



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 Likewise, if a position is being considered outdated, e.g. due to new evolutions in the scientific knowledge including revisions to the applicable guidelines, positions will be removed from this document.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.

Last update: June 2009

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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 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.

1. MR formulation developed for an 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 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.

2. 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[0]). 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).

3. 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 + R 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 does not give any advise regarding the type of meal, therefore the same ‘high fat meal’ meal as recommended by the US-FDA can be used the composition of which is as follows:

approx. 800 – 1000 Kcal (approx. 50-60 % derived from fat; approx. 15 % derived from protein; approx. 25 % derived from carbohydrates)

Example: 2 fried eggs, two stripes of bacon, two slices of toast with butter, approx. 120 g hash brown potatoes, approx. 250 ml whole milk

Obviously, this can be adapted to local European conditions.

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 NfG on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) and the Questions & Answers on the Bioavailability and Bioequivalence Guideline (EMEA/CHMP/EWP/40326/2006).

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

1. 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. However, on a case-by-case basis this might be acceptable if clinically justified and provided that the SPC wording can remain unchanged and no risk is involved for the patient taking the drug either with or without food.

2. 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. However, on a case by case basis the requirements for demonstrating bioequivalence in the non-recommended situation may be less strict than in the situation recommended in the SPC.

3. Bioequivalence studies for paroxetine (single dose versus multiple dose studies)

In general, for applications based upon directive 2001/83/EC, article 10 (1), bioequivalence should be shown under single dose conditions. However in some circumstances (dose- and time dependent pharmacokinetic), multiple-dose studies are requested. The Questions & Answers on the Bioavailability and Bioequivalence Guideline (EMA/CHMP/EWP/40326/2006) clarifies that a multiple-dose study may be needed in addition to a single dose study. In the present NfG on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) there is also an opening to choose to study bioequivalence under multiple-dose conditions, if the intra-individual variability in pharmacokinetics is very high or if analytical sensitivity problems preclude measuring plasma concentrations accurately at single-dose conditions. Presently the opening to choose multiple-dose conditions due to high intra-individual variability is not agreed upon and a single-dose study is still requested in this scenario.

The PK-EWP group was asked to comment on study design for generics containing paroxetine.

The NfG states that “multiple dose studies are required in case of dose- or time dependent pharmacokinetics.” In addition, under question 9 of the Q and A document, dealing with the selection of the strength to be tested in case of non-linear pharmacokinetics, it is stated that “the highest dose should be selected 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)”. The background of this request is to study bioequivalence at the most saturated (worst-case) conditions. Whether a multiple-dose study is needed or not depends on how well the results of the single-dose study can be extrapolated to the (therapeutic) multiple-dose situation. The difficulties to extrapolate will be most pronounced when there is substantial non-linear first pass metabolism of the drug and marked accumulation at steady state which exceeds the accumulation that would be predicted under linear conditions. In this case, differences in rate of absorption as well as amount absorbed could affect the systemic exposure (AUC) of a drug to more marked extent than would be the case under single-dose conditions.

The extent of absorption of paroxetine appears to be high. The elimination of paroxetine is saturable at single doses in the therapeutic dose-range, and in addition, at multiple dose conditions there is a markedly higher accumulation than the moderate accumulation expected from single dose data. Due to the higher accumulation under multiple dose conditions, differences in extent of paroxetine absorption may be potentiated, and this may thus be more sensitive to detect differences between two formulations. Currently no data are available to contradict or to substantiate this.

With regard to the rate of absorption, in general single dose studies are considered most sensitive, which is also considered the case for paroxetine.

Therefore, it is the opinion of the EWP-PK that based on the currently available data on paroxetine pharmacokinetics there is not sufficient evidence to conclude that a single-dose study is sufficient. Therefore at this point in time both a single-dose and a multiple-dose study are needed.

These recommendations are based on the present Note for Guidance and Q&A document (CPMP/EWP/QWP/1401/98, EMA/CHMP/EWP/40326/2006). The bioequivalence guideline is under revision and it should be noted that recommendations regarding these aspects may change in the revised guideline.

4. Interpretation of bioequivalence data in relation to both parent and metabolite PK data

The EWP PK group was asked to comment on the interpretation of C_{\max} data in cases where both parent and metabolite PK data have been provided, where a single parameter (C_{\max} of parent in this case) does not comply with acceptance criteria and of those exceptional situations in which parent C_{\max} data might not prevail.

The use of the parent compound in bioequivalence (BE) studies is usually considered preferable as the concentration-time profile of the parent compound is considered more sensitive to detect differences between two formulations. In this sense, the C_{\max} of the parent drug is more sensitive to detect differences in the rate of absorption.

According to the present NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), metabolite data in addition to parent compound is requested only in specific cases: *“If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately”*. Further regarding interpretation of the results, the Q&A document (EMEA/CHMP/EWP/40326/2006) states that *“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.”* Hence, in the case where metabolites significantly contribute to the net activity of an active substance and the system is non-linear, bioequivalence should preferably be demonstrated for C_{\max} for both parent compound and metabolite. If bioequivalence is not demonstrated for C_{\max} for both parent and metabolite, the parent data should in general prevail. However, this general rule may have exceptions depending on the contribution of parent compound and metabolite to pharmacological activity. An example when C_{\max} of active metabolite may be more important than C_{\max} of parent compound is in the case when parent compound is an inactive pro-drug or has a very small contribution to activity. In this situation the use of metabolite data instead of parent data may be acceptable, but needs to be justified based on contribution of parent compound and metabolite to activity taking into account AUCs of parent and metabolite and potential differences in pharmacodynamic activity.

The NfG on the Investigation of Bioavailability and Bioequivalence also accepts the use of a metabolite to determine the extent of drug input *“if the concentration of the active substance is too low to be accurately measured in the biological matrix (e.g. major difficulty in analytical method, product unstable in the biological matrix or half-life of the parent compound too short)*. However, thanks to the advancement of the bio-analytical methodology, it is nowadays unusual that parent drug cannot be measured accurately and precisely. Although the parent drugs usually can be measured nowadays and better reflect in vivo performance of test and reference products, traditionally those parent drugs with short half-life, that were difficult to measure, and lack completely of pharmacological or toxicological activity (pro-drugs), and, therefore, whose potential differences were considered clinically irrelevant, have been investigated based on the active metabolite (e.g. some ACE inhibitors). As an example, the assessment of trandolapril containing products based on the active metabolite is presently considered acceptable based on the clinical irrelevance of the parent drug.

For some products bioequivalence may need to be demonstrated both for parent and metabolite AUC and C_{\max} . This may be applicable e.g. for some statins for which it has been described that the outcome obtained with the parent does not predict the outcome of the metabolite and this discrepancy does not seem to be related to a high variability. This discrepancy seems to be related to the complex pharmacokinetic of these drugs with active transport in the absorption, hepatic uptake and hepatic elimination. Therefore, for some of the statins both parent and metabolite should presently be measured and evaluated separately. In this situation parent C_{\max} does not prevail over metabolite C_{\max} . Hence, with the current guideline, the need for demonstration of bioequivalence both for parent and metabolite AUC and C_{\max} must be decided on a case by case basis.

These recommendations are based on the present Note for Guidance and Q&A document (CPMP/EWP/QWP/1401/98, EMEA/CHMP/EWP/40326/2006). The bioequivalence guideline is under revision and it should be noted that recommendations regarding these aspects may change in the revised guideline.

5. 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.

6. 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. According to the “Q&A document on the Bioavailability and Bioequivalence Guideline” (EMEA/CHMP/EWP/40326/2006) for modified release products a high-fat high-calorie content meal is required.

Consequently, bioequivalence studies should be performed under both fed and fasting conditions. However, if the SPC of the innovator product contains specific information regarding administration in relation to food intake (e.g. a product is to be taken without food), the requirements for demonstrating bioequivalence in the non-recommended situation may be less strict than in the situation recommended in the SPC. Such situations are considered on a case by case basis. See also section 2 “Requirements for food-interaction studies for modified release formulations” for recommendations regarding study design, content of high-fat meal, 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 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 5.4 of the Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) are applicable also for delayed release tablets and recommendations regarding which strength to study is given in the Q&A mentioned above and 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.

Specific issues related to omeprazole:

A specific issue related to omeprazole, and some other substances increasing the gastric pH, is that the gastric pH becomes more neutral following multiple doses and consequently multiple dose bioequivalence studies would be desirable in order to challenge the gastro-resistance of the formulation. In fact, this has been shown in the literature (Elkoshi et al. Clin Drug Invest 2002; 22(9):585-592). However, single dose studies under fed conditions are considered acceptable as the gastric pH is also increased following food intake. Regulatory experience has also shown that the most discriminative condition to compare the biopharmaceutics quality of the formulations is the single dose study in high fat high-calorie fed conditions.

Further, omeprazole has time-dependent kinetics (omeprazole auto-inhibits its metabolism). Hence, according to section 3.1 of the present Note for Guidance on the investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), a steady state study is required due to this time-dependency.

In conclusion, for omeprazole bioequivalence between a generic product and innovator should be demonstrated in fasted and in fed state after single dose administration and in steady state in a fasted state study.

These recommendations are based on the present Note for Guidance and Q&A document (CPMP/EWP/QWP/1401/98, EMEA/CHMP/EWP/40326/2006). The bioequivalence guideline is under revision and it should be noted that recommendations regarding these aspects may change in the revised guideline.

7. 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:

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

Based on the current *Note for guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98) in most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the parent compound (AUC and C_{max}) as primary criteria for decision. In some situations, however, in particular if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.

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 (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:

Based on the current scientific knowledge on clopidogrel's pharmacokinetic (PK) and pharmacodynamic (PD), the EWP-PK subgroup considers that the demonstration of bioequivalence between the reference and the generic compound should be based primarily on the parent prodrug, clopidogrel. Methodology for determination of clopidogrel has been published in the literature in the past few years. The PK data for the inactive metabolite, clopidogrel carboxylic acid, should be regarded as supportive only. Demonstration of bioequivalence based on the PK parameters for the active metabolite clopidogrel thiol should not be mandatory.

2. 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

¹ EWP Therapeutic Subgroup on Cardiovascular Issues

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:

Bioequivalence studies in fasting conditions are normally recommended as mentioned in the *Questions & Answers on the Bioavailability and Bioequivalence Guideline* (CHMP/EWP/40326/2006): “*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 food effect on the bioavailability (BA) of the unchanged clopidogrel - not recognised in the SPC - has not been investigated by the innovator since a sensitive analytical method was not available at the time of approval. However, the recent 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 recommendation already agreed in the Q&A document (CHMP/EWP/40326/2006) 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.

3. 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 alcohols, such as methanol, are used as (part of) extraction solvent, reconstitution solvent, chromatography mobile phase or for the preparation of calibrators, 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.

4. Could the acceptance criteria for C_{max} be widened to 75-133%?

Based on the current Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) and the Questions & Answers on the Bioavailability and Bioequivalence Guideline (CHMP/EWP/40326/2006), widening of the acceptance criteria for C_{max} can, from a pharmacokinetic perspective, be proposed for compounds showing high within-subject variability (0.75-1.33).

In case of clopidogrel, widening of the 90% confidence intervals of C_{max} has been requested by an applicant. This was based on the observation that in a bioequivalence study the coefficient of variation of C_{max} and AUC was higher (>20%), which resulted in an increased number of subjects to be included in the bioequivalence studies (>80 subjects).

Position of the EWP-PK subgroup:

Although there are some data suggesting that clopidogrel might show high within-subject variability, no definitive confirmation that clopidogrel is a highly variable drug is available. The variability observed during the product use, in particular the food effect, is not sufficient for widening of the acceptance range. Thorough demonstration that clopidogrel is a highly variable drug, in a replicate design study, is a prerequisite for accepting a wider acceptance range based on variability. Moreover, high variability should be demonstrated in the bioequivalence study and not in a separate study. Therefore, the EWP-PK subgroup does not, based on present data, recommend widening the C_{max} acceptance criteria to 0.75-1.33 range.

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.

Note: These recommendations are based on the present Note for Guidance and Q&A document (CPMP/EWP/QWP/1401/98, EMEA/CHMP/EWP/40326/2006). The bioequivalence guideline is under revision and it should be noted that recommendations regarding these aspects may change in the revised guideline.