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**EXPERT ADVISORY COMMITTEE ON  
 BIOAVAILABILITY AND BIOEQUIVALENCE**

**RECORD of PROCEEDINGS**

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

Teleconference April 16, 2003

**Committee Members Present:** Dr. J. Thiessen (Chair), Dr. J.G. Besner, Dr. R. Herman, Dr. F. Jamali, Dr. R. Nair, Dr. E. Palylyk-Colwell, Dr. W. Racz, Dr. K. Renton, Dr. W. Riggs, Dr. D. Sitar, Dr. F. Varin, Mr. S. Walker

**Regrets:** Dr. A. Donner, Dr. M. Kara, Dr. J.N. McMullen,

**Health Canada (HC) Participants:** M.M. Bernard (BMORS\*), L. Cockell (DBE\*), G. Condran(BPS\*), L.N. Cui (DBE), M. Davis (EAC Secretariat Officer, PB\*), C. Ficker (DBE), J. Gordon (DBE), A. Makinde (DBE), C. Pereira (EAC-BB Coordinator, PB), C. Simon (DBE), S. Stojdl (DBE), A. Tam (DBE), P. Wielowieyski (DBE)

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

BMORS	=	Bureau of Metabolism, Oncology and Reproductive Sciences
BPS	=	Bureau of Pharmaceutical Sciences
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
PB	=	Policy Bureau
BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence
EAC - BB	=	Expert Advisory Committee on Bioavailability & Bioequivalence

➤ **ITEM 1 - Roll Call, Conflict of Interest (COI), & Agenda Review (J. Thiessen)**

The Chair welcomed the members and briefly outlined the format for this teleconference. He reminded the members that since this was in essence a continuation of the March meeting, their conflict of interest declarations were still valid. The only item to be discussed will be Levothyroxine from the March agenda.

➤ **ITEM 2 - HC Presentation on Levothyroxine**  
*Is Levothyroxine Sodium a Critical Dose Drug?\** (P. Wielowieyski)  
(\*Powerpoint presentation available upon request)

A short presentation was made giving some background information and posing three main questions to the EAC. The questions will be quoted below with the EAC's final recommendations for each one.

➤ **ITEM 3 - Deliberation of Questions (Members)**

The discussion covered a variety of issues, such as:

- effect of small changes in T4 on T3
- variability of TSH, particularly within an individual
- sensitivity of TSH when suppressed
- variability in assay methods such as radioimmunoassay
- endogenous hormone levels
- sensitivity of T4 to detect differences between formulations
- need for titration in levothyroxine dosing
- harmonization with US and EU requirements for levothyroxine
- diurnal variation in endogenous levels
- methods of baseline correction
- number of strengths to be studied given that eleven strengths are currently marketed (25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 µg)

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

➤ **ITEM 4 - EAC's Final Recommendations (Dr. J. Thiessen)**

**Question 1**

*Is levothyroxine sodium a critical dose drug?*

*"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."*

*Yes, levothyroxine is a critical dose drug. Concern was expressed with respect to adverse effects, for example, potentially life-threatening cardiac effects as a result of aggressive treatment of elderly patients who are hypothyroid. The US FDA's (Food & Drug Administration) classification of this drug as a narrow therapeutic range drug was also taken into consideration.*

## **Question 2**

*Is levothyroxine sodium a drug with a narrow therapeutic range (NTR)?*

### *Report C*

*"A drug with a narrow therapeutic range is one which commonly exhibits adverse effects which limit the therapeutic use in doses close to those required for the therapeutic effect. When there is a known relationship of plasma concentrations to therapeutic and toxic effects, the ratio of the lowest concentration at which clinical toxicity commonly occurs to the median concentration providing a therapeutic effect would not be greater than 2."*

*The EAC did not consider levothyroxine to be a NTR drug because the ratio of the lowest concentration at which clinical toxicity commonly occurs to the median concentration providing a therapeutic effect would be greater than 2 and therefore it would not fit the NTR definition in Report C. However, levothyroxine should be classified as a critical dose drug and until such time as bioequivalence criteria for critical dose drugs are defined, current bioequivalence standards for NTR drugs should be applied to levothyroxine.*

## **Question 3**

*In light of the recent FDA deliberations, is baseline-corrected total T4 an appropriate and sensitive measure?*

*T4 is the preferred measure, T3 is an active metabolite, and TSH is a 'downstream' biomarker that is considerably more variable*

*Doses of 600 µg or greater should be utilized in healthy volunteers, as concentrations are significantly higher than the individual subject's baseline T4 values.*

*Healthy volunteers (allows for the use of a single dose study, more sensitive evaluation of true formulation differences)*

*Total T4, without a baseline correction, is insensitive for bioequivalence analysis.*

The committee came to consensus on the following statements:

- ▶ *T4 is an acceptable marker for rate and extent of absorption.*
- ▶ *T4 alone should be used as a measure of comparative bioavailability.*
- ▶ *A baseline correction is recommended.*
- ▶ *Three appropriately spaced pre-dose samples are recommended, for baseline correction for endogenous T4. The FDA guidance with respect to sampling times is acceptable.*
- ▶ *A 600 µg dose should be used. Greater than 600 µg may increase risk of cardiac complications. Testing of more than one strength is recommended. Strengths should be chosen so as to adequately bracket the proposed range of strengths*
- ▶ *Healthy volunteers should be used in testing.*
- ▶ *Current TPD requirements call for sampling to 72 hours for long half-life drugs. For levothyroxine, the FDA recommends sampling for 48 hours. The committee considered sampling over a 48 hour period to be adequate, in part because of the reduced suppression of endogenous levels after that time and the reduced reliability of the recommended baseline correction method over a longer sampling period.*

▶ **ITEM 5 - HC Announcements concerning next meeting (June 2003) ( C. Pereira )**

HC is planning on having a stakeholder workshop and EAC meeting in June. Work is currently underway towards completion of discussion papers, which will be posted to the HC website before the meeting. The topics for the June meeting are:

- Highly variable drugs
- Fed BE studies

An invitation to participate has been posted on the web site and will also be sent to stakeholder organizations. Stakeholders are invited to attend the meeting as observers or to make short presentations on either/both of the two issues. More details can be found on the HC website at

[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bb\\_jun03\\_web\\_announce\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bb_jun03_web_announce_e.html)

▶ **ITEM 6 - Meeting Adjourned (J. Thiessen)**

Next Meeting: Workshop June 26, EAC deliberations June 27, 2003

Prepared by: M. Davis and C.Pereira

2003-07-07



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### LEVOTHYROXINE

### SUMMARY REPORT

1. Levothyroxine (3,5,3',5'-tetraiodo-L-thyronine, thyroxine, T<sub>4</sub>) is chemically identical with the natural thyroxine hormone, which is synthesised in the thyroid gland. In veterinary medicine the claimed indications for levothyroxine, in combination with 3,5-diiodo-L-thyrosin, are activation of metabolism and digestion. It is used in treatment of insufficient milk excretion, loss of weight, chronic indigestion and convalescence in cattle and pigs. It can also be used in other species. Levothyroxine is administered orally as a single treatment divided into two daily doses. It is given as a powder mixed with the diet, water or sugar-water. The intended dosage level per day in cattle is 0.10 to 0.29 mg/kg bw and in pigs 0.29 to 0.72 mg/kg bw. The treatment can be repeated once, if required, in cattle and for 5 consecutive days in pigs. In humans, levothyroxine is employed in the treatment of thyroid-deficiency states.
2. The secretory products of the thyroid gland are known as iodothyronines. The major product is 3,3',5,5'-tetraiodo-L-thyronine (thyroxine, T<sub>4</sub>), which functions largely as a circulating prohormone to 3,3',5-triiodo-L-thyronine (T<sub>3</sub>). T<sub>3</sub> is secreted in much less quantity from the thyroid gland. This molecule, which provides almost all thyroid hormone activity in target cells, is actually produced mostly in various tissues from thyroxine. The thyroid hormones increase oxygen consumption and heat production to a large extent by stimulating Na<sup>+</sup>K<sup>+</sup>-ATPase in all tissues except brain, spleen and testis. The thyroid hormones affect a great multiplicity of metabolic processes; carbohydrate, protein, lipid and vitamin metabolism, influencing the concentration and activity of numerous enzymes and the secretion and degradation rates of virtually all other hormones. Thyroid hormones are also crucial for growth and development of the skeleton and central nervous system in foetus and infants.

The secretion rate of endogenous thyroxine in humans amounts to 90 µg/day (1.5 µg/kg bw). In cows the normal thyroxine secretion rate show a large seasonal variation, it is usually higher during the winter. Normal thyroxine secretion rate in non-lactating dairy cows ranged from 3.3 to 5.5 µg/kg bw/day in one study. In another study performed during the winter the normal thyroxine secretion rate was 6.6 to 13.2 µg/kg bw/day. The physiological plasma concentration of thyroxine approximates 80 µg/l in humans, 60 µg/l in cows and 30 µg/l in swine.

3. After oral administration daily for 13 weeks to cows of 15000 mg thyroprotein (iodinated casein containing 1% thyroxine, corresponding to 150 mg thyroxine), maximum serum concentration of 134 µg/l is reached after 6 days. Concentration is then maintained on a constant level of approximately 80 µg/l throughout the study. Following cessation of thyroprotein treatment, concentration decreases below the endogenous thyroxine level and approaches normal levels 2 weeks after withdrawal of the treatment.

Following cessation of daily thyroxine injections (route of administration not stated), with a dose corresponding to 150% of thyroxine secretion rate, to cows for 11 to 12 weeks, the uptake of radioactive <sup>131</sup>I in the thyroid is blocked for 10-12 days. The <sup>131</sup>I uptake reaches normal levels 3 weeks after cessation of treatment.

The absorption rate after oral administration of thyroxine in cows is relatively slow. The absorption follows two phases, one rapid and one slow phase, lasting for about 45 hours. This is followed by a declining phase with a plasma half-life of 160 hours. The half-life of thyroxine after intravenous administration is 2.5 days in dairy cows and the turnover rate is 28.4%/day. In cattle thyroxine has a low oral biological effectiveness. The effect after oral treatment of cows is only 10% of that found after subcutaneous injections.

In humans the half-life of thyroxine after oral administration is 6 to 7 days. At hypothyroidism and hyperthyroidism in humans the half-life is 9 to 10 days and 3 to 4 days, respectively.

In human blood thyroxine is bound extensively (more than 99.95%) to plasma proteins. Approximately 60% is bound to T<sub>4</sub>-binding inter  $\alpha$ -globulin and 30% is bound to T<sub>4</sub>-binding prealbumin and about 10% is bound to serum albumin. In cattle, swine, sheep and horses thyroxine is primarily bound to  $\alpha$ -globulin. In humans the absorption of thyroxine from the gastrointestinal tract varies between 75 to 85%. The bioavailability of thyroxine decreases by approximately 35% when taken with food.

Thyroxine is metabolised by different mechanisms in humans. Approximately 80% of the metabolism of thyroxine and the various products derived from it proceeds by enzymatic monodeiodination, which yield in the initial step the more active hormone T<sub>3</sub> (35%) and the inactive 3, 3',5'-triiodo-thyronine (rT<sub>3</sub>, 40%). Minor pathways for inactivation of thyroxin and T<sub>3</sub> are conjugation with glucuronic acid and in small amounts with sulphuric acid, decarboxylation and/or deamination.

4. Studies on acute toxicity and repeated dose toxicity are not provided. However, as levothyroxine is an endogenous substance these data were not considered necessary.
5. The lactational response in lactating cows was studied following administration of thyroxine. Initially a single subcutaneous dose of 26 to 51  $\mu$ g thyroxine/kg bw was administered, followed by daily subcutaneous injections of 10 to 20  $\mu$ g thyroxine/kg bw for 10 weeks (corresponding to 150% of winter thyroxine secretion rate). The mean increase in milk yield at the peak was 27.6% (range 12.1 to 67.9%). Mean body weight loss at termination of the study was 9.7% (range 3.7 to 14.2%). This loss was regained within 2 weeks after withdrawal of treatment. The treatment showed no effect on body temperature. However, no statistical analysis of these effects was performed. In another study lactating cows were injected (route of administration is not stated) with thyroxine daily for a period of 11 to 12 weeks. The dose corresponded to 150% of the thyroxine secretion rate. Following cessation of treatment the milk yield decreased precipitously for 10 to 12 days, thereafter a plateau was established. The maximum milk yield decline after the treatment period, animals were followed for 18 days following treatment, ranged from 39.2 to 68.1%.

Information from old publications, concerning the lactational response in cows following oral administration of thyroprotein was provided. However, given the facts that thyroprotein only contains low concentrations of thyroxine (1%) and that the purity of the substance was not stated, it is difficult to draw any conclusions of the effects observed in these studies.

6. Data on reproduction toxicity have not been submitted. However, as levothyroxine is an endogenous substance these data were not considered necessary.
7. While no data on mutagenicity and on carcinogenicity were provided the Committee considered that these data were not necessary as levothyroxine belongs to a group of substances which are recognised not to be mutagenic or carcinogenic and which have no chemical analogy with known carcinogens.
8. Thyroid agents have a long history of safe use in human medicine. In humans thyroxine is used in the treatment of different forms of hypothyroidism. The initial adult dose of thyroxine sodium is 50 or 100  $\mu$ g daily by the oral route. The dose is slowly increased and the maintenance dose is commonly between 100 to 200  $\mu$ g daily.

Adverse effects of thyroid hormones are generally associated with excessive dosage and correspond to the symptoms of hyperthyroidism (palpitations, tachycardia, cardiac arrhythmias, loss of weight, anginal pain, tremor, headache, diarrhoea, nervousness, insomnia, sweating, intolerance to heat). All reactions usually disappear on reduction of dosage or temporary withdrawal of treatments.

9. No data were presented on the residues of thyroxine in the tissues of the target animals. However, it is noted that levothyroxine is an endogenous substance.
10. No analytical method for determination of thyroxine in tissues was submitted. An analytical method for thyroxine determination in serum was submitted.

#### Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- levothyroxine is only used in a small number of individual animals and for non-regular treatment,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- levothyroxine is an endogenous substance;

the Committee concludes that there is no need to establish an MRL for levothyroxine and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Levothyroxine	All food producing mammalian species	

**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 (EMA) 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

## Status of Levothyroxine Products in Canada

### ISSUE

The United States Food and Drug Administration (US-FDA) has reclassified levothyroxine products as “new drugs” due to potential problems with potency and stability.

### **What is the Status of Levothyroxine Products in the USA?**

On August 14, 1997, the FDA announced in the Federal Register that orally administered levothyroxine sodium drug products are “new drugs” and that manufacturers who wish to continue marketing these products must submit a new drug application for approval. The FDA based its decision on a history of potency and stability problems with levothyroxine sodium products. The notice stated that after August 14, 2000, any unapproved Levothyroxine sodium drug product on the market would be subject to regulatory action by the FDA. On April 26, 2000, the FDA extended the deadline to August 14, 2001. As noted in the FDA Talk Paper issued July 12, 2001 on this subject, there was no public health emergency in the US that required immediate action. Subsequently, the US-FDA approved Synthroid on July 24, 2002.

**What is the Status of  
Levothyroxine Products in  
Canada ?**

Levothyroxine sodium products currently used in Canada, have been on the Canadian market since the 1950's.

In response to the issues raised regarding the quality of levothyroxine sodium tablets, in August 2001, Health Canada analysed a representative sampling of marketed levothyroxine sodium products taken orally in Canada for potency and content uniformity, and reviewed company records regarding quality matters such as stability, recalls, and complaints. The study generated by Health Canada's laboratories revealed that all tested lots of the marketed levothyroxine sodium products taken orally complied with the established standards for potency.

Health Canada also investigated its Canadian database from 1968 until October 2002 for instances of adverse events reported with the use of levothyroxine sodium. There were 7 reports of lack of efficacy and /or hypothyroidism

There is no public health emergency that requires immediate action for the levothyroxine sodium products on the market in Canada. Health Canada's investigation has shown that there was no indication of a quality concern with Synthroid<sup>®</sup> Tablets (marketed by Abbott Laboratories) and Eltroxin<sup>®</sup> Tablets (marketed by GlaxoSmithKline) in Canada. Accordingly, patients are advised to continue using their medication under the supervision of their doctors. Levothyroxine sodium has a narrow therapeutic range and is titrated in very small increments until the dose is optimized for the patient. The information provided below could help patients who are prescribed Levothyroxine products:

**What should you do if you are on Levothyroxine Therapy?**

1. Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.
2. Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking Levothyroxine. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.
3. Use Levothyroxine only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.
4. The Levothyroxine in your prescribed product is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).
5. Take Levothyroxine tablets in the morning on an empty stomach, at least one-half hour before eating any food.
6. It may take several weeks before you notice an improvement in your symptoms.

7. Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
8. Notify your physician if you become pregnant while taking Levothyroxine. It is likely that your dose of Levothyroxine will need to be increased while you are pregnant.
9. Notify your physician or dentist that you are taking Levothyroxine prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of Levothyroxine therapy, but this is usually temporary.
11. Levothyroxine should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep Levothyroxine out of the reach of children. Store Levothyroxine away from heat, moisture, and light.

October 31, 2002

Therapeutic Products Directorate Direction des produits thérapeutiques	Health Products and Food Branch Direction générale des produits de santé et des aliments
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Health Canada

Santé Canada

Version 2002/03/14

Coordinator: Mr. Eric Ormsby, Therapeutic Products Directorate (613) 957-1058  
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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 bioavailability 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 woman gets pregnant after the onset of the study, it is not a violation of the protocol; these conditions must be practical. When unforeseen 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 2<sup>nd</sup> 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:<sup>1</sup>**

- 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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<sup>1</sup>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<sub>3</sub>?

**No. T<sub>4</sub> can be considered a pro-drug with slow metabolism to T<sub>3</sub>. T<sub>4</sub> is also the absorbed moiety (as opposed to T<sub>3</sub>) 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 T<sub>4</sub>/T<sub>3</sub>. 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 gastrointestinal 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  $\pm 5\%$  of the Canadian reference product.) {Exceptions: Penetration enhancers}

**Recommendation:** *The committee agreed to a  $\pm 5\%$  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 essentially similar.*

*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 its 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