



## CHMP EFFICACY WORKING PARTY) THERAPEUTIC SUBGROUP ON PHARMACOKINETICS (EWP-PK)

### Questions & Answers on the Bioavailability and Bioequivalence Guideline

#### 1. Introduction

After the revision of the Note for guidance on the Investigation on Bioavailability and Bioequivalence in 2002, it appears that some harmonisation in the interpretation of critical parts of the guideline is needed. This is the aim of the current Question & Answers document which focuses on demonstration of bioequivalence.

#### 2. Assessment of $C_{max}$ in bioequivalence studies. In which cases is it allowed to use a wider acceptance range for the ratio of $C_{max}$ ?

The NfG states under 3.6.2 that “*With respect to the ratio of  $C_{max}$  the 90% confidence interval for this measure of relative bioavailability should lie within an acceptance range of 0.80 – 1.25. In specific cases, such as a narrow therapeutic range, the acceptance interval may need to be tightened.*”

The NfG also states that “*In certain cases a wider interval may be acceptable. The interval must be prospectively defined, e.g. 0.75 – 1.33, and justified addressing in particular any safety or efficacy concerns for patients switched between formulations*”.

The possibility offered here by the guideline to widen the acceptance range of 0.80 – 1.25 for the ratio of  $C_{max}$  (not for AUC) should be considered exceptional and limited to a small widening (0.75 – 1.33). Furthermore, this possibility is restricted to those products for which at least one of the following criteria applies:

1. Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for  $C_{max}$  does not affect pharmacodynamics in a clinically significant way.
2. If PK/PD data are either inconclusive or not available, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive.
3. The reference product has a highly variable within-subject bioavailability. Please refer to the Question on highly variable drug or drug products for guidance on how to address this issue at the planning stage of the bioequivalence trial.

A post hoc justification of an acceptance range wider than defined in the protocol cannot be accepted. Information that would be required to justify results lying outside the conventional acceptance range at the post hoc stage should be utilised at the planning stage, either for a scientific justification of a wider acceptance range for  $C_{max}$ , or for selecting an experimental approach that allows the assessment of different sources of variability.

### **3. Outliers. When can subjects classified as outliers be excluded from the analysis in bioequivalence studies?**

Under 3.6.3 the NfG states that “*Post-hoc exclusion of outliers is generally not accepted*” but at the same time acknowledges that “*the protocol should also specify methods for identifying biologically implausible outliers*”.

Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules that should be independent from treatment or outcome. In consequence, pharmacokinetic data can only be excluded based on non-statistical reasons that have been either defined previously in the protocol or, at the very least, established before reviewing the data. Acceptable explanations to exclude pharmacokinetic data or to exclude a subject would be protocol violations like vomiting, diarrhoea, analytical failure, etc. The search for such explanations must apply to all subjects in all groups independently of the size of the observed pharmacokinetic parameters or its outlying position. Exclusion of data can never be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish between formulation effects and pharmacokinetic effects.

Exceptional reasons may justify post-hoc data exclusion but this should be considered with utmost care. In such a case, the applicant must demonstrate that the condition stated to cause the deviation is present in the outlier(s) only and absence of this condition has been investigated using the same criteria for all other subjects.

Results of statistical analyses with and without the group of excluded subjects should be provided.

### **4. If one side of the 90% confidence interval of a pharmacokinetic variable for testing bioequivalence lies on 0.80 or 1.25, can we conclude that the products are bioequivalent?**

For establishing bioequivalence, the 90% confidence interval should lie within the acceptance interval (in most cases, 0.80 – 1.25), the borders being included. The conclusion that products are bioequivalent is based on the overall scientific assessment of the PK studies, not only on meeting the acceptance range.

### **5. In which cases may a non-parametric statistical model be used?**

The NfG states under 3.6.1–Statistical analysis: “*AUC and  $C_{max}$  should be analysed using ANOVA after log transformation.*”

The reasons for this request are the following:

- a) the AUC and  $C_{max}$  values as biological parameters are usually not normally distributed;
- b) a multiplicative model may be plausible;
- c) after log transformation the distribution may allow a parametric analysis.

However, the true distribution in a pharmacokinetic data set usually cannot be characterised due to the small sample size, so it is not recommended to have the analysis strategy depend on a pre-test for normality. Parametric testing using ANOVA on log-transformed data should be the rule. Results from non-parametric statistical methods or other statistical approaches are nevertheless welcome as sensitivity analyses. Such analyses can provide reassurance that conclusions from the experiment are robust against violations of the assumptions underlying the analysis strategy.

For  $t_{max}$ , the use of non-parametric methods on the original data set is recommended.

## 6. When should metabolite data be used to establish bioequivalence?

According to the guideline, the only situations where metabolite data can be used to establish bioequivalence are:

1. *“If the concentration of the active substance is too low to be accurately measured in the biological matrix, thus giving rise to significant variability”.*

Comments. Metabolite data can only be used if the Applicant presents convincing, state-of-the-art arguments that measurements of the parent compound are unreliable. Even so, it is important to point out that  $C_{max}$  of the metabolite is less sensitive to differences in the rate of absorption than  $C_{max}$  of the parent drug. Therefore, when the rate of absorption is considered of clinical importance, bioequivalence should, if possible, be determined for  $C_{max}$  of the parent compound, if necessary at a higher dose. Furthermore, when using metabolite data as a substitute for parent drug concentrations, the applicant should present data supporting the view that the parent drug exposure will be reflected by metabolite exposure.

2. *“If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear”.*

Comments. To evaluate the significance of the contribution of metabolites, relative AUCs and non-clinical or clinical pharmacodynamic activities should be compared with those of the parent drug. PK/PD modeling may be useful. If criteria for significant contribution to activity and pharmacokinetic non-linearity are met, then *“it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately”*. Any discrepancy between the results obtained with the parent compound and the metabolites should be discussed based on relative activities and AUCs. If the discrepancy lies in  $C_{max}$ , the results of the parent compound should usually prevail. Pooling of the plasma concentrations or pharmacokinetic parameters of the parent drug and its metabolite for calculation of bioequivalence is not acceptable.

## 7. When using metabolite data to establish bioequivalence, may one use the same justification for widening the $C_{max}$ acceptance criteria as in the case of the parent compound?

In principle, the same criteria apply as for the parent drug (see Question on widening the acceptance range for  $C_{max}$ ). However, as stated above (see Question regarding when metabolite data can be used),  $C_{max}$  of the metabolite is less sensitive to differences in the rate of absorption than  $C_{max}$  of the parent drug. Therefore, widening the  $C_{max}$  acceptance range when using metabolites instead of the parent compound is generally not accepted. When the metabolite has a major contribution to, or is completely responsible for, the therapeutic effect, and if it can be demonstrated that a widened acceptance range would not lead to any safety or efficacy concerns, which will usually prove more difficult than for the parent compound (see Question on widening the acceptance range for  $C_{max}$ ), then a widened acceptance range for  $C_{max}$  of metabolite may be accepted.

## 8. What is a “highly variable drug or drug product?”

The standard approach to the analysis of a two-treatment, two-sequence, two-period crossover trial is an analysis of variance (ANOVA) for the log-transformed PK parameters, where the factors formulation, period, sequence and subject nested within sequence are used to explain overall variability in the observations. The residual coefficient of variation (CV) is a measure of the variability that is unexplained by the aforementioned factors. Amongst others, within-subject variability, formulation variability, analytical errors, and subject by formulation interaction can contribute to this residual variance.

A drug product is called highly variable if its intra-individual (i.e. within-subject) variability is greater than 30%. A high CV as estimated from the ANOVA model is thus an indicator for high within-subject variability. However, a replicate design is needed to assess within-subject variability.

**9. When testing for bioequivalence of a product with a non-linear PK, how should one select the strengths with the largest sensitivity to detect differences in the two products?**

Section 5.4 of the Guideline states: “If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable” provided five conditions are fulfilled, among which, when pharmacokinetics is not linear over the therapeutic dose range: “the strengths where the sensitivity is largest to identify differences in the two products should be used”. Non-linear PK, in this case, should reflect a non-linear drug input rate as stated in the guideline.

Generally, it is the studied dose and not the studied formulation strength that is of importance when considering bioequivalence for drugs with non-linear pharmacokinetic characteristics. An exception is when bioavailability is governed by the solubility of the active ingredient. Then bioequivalence studies should include the highest formulation strength (see below).

When studies are warranted at the high dose range, they should be performed at the highest commonly recommended dose. If this dose cannot be administered to volunteers, the study may need to be performed in patients. If the study is conducted at the highest acceptable dose in volunteers, the Applicant should justify this and discuss how bioequivalence determined at this dose can be extrapolated to the highest commonly recommended dose.

When proof of linear absorption or elimination kinetics is lacking, or if evidence of non-linearity is available, bioequivalence between test and reference formulations should be established with both the lowest and the highest doses unless adequately justified by the Applicant. This approach is the most sensitive for detecting differences in rate and extent of absorption for substances with dose-dependent pharmacokinetics. On the other hand, if only one dose is chosen in the bioequivalence studies, which dose to choose depends on the cause of non-linearity. For instance, single-strength studies may be conducted:

- on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or  $C_{max}$  with increasing dose during single or multiple dose studies. In this case an additional steady state study may be needed if the drug accumulates (steady state concentrations are higher than those reached after single dose administration);
- on the lowest dose (or a dose in the linear range) for drugs with a demonstrated less than proportional increase in AUC or  $C_{max}$  with increasing dose, e.g. if this phenomenon is due to saturable absorption.

When bioavailability of a substance with non-linear PK is governed by the solubility of the active substance, resulting in a less than proportional increase in AUC with increasing dose, bioequivalence should be established with both the lowest and the highest dose (which may exceed the recommended initial dose) and should include the highest formulation strength.

It is worth mentioning that in case of linear kinetics but low or critical solubility there is a similar need to test the highest strength and dose.

**10. What are the conditions for using urinary pharmacokinetic data for bioequivalence assessment?**

Section 3.3 of the Guideline states: “The use of urinary excretion data may be advantageous in determining the extent of drug input in case of products predominantly excreted renally, but has to be justified when used to estimate the rate of absorption.”

The extent of drug input may be determined by the use of urinary excretion data provided elimination is dose-linear and is predominantly renal as intact drug. However, the use of urinary data has to be carefully justified when used to estimate the rate of absorption. If a reliable plasma  $C_{max}$  can be

determined, this should be combined with urinary data on the extent of absorption for assessing bioequivalence.

#### **11. Standardisation of bioequivalence studies with regard to food intake. How strictly should the Guideline be interpreted?**

Section 3.2.2 of the Guideline states: *“If the Summary of Product Characteristics (SPC) of the reference product contains specific recommendations in relation to food intake related to food interaction the study should be designed accordingly.”*

The recommendations concerning food intake in the SPC are not sufficient for regulatory decisions on the adequacy of bioequivalence studies. Preferably, the following conditions should be considered separately when the SPC recommends administration of the substance together with food intake:

1. If the recommendation of food intake in the SPC is based on pharmacokinetic properties such as higher bioavailability, then a bioequivalence study under fed conditions is generally required.
2. If the recommendation of food intake is intended to decrease adverse events or to improve tolerability, a bioequivalence study under fasting conditions is considered acceptable although it would be advisable to perform the study under fed conditions.
3. If the SPC leaves a choice between fasting and fed conditions, then bioequivalence should preferably be tested under fasting conditions as this situation will be more sensitive to differences in pharmacokinetics.

The composition of the meal should be described and taken into account, since a light meal might sometimes be preferable to mimic clinical conditions, especially when the fed state is expected to be less sensitive to differences in pharmacokinetics. However, for modified release products, a high fat meal is required.

For products with release characteristics differing from conventional immediate release (e.g. improved release, dissolution or absorption), even if they cannot be classified as modified release products with prolonged or delayed release, bioequivalence studies may be necessary in both the fasted and fed states.