

## Background Information for Advisory Committee Meeting October 6, 2006

### Bioequivalence Requirements for Highly Variable Drugs and Drug Products

#### Introduction

Bioequivalence studies are generally conducted by comparing the *in vivo* rate and extent of drug absorption of a test and a reference drug product in healthy subjects. In a standard *in vivo* bioequivalence study design, participants receive a single dose of test and reference products on separate occasions with random assignment to the two possible sequences of product administration. Samples of an accessible biologic fluid such as blood or urine are analyzed for drug concentrations, and pharmacokinetic measures such as area under the curve (AUC) and peak concentration ( $C_{\max}$ ), are obtained from the resulting concentration-time profiles. To evaluate bioequivalence, the U.S. Food and Drug Administration (FDA) has employed a testing procedure termed *the two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures from the test and reference products are comparable<sup>1</sup>. This procedure involves the calculation of a confidence interval for the ratio between the average values of the test and reference product<sup>2</sup>. In the U.S., a test product is considered to be bioequivalent to a reference product if the 90% confidence interval of the geometric mean ratio of AUC and  $C_{\max}$  between the test and reference fall within 80-125%. Currently, the bioequivalence limits of 80-125% have been applied to almost all drug products by the FDA<sup>3</sup>.

Concerns have been expressed at times regarding the difficulty of meeting the standard bioequivalence criteria for highly variable drugs and/or drug products<sup>4,5</sup>. To date, there is no regulatory definition for these drugs or drug products. In the context of bioequivalence, however, drugs and drug products exhibiting intra-subject variability greater than 30% C.V. (coefficient of variation) in the pharmacokinetic measures, AUC and/or  $C_{\max}$  are considered highly variable<sup>4,5</sup>. To pass the conventional “goalposts”, the number of subjects required for a study of these drugs or drug products can be much greater than normally needed for a typical bioequivalence study. Thus, the resource implications coupled with the ethical concern of exposing a large number of healthy subjects to a test drug further challenges the appropriateness of the conventional bioequivalence criteria for highly variable drugs/products. Examples exist of a highly variable reference product failing to demonstrate bioequivalence with itself using the standard design/sample size for a bioequivalence study<sup>6</sup>.

The issue of highly variable drugs/products in bioequivalence has been discussed in many conferences and meetings, nationally and internationally. However, there is no universal consensus or solution at this time.

## Background

Although global harmonization is a general goal, to date, bioequivalence has not been accepted as a topic by the International Conference on Harmonization (ICH). Nonetheless, the resource and ethical concerns for highly variable drugs/products in bioequivalence are generally recognized by international regulatory agencies. It is thus useful to review the differing regulatory approaches before an informed recommendation is made on the topic. The following outlines the bioequivalence standards used in different regions:

In Canada, for drugs with uncomplicated characteristics, a 90% confidence limit of 80-125% is required for AUC. However, a limit is placed only on the means (or point estimate) for  $C_{\max}$ <sup>7</sup>. As a result of random variation or a larger than expected relative difference, the sponsor may add more subjects. If this option is chosen, it must be stated in the study protocol. In addition, two criteria must be met before combining is acceptable:

- 1) The same protocol must be used; and
- 2) Consistency tests must be met at an alpha error rate of five percent.

The European Agency for the Evaluation of Medicinal Products (EMA) has similar bioequivalence standards to those in the FDA, *i.e.*, 90% confidence limits of 80-125% on AUC and  $C_{\max}$ , with the qualification that these limits may be expanded in certain cases for  $C_{\max}$  (*e.g.*, 75-133%) provided that there are no safety or efficacy concerns<sup>8</sup>.

In Japan, the bioequivalence standards also rely on the 90% confidence limits of 80-125% for both AUC and  $C_{\max}$ , although wider limits are allowed for less potent drugs. Additionally, if the confidence limits are outside of 80-125%, bioequivalence may be claimed on the grounds that the study meets all three conditions listed below<sup>9</sup>.

- 1) The total number of subjects in the initial bioequivalence study is no less than 20 ( $n=10/\text{group}$ ), or pooled sample size of the initial and add-on studies is no less than 30;
- 2) The differences in average values of logarithmic AUC and  $C_{\max}$  between two products are between  $\log(0.9) - \log(1.11)$ ; and
- 3) Dissolution rates of test and reference products are determined to be equivalent under all dissolution testing conditions specified.

Japan allows the addition of subjects to increase the power of a failed bioequivalence study. However, the add-on subjects can not be less than half the number in the original study.

South Africa accepts an acceptance interval of 75-133% for  $C_{\max}$ , except for narrow therapeutic range drugs, when an acceptance interval of 80-125% applies<sup>10</sup>. For highly variable drugs, a wider interval or other appropriate measure may be acceptable, but

should be stated a priori and justified in the protocol.

### **FDA Research**

At the conclusion of the April 13-14, 2004, Advisory Committee Meeting on Pharmaceutical Science, the Agency was encouraged to research scaling approaches for BE evaluation of highly variable drugs. Accordingly, the FDA initiated a study internally, which compared the power of a given study design when using average scaled BE with average BE. The study design used in this simulation project was a three-way cross over replicate design, where the reference (R) product is given twice and the test (T) product is given once (*e.g.*, R T R). The number of subjects for each simulated study was 24. The within-subject variability for the reference was the scaling factor for determination of the BE limits. Additionally, the point estimate for the T/R ratio had to fall between 80-125%. Preliminary results suggest that the scaling approach, with constraints on the point estimates so that they do not exceed  $\pm 20\%$ , present a reasonable approach for the BE evaluation of highly variable drugs. Based on the results of the above study, in addition to discussions with experts in the field, the FDA submits the proposal listed below.

### **FDA Proposal for the BE Evaluation of Highly Variable Drugs:**

Highly variable drugs, defined as those showing within-subject variability of 30% or greater, should have the option of a scaling approach for determination of BE. The BE limits, currently set at 80-125%, would be expanded as a function of within subject variability of the reference product. Drug products whose confidence interval falls within the expanded limits of the scaling approach, must additionally demonstrate a difference of less than  $\pm 20\%$  in the point estimate of the T/R ratio ( $C_{\max}$  and AUC). Only then, a test product may be considered bioequivalent. The second condition, which places a constraint on the point estimate, will reduce the likelihood that a test product with unreasonable differences in bioavailability relative to the reference product would be approved as bioequivalent. This could happen if the BE criterion was dependent on the confidence interval limits only.

## Questions to the Committee

1. Does the committee agree with the use of a point estimate constraint, when applying scaled bioequivalence? If yes, is the 80 – 125% limit on the point estimate appropriate?
2. We propose a minimum sample size of 36 subjects when evaluating the BE of highly variable drugs, does the committee concur?

### 3. References

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- <sup>1</sup> D.J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokinet. Biopharm.* 15: 657-680 (1987).
- <sup>2</sup> W.J. Westlake. Response to Kirkwood, TBL.: Bioequivalence testing – a need to rethink. *Biometrics.* 37:589-594 (1981).
- <sup>3</sup> U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products--General Considerations*, Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, Rockville MD 20857, March 2003.
- <sup>4</sup> H. Blume and K.K. Midha. Report of Consensus Meeting: Bio-international '92. Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies. Bad Homburg, Germany, 20-22 May, 1992. *Eur. J. Pharm. Sci.* 1:165-171 (1993).
- <sup>5</sup> Bio-international '94, Munich Germany. 14-18 June, 1994.
- <sup>6</sup> Health Canada, Therapeutic Products Directorate (TPD). Discussion paper on 'Bioequivalence requirements - highly variable drugs and highly variable drug products: issues and options'. Expert Advisory Committee on Bioavailability and Bioequivalence (EAC-BB) Meeting, June 26-27, 2003.
- <sup>7</sup> Health Canada, Ministry of Health, *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A: Oral Dosage Formulations Used for Systemic Effects.* 1992.
- <sup>8</sup> Committee for Proprietary Medicinal Products (CPMP), the European Agency for the Evaluation of Medicinal Products (EMA). *Note for Guidance on the Investigation of Bioavailability and Bioequivalence.* 2001.
- <sup>9</sup> Japan National Institute of Health, Division of Drugs. *Guideline for Bioequivalence Studies of Generic Drug Products.* 1997.
- <sup>10</sup> Medicines Control Council, Department of Health, Republic of South Africa. *Registration of Medicines: Biostudies.* 2003.