comment was made that the distribution of inadequate profiles should be similar for the comparative products.
<The section on exclusion from analysis (lines 16 - 19, TAB 3) needs to be more rigid on the issue of potential outliers.
<Non-compliance is not a valid reason to remove a subject.
<Inadequate profiles are rarely an issue for conventional products; they arise predominantly in trials of non-conventional dosage forms (e.g. enteric coated formulations.)

<Again, it was identified that there is a need to better differentiate between outliers and inadequately characterized profiles, (better definition) i.e.:

Outlier = observed values are aberrant

Missing data/inadequate profiles = do not have adequate data to calculate a value

<Missing data likely arise most often due to problems in the blood sampling schedule.
<Removing outliers is discouraged because the observation may be due to a defective dosage unit or a subject by formulation interaction.
<The criteria for removal of inadequate profiles (lines 85 - 91, TAB 3) need more clarification.
<An *a priori* criteria statement is needed to justify removal.

Recommendation: *TPD to re-draft guidance and send out for stakeholder comment. This would include the EAC.*

- **ITEM 6 - Exclusion of Data from Bioequivalence Studies**

A presentation was given by N. Pound asking the EAC to address the issue of defining criteria for the identification and exclusion of outliers from comparative bioavailability studies for the purpose of establishing bioequivalence. An Issue Analysis Summary was contained in the Information package (TAB 4).

A discussion ensued, with the following points of interest arising:

<The committee questioned the recommendation (line 93, TAB 4) stating that "subjects (observations) to be removed are to be identified before the statistical analysis is undertaken." Ideally they should be identified prior to any analysis (i.e. analytical or statistical) being undertaken.
<The design of a protocol should include filters to include or exclude subjects on the basis of baseline characteristics, and not on the basis of what occurred during the study.
<Conditions for exclusion should be set before a study begins (*a priori*), e.g. if a women gets pregnant after the onset of the study, it is not a violation of the protocol; these conditions must be practical. When unforseen or unanticipated conditions arise, they could offer a logical and reasonable reason for removal of outliers providing this is not an abuse of the intent to treat principle.
<There is a need for logical and scientifically defensible reasons for exclusion.
<It was pointed out that the standards are based on a parametric analysis and statistical tests are related to normality assumptions.
<A study should not be allowed to pass based on:

-bogus conclusions
-"mining for data"
-non-legitimate reasons

<The sponsor must be able to prove if it is a formulation effect, or a physical event on a given day.
<Retesting can only be done on the basis of factors other than "bad observable results."
<Retesting could be done to remove potential "Subject by Formulation" interaction only.

The committee members summarized the above debate with these criteria for exclusion:

Removal of Subjects

1. Justification to exclude subjects on a statistical basis alone is not acceptable.
2. Subject exclusion may be permitted if a protocol violation has occurred (that was stated *a priori*), provided the reason(s) for removal are medically and/or scientifically justified, and no more than 5% of subjects in total are excluded.
3. An unanticipated event such as an inadequately characterized profile (as defined elsewhere) or a serious medical event has occurred.

Requirement - To exclude any subject on the basis of the above, the decision to do so would have been made prior to any analysis (i.e. analytical or statistical) being undertaken. The likely underlying causes (medical and/or scientifically justified) must be given, and no more than 5% of subjects can be excluded in total.

The debate resumed, with further issues discussed:

<A sponsor could include extra subjects to compensate for those that had to be excluded. These individuals would have been subjected to similar conditions and time frames as the original set to be observed, but the sponsor's data will have to be scrutinized before decision to replace them is allowed.
<If subjects do not complete the study and the samples are not analyzed, then they could be removed, as long as it is deemed to be "pre-analysis" removal. These pre-analysis exclusions could be excluded from the 5% maximum exclusion limit. Once the analysis occurs, then all subjects must be included and the 5% maximum exclusion limit would apply.
<Some acceptable reasons to exclude subjects could be:

-pre-screening (pre-dose) blood samples demonstrating a concentration of the drug;
-analytical interference, i.e. concomitant substance;
-disease state that can impact absorption, (e.g. GI cancer that progresses, or migraines, which could impair absorption, that occur during the 2nd arm of the trial;
-subject vomits.

<In principle, recall and retesting of subjects is considered to be unacceptable. Such a practice raises questions regarding the statistical analysis of such data and does not address potential observations caused by defective dosage units. This is not to be confused with the practice of re-analyzing samples during the analysis portion of a study.

Recommendation: *The EAC members want to revisit the issue of recalling and retesting subjects at the next meeting, with additional information from USA or European thinking on the subject.*

' **ITEM 7 - Critical Dose Drugs**

A presentation was given by N. Pound. This issue was previously addressed at the March 2001 meeting under the title of Narrow Therapeutic Range (NTR) Drugs. HC would like the EAC's recommendations regarding the addition of highly toxic drugs into this category and renaming the group

with a designation of Critical Dose Drugs, and would also like feedback on the new draft guidance (TAB 5) for this issue. The EAC members would also be invited to assist in revising and updating the current list of NTR drugs to include toxic drugs.

Recommendation: *The EAC members unanimously agreed to combine NTR and toxic drugs into one category called Critical Dose Drugs.*

The first filter for critical drugs is "dose and concentration causing marked effects." The following list was formulated from committee discussion:

Factors to consider when including drugs in a list of Critical Dose Drugs:[1]

-serious dose-dependent adverse effects exist close to the dosing range
-Narrow Therapeutic Range (NTR) or narrow tolerance range
-requirement for blood level monitoring to control and individualize treatment; this is the standard of care or normal condition of use
-dosing based on body weight or other highly individualized dosing requirements
-serious clinical consequences of overdosing (toxicity) or under-dosing (lack of effect)
-steep dose response relationship for efficacy and/or toxicity, or both

The Chair presented an example (Disopyramide) to illustrate the evidence and process needed to define whether a drug falls into the "Critical Dose Drugs" category.

Recommendations: *Members agreed on the following revised definition for critical drugs (lines 6-8, TAB 5) outlined in the new draft guidance document:*

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

(The Chair asked committee members how they would like to proceed for revising the current list? The members agreed that they will help, but the format for their contribution was not decided. It was suggested to modify the title of the list to "Examples of Critical Dose Drugs.")

' **ITEM 9 - Bioequivalence Criteria for Levothyroxine Tablets**

A presentation was made by N. Pound requesting the EAC to comment on the bioequivalence criteria required for Levothyroxine sodium solid oral dosage forms. In addition, G. Condran provided background on the history of stability and reproducibility of levothyroxine sodium tablets marketed in Canada in contrast to concerns that had arisen over these issues for products marketed in the USA.

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[1]Reference to Am J Kidney Dis 1999 Feb;33(2):389-97 in formulation of list

HC had a specific list of questions on this issue which the committee responded to :

1. What would be an appropriate Canadian Reference Product: Eltroxin and/or Synthroid, or an oral solution?

Eltroxin and Synthroid have been determined to be interchangeable in some provinces. The committee members agreed that for practicality, comparisons should be made to one of the solid (tablet) forms rather than the solution form. This is particularly important if the bioequivalence studies are to be used as a basis for provincial interchangeability decisions.

2. Is Levothyroxine an NTR drug? If so, presumably it follows that criteria for "Critical Drugs" will apply?

With the absence of compelling evidence, the committee does not consider it to be a NTR.

3. Should these criteria also be applied to the metabolite, T_3?

No. T_4 can be considered a pro-drug with slow metabolism to T_3. T_4 is also the absorbed moiety (as opposed to T_3) and can be measured in plasma. Therefore it makes no sense to measure the metabolite.

4. Is it appropriate to approve eleven pharmaceutically proportional strengths based on studies conducted on only one strength (preferably the highest?)

Yes, if evidence is provided that all strengths are proportionally formulated.

5. The FDA recommends a 600 µg dose, presumably to suppress, and thereby reduce the interference from endogenous T4/T3. Is this appropriate?

A 600 µg dose has been deemed to be appropriate.

6. Current TPD requirements call for sampling to 72 hours (FDA states 48 hrs). Can one assume that the suppression of endogenous levels is sufficient to permit meaningful data up to (only?) 48 hrs? 72 hrs?

72 hours is consistent with current TPD practice for drugs with long half-lives; however, 48 hours is considered adequate. This issue will be revisited when long half-life drugs are discussed in the future.

- **ITEM 11 - Drugs Exhibiting Non-linear Pharmacokinetics**

A presentation was given by N. Pound asking the EAC members to comment on the minimum number and type of comparative bioavailability studies required, and the standards to be met to establish bioequivalence for drugs that exhibit non-linear pharmacokinetics (NLPK.) A draft Guidance was contained in TAB 6.

Again, a question and answer format was used for this issue:

1. Do NLPK drugs require more stringent bioequivalence requirements than "uncomplicated" drugs?

No, the same standards as required for uncomplicated drugs apply.

2. Are both fasting and fed single dose studies necessary?

A fed study would be required when the non-linearity is related to a capacity-limited process such as absorption and/or pre-systemic metabolism. Food may affect the rate of disintegration/dissolution of the drug, which in turn would affect the rate of availability of the drug to the capacity-limited absorption or pre-systemic metabolic site, thus influencing the observed concentrations.

3. Should bioequivalence criteria be the same for fasted and fed conditions?

Yes.

4. How should drugs with NLPK be defined/identified? (What degree of non-linearity is considered significant?)

Dose normalized AUC values giving a 25% or greater deviation (increase or decrease) should be considered non-linear. This criterion applies over the practical clinically recommended single dosage range.

Recommendation: *The EAC proposed a wording change to the Guidance, for pg. (v), section i)* TAB 6 *which now reads:*

"For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in **greater than proportional increases in AUC** with increasing dose, the comparative bioavailability studies must be conducted on at least the **highest** strength."

Proposal: change the wording "highest strength" to "highest labeled (common) dose"

- **ITEM 14 - Food Administration Requirements for Comparative Bioavailability Studies**

A presentation was made by N. Pound outlining the need to define appropriate food administration protocols for comparative bioavailability studies undertaken to demonstrate the bioequivalence of two oral dosage forms. An IAS and a draft guidance were contained in TAB 7 of the information package.

The questions for the EAC members were as follows:

> Should bioequivalence studies always be conducted under fasted conditions, if at all possible? If so, are there situations where waiver of the fasted study is appropriate?
>
> **The wording of Product Monographs is important to determine whether fasted or fed studies are required. For uncomplicated products, fasted studies are generally required. The wording of the guidance under section 5.1 (pg 2) TAB 7 (Immediate release products with uncomplicated pharmacokinetic characteristics) was accepted:**
>
> **"It is recognized that in some very rare instances, the conduct of a comparative bioavailability study under fasted conditions may be precluded due to the very poor, or highly variable absorption of an active ingredient in the absence of food, or the development of serious gastric upset when dosing occurs under fasted conditions. In such situations, when the accepted Canadian labeling for the reference product indicates that the product is to be taken only with food, it may be possible to provide a scientific justification for conducting a comparative bioavailability study under fed conditions in lieu of the standard fasted study."**

Recommendation: *Generally, every attempt should be made to determine bioequivalence in the fasted state. In the event that a study cannot be conducted in the fasted state due to gastro-intestinal disturbances, a low-fat meal (defined elsewhere) could be an acceptable compromise. If the label says "food must be given," then the committee felt that a fed study is necessary, and a low-fat study could be an acceptable replacement for a fasted study.*

The EAC also felt that bioequivalence criteria should be the same for studies conducted under fasted and fed conditions.

A 1997 draft Food and Drug Administration (FDA) guidance document on food effect was cited. It suggested that other factors such as solubility and permeability be reviewed if there is evidence that an excipient affects absorption.

- **ITEM 16 - Abbreviated New Drug Submissions for Subsequent Market Entry, Topical Dermatologic, Ophthalmic, Otic and Nasal Drug Products**

Two presentations were given on this topic. The first, by N. Pound outlined the request to the EAC for guidance regarding data required to evaluate bioequivalence of topical dermatological, ophthalmic, otic and nasal drug products.

The second presentation by G. Condran put the following two proposals to the committee regarding requirements for subsequent market entry topical solutions:
(numbering refers to the corresponding section in the guidance document) TAB 9

> 2a) A quantitative and qualitative comparison of non-medicinal ingredients in the subsequent market entry and Canadian reference product must be provided.
> Proposal: The amount/concentration of the inactive ingredients should be essentially the same, (i.e. each within ± 5% of the Canadian reference product.) {Exceptions: Penetration enhancers}

Recommendation: *The committee agreed to a ± 5% tolerance around the labeled content and stated that tighter tolerances are a likely requirement for penetration enhancers; these must be clearly identified.*

> 2c) Physicochemical properties might include, but are not limited to pH, buffering capacity, tonicity, viscosity and surface tension.
>
> Proposal: Should criteria for comparative physical/chemical properties: e.g. viscosity, droplet size, be established? How much tolerance is acceptable?

Recommendation: *The committee members felt that reasonable criteria and tolerance limits should be established for comparative physical/chemical properties. In determining tolerance limits, consideration must be given to the individual parameter (i.e. viscosity, surface tension, etc.), as well as the manufacturing tolerances permitted. Furthermore, it was noted that the container or delivery system can be very important (i.e. to ensure comparable droplet size, etc.); therefore such aspects should be the same as for the reference product.*

' **ITEM 17 - Waiver of Comparative Bioavailability Studies for Drug Solutions with Nasal Delivery for Systemic Therapeutic Actions**

A presentation by N. Pound outlined the issue for the EAC. HC requests guidance in defining conditions for and factors to be addressed in justifying a waiver of comparative bioavailability/clinical studies for solutions for nasal delivery with systemic therapeutic action.

Recommendation: *The committee stressed that it is imperative to clarify very precisely what the ingredients are in such products. They agreed that a waiver is permissible for simple aqueous solutions (with no thickening agents, surfactants, etc. as defined in group 1 uncomplicated drugs.) This refers basically to the drug in an aqueous solution with buffers only. The solutions must be <u>essentially similar.</u>*

The committee felt that there may be cause to sharpen the definition of a simple true solution, and therefore, the description of the drug (solution).

- **ITEM 18 - Review of Section C.08.001.1(b) of the Regulations to the Food and Drugs Act: DESIGNATION OF A CANADIAN REFERENCE PRODUCT**

A presentation was made by N. Pound explaining section C.08.001.1 of the *Regulations* which defines a Canadian Reference Product (CRP). HC wishes to recommend changes to paragraphs (b) and (c) to amend the criteria to be used in designating a product for use under this section.

Concern was expressed over the need to ensure that subsequent-entry generics are compared to the same single reference product in Canada (i.e. same common denominator). There is a clear need to be consistent, from the provincial perspective, because subsequent entry generics are generally considered to be interchangeable with each other if they have been designated bioequivalent with the same reference product. The CRP is usually the innovator product. However, if the innovator product is no longer available, the CRP could be the first-entry generic product, the market leader generic product, or a cross-licensed product with the innovator.

Problems arise when the CRP is no longer available. In the absence of the CRP, there is provision in the Regulations to allow selection of an alternate reference product; however, it should be noted that the ability to do so was precipitated by a court case. In practical terms, the use of a non-Canadian reference product is problematic due to the difficulty for the TPD to verify that a foreign reference product has been manufactured to standards comparable to those required by Canada, or if the approval of the foreign product was granted in a country with a regulatory system that would be acceptable to Canada. It was also noted that from a post-marketing perspective, the TPD would have data on the CRP throughout the product's life-cycle; however, the TPD would not have similar data on a foreign product.

The use of a reference product purchased in Canada is essential when assessing the acceptability of a subsequent-entry product for a provincial formulary.

The International Conference on Harmonization, with the development of it's common technical document, is moving towards accepting foreign reviews, but is not there just yet.

The committee came to the following conclusion:

Recommendation: *The reference product should always be the CRP (innovator), unless it is no longer available on the market in Canada. The reference product could then default to a second entry product,* ***purchased*** *in Canada, such as the first-entry generic, the market leader generic product, or a cross-licensed product with the innovator. (Any product used would be assumed to have a Notice of Compliance.) Any reference product so designated shall thereafter be used consistently to ensure that all subsequent-entry generic products are compared to a single reference product.*

- **ITEM 21 - Bioanalytical Method Validation**

A presentation was made by N. Pound requesting the EAC's opinion on the removal of the current requirement that 15% of the clinical (incurred) samples be randomly selected and re-assayed when single assays are performed.

Recommendation: *The committee agreed unanimously to the proposal to remove the requirement of 15% of clinical samples.*

A short discussion of the issue of sample size (n) for resampling followed.

' ITEM 22 - Future Agenda Item Proposals/Administrative Details/Closing remarks

<As issues from this meeting are finalized, documents will be e-mailed to committee members for approval, and unless concerns are expressed, no future debate will occur.
<Committee members must confirm agreement within 7 working days of receipt of documents.
<If comments or concerns arise on these issues, the committee members will be advised before the next meeting, and discussions can be reopened.
<Teleconferences were proposed as a possible means of finalizing some issues before the next meeting if debate is needed.

' ITEM 23 - Scheduling of next meeting and adjournment

Meeting adjourned.
Next proposed meeting: April or May, 2002
Prepared by: M. Davis