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CHMP efficacy working party therapeutic subgroup on pharmacokinetics (EWP-PK)

Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics

Background

In the context of assessment procedures, the Therapeutic Subgroup on Pharmacokinetics of the Efficacy Working Party (EWP-PK subgroup) is occasionally consulted by the CHMP or, following CHMP's agreement, by other Committees, Working parties or the CMD(h). The objective is to address specific questions in relation to pharmacokinetic evaluations and particularly the requirements and assessment of bioequivalence studies. The positions, which are being elaborated by the EWP-PK subgroup in response to such questions, are being forwarded to the enquiring party for consideration in their assessment.

It is understood that such position will be reflected in the procedure-related assessment reports if applicable. In some cases however, these position might also be of more general interest as they interpret a very specific aspect that would not necessarily be covered by guidelines. This paper summarises these positions which have been identified as being within this scope.

It should be noted that these positions are based on the current scientific knowledge as well as regulatory precedents. They should be read in conjunction with the applicable guidelines on bioequivalence in their current version. As the questions have initially been raised in the context of specific assessment procedures, details of these procedures have been redacted for reasons of confidentiality.

This compilation will be updated with new positions as soon as they become available. Likewise, if a position is being considered outdated, e.g. due to new evolutions in the scientific knowledge including revisions to the applicable guidelines, positions will be removed from this document.

The positions in this document are addressing very specific aspects. They should not be quoted as product-specific advice on a particular matter as this may require reflection of specific data available for this product. By no means should these positions be understood as being legally enforceable.

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Note: The following positions have been deleted:

Position	Date of deletion	Reasoning
Bioequivalence studies for paroxetine (single dose versus multiple dose studies)	July 2010	Covered by the revised Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)
Interpretation of bioequivalence data in relation to both parent and metabolite PK data	July 2010	Covered by the revised Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)

1. Cocktail studies for investigating *in vivo* drug interaction potential

During the last decade, use of cocktail studies has become a more common tool for investigating a drug's interaction potential *in vivo*. A cocktail study is a study where a number of *in vivo* probe drugs for enzymes (and transporters) are administered together for simultaneous assessment of enzyme/transport activities before and during treatment with another drug. The approach is used for investigating the induction potential *in vivo*, as induction generally affects multiple enzymes and transporters, as well as for studying inhibition of enzymes or transport proteins. Concerns have been raised regarding the validity of cocktail studies, how cocktails should be composed and if the results can be extrapolated to other drugs.

The position of the EWP PK Group on these issues is as follows:

Composition of satisfactory drug cocktails for use in interaction studies

The cocktail should consist of safe, validated probe drugs for the specific enzymes intended to be studied. Preferably, only one enzyme, or one transporter, should be involved in the elimination of each of the included probe drugs. If a second enzyme is catalysing metabolism of the parent drug, its contribution to total clearance should be very small (<10%). The cocktail of probe drugs should have been validated. The validation could have been performed by the applicant or have been published in the scientific literature. The validation of the cocktail includes a validation of the included probe drugs *per se* by investigation of the effect of a selective potent enzyme (or transporter) inhibitor on the pharmacokinetics of the probe drug. In addition, it should also have been verified that the probe drugs used in the cocktail do not affect each others pharmacokinetics. The doses used should preferably be the doses used in the validation. Deviations from this should be justified.

Pharmacokinetic parameters

The use of a cocktail study and conclusions that can be drawn from such a study depends on the objectives of the study and the design and conduct of the study. As in all interaction studies, the dose and duration of the investigational drug should be sufficient for estimating the maximum induction and/or inhibition achieved at a clinically relevant dose. When the objective of the study is to quantify the effect on different enzymes or transporters, it is recommended to determine complete AUCs for the probe drugs in order to estimate effects on (oral) clearance. Simpler ratios such as metabolite to parent drug ratios in urine are usually not a satisfactory parameter as results may have more confounding factors and as the magnitude of an effect is difficult to translate into inhibition or induction potency and to treatment recommendations in the SPC. Additional conventional interaction studies with a probe drug measuring drug clearance may in that case be needed.

Extrapolating results from cocktail studies

If satisfactorily performed, the results of the cocktail studies could be extrapolated to other drugs and to treatment recommendations of the SPC. The extrapolation could then be performed in the same way as from *in vivo* studies using only one probe drug.

2. Requirements for food-interaction studies for modified release formulations

The position of the EWP PK Group is as follows:

a. Guideline recommendations (CPMP/EWP/280/96) and general aspects

Food interactions may be related to the drug substance itself and/or the formulation, the latter being most important in the case of modified release (MR) products.

The aim of food effect studies for new MR formulations (developed either for a new substance or for a substance previously approved in an instant release formulation) is to evaluate the influence of food on the absorption of the drug substance from the new formulation, to evaluate the clinical relevance of a potential food effect and when needed to provide appropriate dose recommendations with respect to intake of the product in relation to meals. This is clearly stated in paragraph 4.1.4.1 of the guideline:

"Different modified release formulations of the same drug substances may differ with respect to food interaction. Hence, the influence of food on the bioavailability of oral modified release formulations must be investigated for safety and efficacy purposes.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high fat meal immediately before dosing. For the assessment of food effects besides AUC and C_{max}, it may also be valuable to compare the modified release characteristics.

If a significant food effect is found, applicant should give a justified dose recommendation with respect to the intake of the product in relation to meals.

Possible approaches for the investigation of the effect of food on the bioavailability of modified release forms reflecting the present scientific approach are presented in Annex 1. However, due to the complexity of the food-drug interaction with any particular dosage form a different approach for in vivo studies can be accepted if adequately justified."

Food effect studies for new MR formulations should be conducted early during drug development so that appropriate recommendations regarding intake in relation to food can be included in clinical efficacy and safety studies.

In contrast to new MR formulations, for **generic MR products** bioequivalence under fed conditions is required rather than the investigation of food interaction as described in paragraph 4.1.4.1, i.e.

- paragraph 5.1 reg. prolonged release formulations states that *"the effect of food on the in vivo performance is comparable for both formulations when a single dose study is conducted comparing equal doses of the test formulation with those of the reference formulations administered immediately after a predefined high fat meal. This study should be conducted with the same strength as those of the pivotal bioequivalence studies."*
- paragraph 5.2 regarding delayed release formulations states that *"As food can influence the absorption of an active substance administered in an enteric-coated formulation, post-prandial bioequivalence studies are necessary."*

It has been shown that food composition (fat content) and timing may be crucial for drug product bioavailability. Administration immediately after completing a high fat meal serves as kind of "worst case" situation in terms of product performance/robustness. Therefore, a food interaction study should be performed accordingly.

Section 4.1.5.1 of the guideline states

If the modified release formulation contains a higher dose compared to the approved immediate release product, the possibility of unexpected release resulting in unacceptable higher exposure should be excluded.

One issue that is important to consider for both new MR formulations and generic MR formulations is the influence of alcohol on the MR formulation and the risk for unexpected release caused by alcohol ingestion.

b. Study design - Guideline recommendations (CPMP/EWP/280/96) based on App. 1

Appendix 1 of the guideline provides recommendations regarding study design in different scenarios. Some explanation and comments to these recommendations are given below.

Bioanalytical measurements should include quantification of metabolites or enantiomers if respective requirements apply.

0. MR formulation developed for a New Chemical Entity (NCE)

For MR formulations developed for a new chemical entity the guideline recommends a single dose 4 way crossover study ; MR fed and fasted + oral solution (or immediate release (IR) formulation if a solution is not feasible) fed and fasted. With this study design the effect of food on both the substance and the MR formulation can be evaluated.

However section 4.1.4.1 of the guideline also states that a different approach for in vivo studies can be accepted if adequately justified. Hence, a 2-way cross over study (MR formulation fasting and fed) could be sufficient to evaluate the formulation related food effect.

The guideline also states that a single dose 3 way crossover study may be required in case the clinical trial formulation differs from the to-be-market product; i.e. comparing clinical trial formulation fasted with to-be-marketed formulation fed and fasted. However, if there is a marked food effect on the clinical trial formulation and the formulation has been taken under non-fasting conditions in the clinical studies, it may be advantageous to have comparative data on the food-effect on the marketing formulation in the same study, i.e. also here a 4-way crossover study with clinical trial and marketing formulation under fasting and fed conditions. This information may be important in the evaluation of dosing recommendations.

In case there is a marked food-effect, additional food-interaction studies might be needed to support dosing recommendations, i.e. studies of the effect of different kinds of food, studies investigating the effect of a meal taken at certain time period before and after the drug, etc.

0. MR formulation developed after an approved IR formulation

The guideline recommends a single dose 3 way crossover study; MR fed and fasted + IR fasted. However, the design of this study depends on which other studies that are conducted comparing the new MR formulation with the approved IR formulation and if there is a clinically significant food effect on the IR formulation. If there is no food effect on IR formulation, a 2-way cross-over study comparing MR formulation fasted and fed could be sufficient (given that other studies compare the MR and IR formulation under fasting conditions). In case of a clinically significant food effect for the IR formulation, a 4-way cross-over study comparing MR formulation fasted and fed and IR formulation fasted and fed could be useful to quantify the food effect on each formulation. If a 3-way cross-over study is conducted with IR formulation in one arm, consideration should be given to whether the IR formulation should be taken fasted or in a fed state (i.e. intake in accordance with the recommendation in the SPC).

0. MR formulations developed as generics

For generic products, the guideline recommends two single dose 2 way crossover studies evaluating test and reference fasted, and test and reference fed, respectively. Alternatively a single dose 4 way crossover study (MR generic fed and fasted + reference fed and fasted) can be conducted to demonstrate bioequivalence between generic and reference in both fasting and fed state. In a 4 way crossover study a comparison of the food effect for test and reference is possible, which will not be the case if two 2 way cross over studies are conducted, as between study comparison of food effect is not recommended.

For both single-unit formulations and multiple-unit formulations, the highest strength should in general be studied. In case a non-linearity in the food effect is suspected, the food interaction study should be performed with the highest and the lowest strength.

c. Defining a "high fat meal"

Presently, the guideline on modified release formulations does not give any advise regarding the type of meal, but the composition of a 'high fat meal' meal is recommended in the revised Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1) as follows:

...the meal should be high fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

d. Evaluation

Evaluation of food study results includes metabolites or enantiomers in case respective requirements apply.

New MR formulations

For MR formulations developed for a NCE or MR products developed after an approved IR formulation the food interaction study will provide quantitative data on the extent of influence of food on the pharmacokinetics. The clinical relevance of the effect of food should be discussed both from an efficacy and a safety perspective. When needed dose recommendations with respect to intake of the product in relation to meals should be given. Additional studies with other types of food, or with intake of the drug at certain time intervals before and after a meal may be needed to support the proposed dose recommendations.

Generic MR formulation

The bioequivalence approach considering usual acceptance limits (80 – 125 %) is applicable for generic MR products. If bioequivalence between generic and reference has been demonstrated both in fasting and in fed state the MR generic product and the reference can be considered to behave similar under fed conditions.

Any widening of the acceptance criteria for C_{max} should follow the recommendations of the revised guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 rev 1).

For delayed release formulations with single unit dosage forms differences in t_{max} is also recommended to be assessed, especially for products where a fast onset of action is important.

e. Special cases

0. Can a MR product be considered a generic if it has no food-effect as opposed to the innovator which has one?

In general a generic is meant to be bioequivalent with the innovator under fasted and fed conditions. A difference regarding formulation related food interactions indicates product differences thus contradicting the generic by definition. Accordingly, for products where bioequivalence can be shown in the SPC recommended condition but not in the non-recommended state due to a different food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application.

0. What studies are needed for a generic if the innovator's SPC states that it should be taken with a meal only or only in the fasted state?

Comparative studies should be performed under both fed and fasted conditions. See also response above.

Since the guideline on modified release formulations (CPMP/EWP/280/96) is currently under revision certain requirements may be changed with a revised document.

3. Bioequivalence studies in children

The EWP-PK subgroup was asked to address the following questions: "Treatment of children often requires that new formulations or strengths are developed. If chemical-pharmaceutical data are not considered sufficient to establish bioequivalence should bioequivalence studies be conducted in children or would healthy volunteers suffice?"

The position of the EWP-PK subgroup is as follows:

In vivo bioequivalence is almost always established in healthy volunteers unless the drug carries safety concerns that make this unethical. This model, *in vivo* healthy volunteers, is regarded adequate in most instances to detect significant formulation differences and the results will allow extrapolation to populations in which the drug is approved (the elderly, patients with renal or liver impairment etc). The same reasoning applies also to children. Hence, in the vast majority of cases BE studies in healthy volunteers are adequate for products intended for use in children.

4. Bioequivalence of gastro-resistant preparations (e.g. omeprazole)

The EWP-PK subgroup was asked to address the following question: "What are the recommendations for demonstration of bioequivalence of gastro-resistant preparations (e.g. omeprazole)?"

The position of the EWP-PK subgroup is as follows:

General aspects:

According to section 5.2 Delayed release formulations of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), in gastro-resistant or enteric products bioequivalence should be demonstrated not only in a single dose study in fasted conditions, but also in a single dose study under fed conditions. The fed study should be conducted using a high-fat meal (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

Consequently, bioequivalence studies should be performed under both fed and fasting conditions. In general a generic is meant to be bioequivalent with the innovator under fasted and fed conditions. A difference regarding formulation related food interactions indicates product differences thus contradicting the generic by definition. Accordingly, for products where bioequivalence can be shown in the SPC recommended condition but not in the non-recommended state due to a different food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application. See also section 2 "Requirements for food-interaction studies for modified release formulations" for recommendations regarding study design, etc.

Gastric emptying of single unit dosage forms non-disintegrating in the stomach (e.g. enteric coated tablets) is prolonged and highly erratic, most likely due to the effect of the inter-digestive cycle within the Migrating Myoelectric Complex. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable: if e.g. the active pharmaceutical ingredient (API) release occurs prior to stomach emptying because of prolonged residence in the stomach either degradation can occur or the release may be considerably delayed. In either case erratic concentration profiles (either non-existing or extremely delayed) can be obtained. Therefore the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the drug but the possible occurrence of this effect as well. This should reduce the risk of obtaining incomplete concentration-time profiles due to delay to the most possible extent. These effects are highly dependent on individual behaviour. Therefore, but only under the conditions that sampling times are designed to identify very delayed absorption and that the incidence of this outlier behaviour is observed with a comparable frequency in both, test and reference products, these incomplete profiles can be excluded from statistical analysis provided that it has been considered in the study protocol.

The general requirements for biowaiver of an additional strength detailed in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 rev 1) are applicable also for delayed release tablets and recommendations regarding which strength to study is given in the same section of this guideline and also in section 2 "Requirements for food-interaction studies for modified release formulations". When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm^2).

The dissolution profiles should be compared not only in Pharmacopoeial conditions (2 hours at pH 1.2 followed by 45 minutes at pH 6.8), but also at more neutral pHs in the range 2-5, both for single unit non disintegrating and disintegrating dosage forms with multiple units. Hence, at least, two dissolution tests in two steps are required. First a comparison at pharmacopoeial conditions, 2 hours at pH 1.2 followed by 45 minutes in pH 6.8 and then a second separate dissolution test at a higher initial pH mimicking fed state e.g. 2 hours at 4.5 followed by 45 minutes in pH 6.8.

Concluding similarity if dissolution of more than 85% is obtained within 15 minutes is not applicable for gastro-resistant formulations. In case of gastro-resistant formulations the release occurs after gastric emptying (median approx. 13 – 15 min). Therefore, the comparison of dissolution profiles should be performed even if dissolution is more than 85% before 15 min in either products or strengths. Hence, a tight sampling schedule is recommended after the product has been investigated for 2 h in media mimicking the gastric environment (pH 1.2 or 4.5) since profile comparison (e.g. using the f2 calculation) is required.

5. Bioequivalence studies for generic products containing clopidogrel

The platelet aggregation inhibitor clopidogrel is pre-systemically hydrolysed to the inactive metabolite clopidogrel carboxylic acid. The plasma levels of the unchanged drug are up to 2000 fold lower than those of the carboxylic acid metabolite. Another metabolite, clopidogrel thiol, formed by a parallel pathway, is the pharmacologically active form of clopidogrel and is generated in the intestine and liver primarily by the CYP2C19 enzyme isoform. Due to its chemical instability and low circulating levels, its detection in plasma is problematic. Clopidogrel thiol irreversibly binds to the P2Y₁₂ receptors of ADP on the platelet membranes in portal and systemic circulation, leading to the inhibition of platelet aggregation.

During the evaluation of the Marketing Authorisation applications for generic product of clopidogrel, the following questions were addressed by the CHMP to the EWP-PK subgroup and the EWP-CVS subgroup group¹, respectively:

0. Which substance should be studied in bioequivalence studies: the parent compound clopidogrel or the metabolite(s) of clopidogrel?

The *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) states "Also for inactive prodrugs, demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured."

At the time of approval of the reference product Plavix, no reliable and validated methodology for the determination of the pharmacokinetics of the parent prodrug clopidogrel or of the active metabolite clopidogrel thiol was available. Thus, at the time, the pharmacokinetic profile of clopidogrel was established based on the pharmacokinetics of clopidogrel carboxylic acid, which is the non-active metabolite. In the meantime, the pharmacokinetic profile characterisation of clopidogrel has improved by development of a sensitive analytical technique (e.g. LC-MS-MS) enabling for a suitable investigation of the parent prodrug, clopidogrel. A more accurate picture of the PK profile of clopidogrel can be obtained.

Position of the EWP-PK subgroup:

The demonstration of bioequivalence between the reference and the generic compound should be based on the parent prodrug, clopidogrel.

0. Is demonstration of bioequivalence under fed conditions necessary in addition to the demonstration under fasting conditions?

At the time the innovative drug-product was developed, no data regarding the effect of food on the bioavailability of clopidogrel parent compound were available. More recently, the investigation of food intake influence on the bioavailability of clopidogrel has been investigated. The results obtained by Nirogi *et al.* (Nirogi, RV *et al.*, *Arzneimittelforschung* 2006; 56(11); 735-9: *Effect of food on bioavailability of a single oral dose of clopidogrel in healthy male subjects*) indicate that in the fed state the bioavailability of a single oral dose of clopidogrel increases dramatically (500 - 600 %) but the systemic exposure to the major but inactive carboxylic acid metabolite increases only by approximately 10-20 %. The current Summary of Product Characteristics (SPC) for the originator states that clopidogrel should be given as a single daily dose of 75 mg with or without food.

Position of the EWP-PK subgroup:

¹ EWP Therapeutic Subgroup on Cardiovascular Issues

The Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) states *“In general, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the reference medicinal product on an empty stomach or irrespective of food intake, the bioequivalence study should hence be conducted under fasting conditions.”*

The food effect on the bioavailability (BA) of the unchanged clopidogrel - not recognised in the SPC - was not investigated by the innovator before approval of the originator product since a sensitive analytical method was not available at the time of approval. However, a publication by Nirogi et al. (2006) suggested a significant food effect with a high-fat meal. Similar results have been observed in applications for generic medicinal products. The food effect might be due to a protection from acidic hydrolysis in the stomach in a fasting state, since the BA is enhanced under fed conditions. The EWP-PK subgroup reviewed the solubility properties of clopidogrel salts and these indicate that when administration of clopidogrel occurs under fasting conditions, the dissolution in the gastric media with a subsequent hydrolysis and formation of the inactive carboxy-acid metabolite is maximal. As a consequence, the extent of unchanged drug that still is available for absorption (at the intestine level) is reduced. Conversely, the dissolution of clopidogrel is limited in the gastric media under fed conditions, the acidic hydrolysis in the stomach is reduced and the BA of clopidogrel is improved.

The EWP-PK subgroup acknowledges that as a consequence, the solubility of salts might be important. However, all clopidogrel salts have high solubility at low pH and the risk for acidic hydrolysis may therefore be similar. The food effect could consequently be expected to be similar to the reference product for different salts. Hence, the EWP-PK subgroup considered that there was currently an insufficient scientific rationale to justify a deviation from the revised bioequivalence guideline and bioequivalence should be demonstrated under fasting conditions irrespective of the salt.

Should further information on the food effect of clopidogrel become available, the SPC would be amended accordingly.

0. Bioanalytical methods: Should there be any special requirements to ensure that the risk of back-conversion of the major metabolite to clopidogrel could be excluded?

Within several centralised clopidogrel applications, the CHMP raised concerns about the possible back-conversion of the major metabolite of clopidogrel (clopidogrel carboxylic acid) to clopidogrel during the bio-analytical analysis of the samples. Considering that plasma levels of clopidogrel carboxylic acid observed in patients or healthy volunteers treated with clopidogrel are much higher than that of the parent drug, a minimum back-conversion of the metabolite could potentially lead to a huge over-estimation of clopidogrel plasma levels and would bias the outcome of bioequivalence study.

Position of the EWP-PK subgroup:

The EWP-PK subgroup confirmed that back-conversion could potentially occur when methanol is used as (part of) extraction solvent, reconstitution solvent, chromatography mobile phase or for the preparation of calibrators, quality control (QC) solutions and internal standards during bioanalysis. Therefore, testing for the back-conversion of clopidogrel carboxylic acid metabolite should be part of the validation process of analytical methods used for the measurement of clopidogrel plasma levels.

It should be demonstrated that there is no back-conversion of the major metabolite to the parent drug clopidogrel under all conditions for sample handling (including extraction procedures) and storage.

0. Could the acceptance criteria for C_{max} be widened?

According to the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) widening of the acceptance criteria for C_{max} is possible for highly variable drug products provided that a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification. The revised bioequivalence guideline provides detailed advice on how the acceptance criteria can be widened for highly variable drug products with a bioequivalence study of replicate design and using the scaled-average-bioequivalence approach. However, a prerequisite for widening the acceptance criteria is that a wider difference in C_{max} is considered clinically irrelevant. This issue was assessed by the EWP-CVS subgroup.

Position of the EWP-CVS subgroup:

The EWP-CVS subgroup evaluated the request from widening the 90% confidence interval for C_{max} from the efficacy and safety perspectives. The EWP-CVS subgroup considered what would be the degree of the impact of the possible variations in the C_{max} following the 75 mg dose, since some data suggest the existence of a plateau response in the inhibition of platelets aggregation. However, it is currently not entirely clear what would be the influence of variable clopidogrel concentrations on pharmacodynamics. It is important to note that clopidogrel is approved and recommended for use in acute clinical conditions, for which a high loading dose is advised in order to attain a fast antiplatelet action. Whether in these situations a lower C_{max} might be of clinical relevance is unknown, but cannot be completely excluded.

In conclusion, it is not definitely proven that widening C_{max} acceptance range for clopidogrel is devoid of clinically relevant implications, both in terms of safety and efficacy, for all situations where the drug is used in clinical practice. Under these circumstances, the widening of 90% confidence intervals for C_{max} is not recommended.

6. Acceptance criteria for bioequivalence studies for losartan

The EWP-PK subgroup was asked to address the following question: Which analyte, parent and/or metabolite, should be used for the decision of bioequivalence in the case of losartan, and which acceptance criteria should be applied.

Position of the EWP-PK subgroup:

Losartan is not a pro-drug. It is an angiotensin II antagonist at the AT1-subtype receptor. In humans, losartan competitively binds to the AT1 receptor, while the metabolite E3174 binds non-competitively.

The active metabolite E3174 is not directly formed from losartan, but from an intermediate product, metabolite E3179. Alternatively, the E3179 intermediate can also be hydroxylated to an inactive metabolite. It has been estimated that about 14% of the orally administered losartan dose is converted into E3174. In addition, 5 other minor metabolites exist that exhibit activity but much less than parent.

AUC of the active metabolite is 4 – 8 fold higher than parent, as it is cleared about 10-fold slower than parent.

Plasma free fractions of parent are 1.3% and that of the active metabolite 0.2%. Losartan and its metabolite E3174 shows linear pharmacokinetics.

It has been shown in vitro that the IC₅₀ for binding to the AII receptor in smooth muscle cells is 10-fold more potent for the metabolite than parent and that the in vitro AII concentration dependent contractile response in rabbit aorta is 33-fold higher for the metabolite. In vivo, in normotensive and renal hypertensive rats, the active metabolite has been shown to be 15 – 20-fold more potent compared to the parent.

Based on in vivo studies in rat, in which the potency was 15 – 20-fold higher for the metabolite, and assuming a more or less comparable protein binding as that observed for human plasma (literature indicated for losartan a binding >99% in rat plasma), the metabolite activity is about 76 – 100-fold higher than the parent compound.

Hence, based on total exposure (AUC), the metabolite accounts for the majority of the activity. However, losartan and the active metabolite have different plasma-concentration time course, with considerably higher losartan plasma concentrations during the first hours after administration. Considering the plasma concentration time course, difference in activity and protein binding, losartan may account for a large part of the activity during the first hour after the first drug administration, and at losartan t_{max}, which occur after about one hour, contribution to activity may be almost equal for losartan and the metabolite. Thereafter, the metabolite's contribution to activity is much larger.

Moreover, as the active metabolite E3174 is formed via an intermediate product and not direct from the parent, the pharmacokinetic data for metabolite E3174 may not reflect the rate of absorption of parent.

Therefore, bioequivalence for losartan should be proven based upon parent data. Regarding what acceptance criteria to apply, the submitted documents do not allow any conclusion to be drawn on this and consequently a conservative approach using 90% CI of 80 – 125% for AUC and C_{max} applies.

7. Bioequivalence assessment of generics for tacrolimus

In relation to the bioequivalence guideline, which has been drafted by the EWP-PK subgroup, a question was raised regarding the assessment of bioequivalence for tacrolimus generic products. There were different views whether the normal (80-125%) or a tightened (90-111%) acceptance range for the 90% CIs, for both AUC and C_{max}, should be applied.

The decision on the bioequivalence criteria requires the clinical judgement whether tacrolimus is considered a narrow therapeutic index drug (NTID). Therefore, the response to this question has been prepared by the Efficacy Working Party (EWP) taking the EWP-PK's general position on bioequivalence criteria for NTIDs into account.

The position of the EWP is as follows:

The decision on whether a particular active substance may be considered to be a narrow therapeutic index drug (NTID), and whether narrowing of the bioequivalence acceptance limits should apply, needs to be based on clinical considerations of the dose- or concentration-response relationships for both efficacy and safety.

The following key issues are identified for tacrolimus:

- Tacrolimus is a drug that requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose related toxicity. Plasma level monitoring is routinely employed to facilitate dose titration.
- Recommended Therapeutic Drug Monitoring schemes often set desirable levels close to the upper or lower limit of the therapeutic window (5 ng/ml or 20 ng/ml), for example the use of "minimisation protocols" using low levels during maintenance phase. It is well established from clinical experience with the drug that even small changes of dose can lead to crossing the upper or lower limits of the therapeutic window
- In the case of kidney and heart transplantation, there is only a two fold difference in the upper and lower limit of the proposed therapeutic range (whole blood levels from 10 to 20 ng/mL). This is comparable to the therapeutic range for "classical" NTIDs such as digoxin.
- The consequences of over-dosing and of under-dosing (including morbidity/mortality associated with graft rejection) are of major clinical importance and can substantially affect clinical outcome.

For the above reasons the EWP considers that tacrolimus is a drug with a narrow therapeutic index.

In a number of EU countries generic prescribing is the norm and pharmacies may dispense either the branded product or a generic. Where multiple generics are available patients may be switched from one generic to another when renewing their prescription. Changes of formulation in this situation would not normally be accompanied by re-titration. The usual frequency of whole blood drug level measurements in clinical practice (typically once per month during maintenance phase) is not sufficiently frequent to ensure avoidance of over or under dosing as a result of a patient switching to a different formulation in the event of generic substitution of tacrolimus. Therefore, in order to ensure the safety and efficacy of generic tacrolimus products it is necessary to apply tighter bioequivalence acceptance criteria than the conventional 80-125%.

The EWP discussion also covered whether the narrowing of the bioequivalence acceptance criteria to [90-111%] can be limited to AUC and will not be needed for C_{max} . For tacrolimus, this is supported by the following PK and PK/PD characteristics. Total drug exposure (AUC) is considered to be the key parameter of importance for dose titration of tacrolimus; in comparison peak whole blood levels do not seem to be critical for either safety or efficacy. As tacrolimus has a long elimination half life C_{min} trough levels can be used as a surrogate for AUC in clinical practice. Given the long terminal half-life, tacrolimus accumulates during repeated dosing. Due to this accumulation, a potential difference between formulations in C_{max} after single dosing can be expected to be less at steady state, if AUC is the same for the two formulations. Therefore, the normal acceptance criteria for C_{max} [80-125%] can be used in single dose bioequivalence studies for tacrolimus.

Conclusion: The EWP recommends that the bioequivalence acceptance criteria for tacrolimus should be [90-111%] for AUC and [80-125%] for C_{max} .

8. Requirements for demonstration of bioequivalence for ciclosporine generics

The reference product Neoral soft gelatine capsule concerns a specific formulation of ciclosporin which undergoes microemulsification process at administration (in the presence of water). For Neoral, the SmPC indicates a 26% decrease in C_{max} and a 15% decrease in AUC, in case the product is taken with a high fat meal.

As indicated in the guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1.), for products with specific formulation characteristics, like Neoral, bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state. Neoral may be taken with or without food, and in clinical practice, ciclosporin is often recommended to be taken in a standardised way in relation to food. Hence, a generic ciclosporin product must be bioequivalent with the originator product both in fasting and in fed state.

As EWP has defined ciclosporine to be a NTID, for which both AUC and C_{max} are important for safety and efficacy, a narrowed (90.00-111.11%) acceptance range should be applied for both AUC and C_{max}, under fasting as well as under fed conditions, in line with the guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1.).

Although a generic product with a reduced food effect could be considered an improvement, this would not be considered acceptable for a 'generic application', but could be considered for a "hybrid" application, article 10(3) with additional data to support an application under this legal basis.