

**MINISTRY OF HEALTH  
OF THE TURKISH REPUBLIC  
Pharmaceutical General Directorate**

**Number: B100IEG01000007-BA/BE**

**Re: Submission of BA/BE Dossiers**

**ANKARA**

**16 January 2006**

**ASSOCIATION OF RESEARCH-BASED PHARMACEUTICAL COMPANIES  
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As a result of the observations of the “Bio-availability and Bio-equivalence Identification and Evaluation Committee” with respect to the assessment of the BA/BE dossiers, the shortcomings frequently observed in the BA/BE dossiers have been stated in the attached letter.

Correcting these shortcomings will be beneficial not only for the industry itself but also for the workflow of the BA/BE Identification and Evaluation Committee. We request that this observation is shared with members of your association and followed up accordingly.

**ANNEX: General shortcomings observed in the BABE dossiers. (6 pages)**

**Dr. Saim Kerman  
Assistant General Director**

- **Exemption for low dosages**
  - The BE approval for high dosages,
  - A comparative table of formula contents,
  - A comparative table of dissolution profiles (together with their validation) should be provided.
  - When calculating the similarity factor ( $f_2$ ) dissolution profiles containing at least 6 points should be compared. The profile should be presented in such a manner that it contains only one point after the point that 85% of the active substance has been dissolved.
  
- **Main Drug or Metabolite Measurement**
  - The BE approval for high dosages,
  - In the event that the main drug cannot be measured by means of the analytical method employed, any of the active or inactive metabolites can be measured.
  
- **Statistical Assessment**
  - The method and program used for statistical calculations should be indicated.
  - The data used in the study and the analysis of the study should be provided in a detailed manner allowing for computer duplication.
  - The plasma drug concentrations for each subject against the sampling times should be presented in tabular format.
  - Together with the summary parameter estimations for both the test and the reference product the mean, standard deviation and variation coefficient should be provided.
  - A comparison of the test and reference product as well as a detailed statistical analysis of the respective parameters (variance analysis table, 90% confidence interval etc.) should be conducted.  
*(Detailed information provided in Annex-1)*
  
- **Acceptance Range for Pharmacokinetic Parameters**
  - The acceptance interval for AUC and  $C_{max}$  of test products and reference products should be between 0.80-1.25 at the 90% confidence level.
  - This limit may be narrowed down for medical products with a narrow therapeutic index.
  - Taking into account the efficacy and safety of the medicinal product, where it is scientifically proven that the active substance demonstrates high intra-individual variability, the accepted range for  $C_{max}$  only may be between 0.75-1.33.
  
- **Bio-analysis and Bio-analytical Validation**
  - The acceptance interval for AUC and  $C_{max}$  of test products and reference products should be between 0.80-1.25 at the 90% confidence level.
  - Method (device, form of measurement and processes should be provided in detail.)
  - Validation parameters:
    - Recovery
    - Limit of determination (LOD) and Limit of Quantification (LOQ)
    - Specificity
    - Accuracy
    - Precision
    - Sensitivity
    - Selectivity
    - Study concentration range

- Regression equivalence
- Stability
- Raw data (together with the date of the study, name of study, name of study center, and signature of the analyst).
- Sampling
  - The sampling time should cover at least three or more times the terminal half-life of the active substance.
  - Sampling should be done frequently enough to express  $C_{\max}$  and the terminal elimination phase.
- **Comparative *in vitro* dissolution tests and *in vivo* BE tests with the reference product should be provided in the same dossier.**
- **Outlier calculations**
  - Due to reasons such as an outlier device error, measurement error or where the subject is ill at the time of measurement such subjects may be excluded from the calculation.
  - Where there is an outlier due to any reason apart from the above stated, a statistical outlier test should be conducted and detailed results of the test should be provided.
  - Where there are outliers, calculations containing or excluding the outlier as well as the results obtained should be provided together.

## **SHORTCOMINGS OBSERVED IN THE PROTOCOL**

- Company Name / Sponsor
- Active substance being tested
- Study title

### **Study Centers**

- Clinical trial center
- Local and/or central ethics committee approval
- Center for bio-analyses

For centers in which clinical and bio-analytical studies are conducted, an official copy of the EN 45001 or ISO 17025 or OECD-GLP accreditation certificate as well as documents evidencing compliance to GCP-ICH rules must be provided. If deemed necessary, audit reports pertaining to the company and/or sponsor may be requested.

### **Study Design**

- Objective of study
- Number of subjects
- Characteristics of subjects (age, gender, weight etc.)
- Test Product (serial number, expiry date)
- Reference Product – Company and Country Name (batch number, expiry date).  
Documentation from relevant literature evidencing that the selected reference belongs to the original product should be provided.
- Route of administration for the test and reference product
- Dosage of administration for the test and reference product
- Detailed pharmacokinetic and pharmacodynamic characteristics of the active substance:

therapeutic index,  $t_{1/2}$ ,  $t_{max}$ ,  $V_d$ ,  $C_{max}$ , AUC, linear-nonlinear pharmacokinetics, protein binding, whether high variability (intra-individual) is demonstrated or not should be provided through the support of various sources.

### **Sampling**

- Sample type (plasma, serum, urine vs.)
- Sampling method
- Sampling time (time intervals)
- Washout
- Analytical method(s)
- Assessment of target pharmacodynamic parameters
- Statistical analyses

### **Statistical method**

- Acceptance limits
- Inclusion/exclusion criteria for subjects
- Evidence of excluding outliers from the assessment

### **Bio-availability Dossiers Should Contain the Following:**

- Product name
- Formula and dosage per unit
- Place of manufacture
- Name of registration holder
- Physiochemical and pharmacokinetic characteristics of the active substance
- Documentation of the product's authenticity
- Indication of the whether the product is manufactured or imported
- Turkish executive summary of the BA/BE Study/Studies (study location etc.) and 20% raw data
- Bio-analytical validation information

## **Annex-1**

### **Statistical Evaluation**

Data used in Bio-availability/Bio-equivalence (BA/BE) studies as well as the analysis of the study used be provided in detail allowing for computer duplication. All data pertaining to the statistical analysis of the study as well as the statistical outcomes should additionally be copied to a CD. The statistical model and statistical hypotheses should be clearly indicated and the name of the package programs used should be specified. Attention should be paid to conform with the style of the statistical calculations laid down below.

1. The number of subjects to be included in the study should be estimated and determined taking into account specific standards. In addition, in the event that any subject included in the study is later withdrawn the justifications for such a withdrawal should be provided. In such a case, a maximum of 10% of the subjects may be withdrawn from the study. For each formulation, subjects should be allocated randomly to the sequences and periods. Inter-sequence variations and inter-treatment variations should be homogenous. The model's residual errors should be independent and distributed normally.
2. For sampling times and formulations, data pertaining to the drug concentration in the plasma of each individual should be presented in tabular form.
3. Together with the specific parameter estimations for both the test and reference formulations the mean, standard deviation and variation coefficient should be provided.
4. A comparison of the test and reference product as well as a detailed statistical analysis of the respective parameters (variance analysis table, 90% BE confidence interval etc.) should be conducted.
5. Statistical Analysis

The *Parametric General Linear Model (normal theory)* is recommended for the analysis of pharmacokinetic parameters obtained in in vivo bio-equivalence studies. It is necessary to conduct an ANOVA Variance Analysis with respect to AUC and  $C_{\max}$  pharmacokinetic parameters using appropriate statistical programs and models. (The variance analysis will

produce very successful results if the assumptions stated in article one have come about. Otherwise, non-parametric tests should be applied.) For example, in a standard double formulation (treatment), double period, double sequence, conventional, unrepeated design, ANOVA enables to not only to identify the sequence, the subjects in the sequence, the period and the effects of the formulation but also to obtain the variance pertaining to the error term (estimated error squares) which is the measure of the intra-individual variability. The 90% BE confidence interval to be applied in the bio-equivalence/bio-availability assessment should be based on these calculations. In addition, it is necessary to identify whether there is any interaction between the effects or not.

In single-dose studies: the ratios of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ , as well as  $T_{max}$ , and  $\lambda$  should be calculated. In steady state studies: the ratios of  $AUC_{\tau}$ ,  $C_{min}$  and  $C_{max}$ , as well as the changes in the differences pertaining to the test product against the reference product should be calculated.

The 90% confidence intervals for the means for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $AUC_{\tau}$ , as well as a summary of the comparisons of the degree of fluctuation for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $AUC_{\tau}$ ,  $\lambda$ ,  $C_{pd}$ ,  $C_{min}$ ,  $C_{max}$  and  $(C_{max} - C_{min})/(AUC_{\tau}/\tau)$ .  $T_{max}$ ,  $\lambda$  and  $(C_{max} - C_{min})/(AUC_{\tau}/\tau)$  should be calculated based on raw data. The other parameters should be calculated using both the raw data scale and the logarithmic (ln) scale.

6. The pharmacokinetic parameter values pertaining to subjects included in bio-equivalence studies may sometimes reach extreme values (extremely high or extremely low values). These values are defined as outliers. An outlier is a value that does not fit in with the remaining values of the study. If an outlier is identified in a study the reasons for such a case should be investigated. The subject in question may be excluded from the analysis due to reasons such as a device error, measurement error or the patient's illness at the time of measurement. In the event that there is an outlier or adverse value due to any reason other than the above stated an outlier test based on the *robust regression* methods in statistics should be conducted (indicating the technique applied) and the results of the test should be provided in detail. The outlier must be evidenced in statistical terms. The presence of an outlier indicates that that some values contradict with all of the remaining values. However, it may also indicate that the method applied is not pertinent (failure

the correct model, it may be excluded from the analysis. In the event that there is an outlier both the results taking the outlier into account as well as the results excluding the outlier should be provided.