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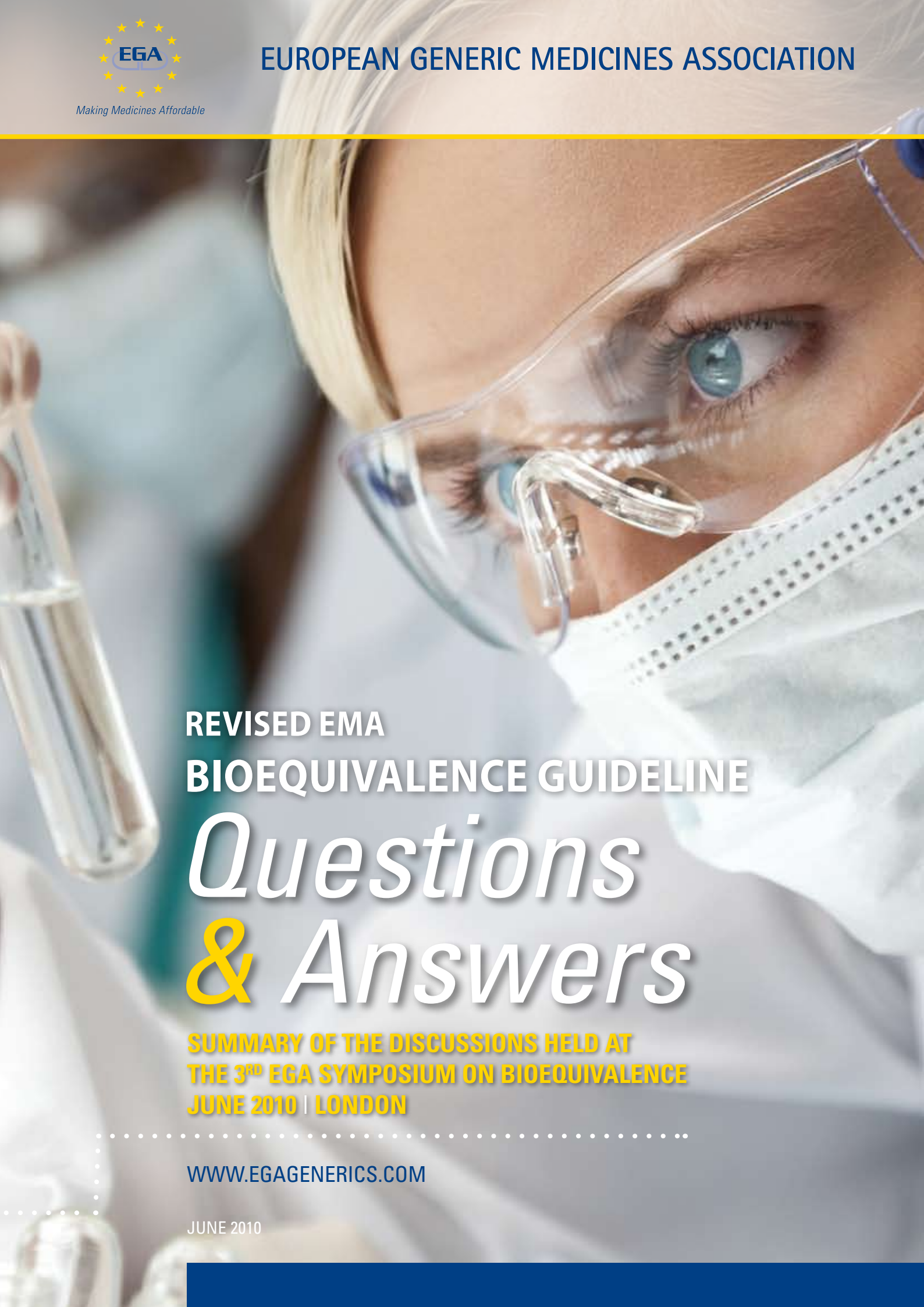

REVISED EMA BIOEQUIVALENCE GUIDELINE

Questions & Answers

SUMMARY OF THE DISCUSSIONS HELD AT THE 3RD EGA SYMPOSIUM ON BIOEQUIVALENCE JUNE 2010 | LONDON

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QUESTIONS & ANSWERS ON THE REVISED EMA BIOEQUIVALENCE GUIDELINE

Summary of the discussions held at the
3rd EGA Symposium on Bioequivalence
June 2010 | London

DISCLAIMER

This document represents opinions expressed by speakers at the 3rd EGA Symposium on Bioequivalence (1 June 2010) aimed at facilitating a common interpretation of the revised guideline requirements. These should not be interpreted as regulatory requirements. The contents of this publication are subject to changes and should always be seen in conjunction with more recent official EMA and CMD(h) publications and decisions on the matter.

Q&A

June 2010

QUESTIONS & ANSWERS ON THE REVISED EMA BIOEQUIVALENCE GUIDELINE

Summary of the discussions held at the 3rd EGA Symposium on Bioequivalence June 2010 | London

The **3rd EGA Bioequivalence Forum** was set to focus exclusively on the revised Guideline on the Investigation of Bioequivalence[1]. Through extensive interaction with a variety of high-level speakers, delegates could gain informative insight into the interpretation and practical implementation of the new provisions in the revised guideline. Speakers included: European pharmacokinetics assessors, representatives from the Co-ordination Group for Mutual Recognition & Decentralised Procedures (human medicines) the CMD(h), and bioequivalence experts from the generic medicines industry.

Bioequivalence is the key to ensuring safe and effective generic medicines. The EGA welcomed this opportunity for enhanced co-operation with the CMD(h) and the EU regulatory network in this important field.

Discussions between 160 delegates and representatives from national and EU medicines authorities offered an important opportunity to harmonise the interpretation of the revised guideline among European assessors and to enhance understanding by the industry.

Early dialogue with the industry on the draft guideline, published on 21 August 2008, resulted in significant improvement in the final version published in February 2010. It now offers a more robust set of criteria by which to assess the applications made for generic medicines and increases assurance regarding the acceptance of their applications and reduces the amount of time the authorities need to debate borderline issues.

Key improvements offer clarification on many study design issues, including the inclusion of a scaled approach for highly variable drugs. With the acceptability of two stage design studies and the combining of study data now added, this ensures that data generated is used to its maximum effectiveness, whilst shielding people from exposure to unnecessary clinical intervention. Robust rules on precisely what data can be used will ensure a common interpretation of outcome across the industry and all the EU competent authorities.

This document captures the various explanations given during the symposium on the different chapters of the revised Bioequivalence guideline with a view to clarify the intentions of the EMA drafting team. Now that the new guideline has entered into force (1 August 2010), we hope this document will contribute to further harmonizing interpretations by both industry and regulators.

[1] http://www.ema.europa.eu/pdfs/human/qwp/140198enrev1fin.pdf.

CONTENTS

Session 1

In Vitro Testing and Biowaiver

KEY WORDS

- *Protocol*
- *CTD*
- *Excipients*
- *Proportionality*
- *Dissolution Testing*
- *Production Batches Low Solubility Drug Substance*
- *Fixed Dose Combination*
- *Bracketing*
- *Variations*
- *Sink Conditions*
- *Narrow Therapeutic Index Drug Substances*

1. BCS BIOWAIVER – REGULATORY ISSUES / SCOPE AND CONTENT OF THE PROTOCOL

Q Is it expected that the protocol includes a detailed description of all aspects of the experiment or would a general outline of products, methods and assessment?

ANSWER

The protocol can be kept general and should describe what is planned to be investigated. All relevant aspects should be covered, including:

- the number of batches intended to be tested,
- experimental conditions,
- standards applicable for validation of analytical methods and,
- the evaluation and presentation of data.

2. BCS BIOWAIVER – REGULATORY ISSUES / LOCATION IN CTD STRUCTURE OF DOSSIERS

Q Where would the information regarding BCS Biowaiver be best placed in the CTD (Common Technical Document) structure?

ANSWER

In vitro data should be included and presented in Module 5, section 5.3.1.2. Comparative Bioavailability and Bioequivalence Study Reports of Marketing Authorisation Application dossiers, as this in vitro data replaces the in vivo data.

3. BCS BIOWAIVER - EXCIPIENTS /SIMILARITY OF AMOUNTS OF EXCIPIENTS

Q Similar amounts of excipients are now required for test and reference products. How shall this requirement be followed in new drug product application when the quantitative composition of the reference product is generally not known to generic medicines applicants?

ANSWER

Information on composition of reference product cannot be disclosed by regulatory authorities due to confidentiality reasons. Although hard to come across, information on the composition of the reference product can be found by way of different means including reverse engineering methods which can allow for accurate assessment of qualitative and quantitative composition of the reference product.

4. BIOWAIVER / FIXED DOSE COMBINATION

Q What is the allowance for deviations from proportionality / pseudo-proportionality criteria for Fixed Dose Combinations? Eg, Some minor Drug Substance deviations (like compensating the different amount of DS with a filler) should not have impact on bioavailability based on publicly available information, assuming in vitro similarity. Are such "pseudo-proportional type" deviations acceptable in justified cases?

ANSWER

Deviations from the guideline recommendations on proportionality / pseudo-proportionality criteria for biowaiver of other strengths could be considered possible in justified cases. This requires case by case assessment of the supportive data provided by the applicant as it is difficult to define upfront general criteria.

5. ASSESSMENT OF ALL SUBMISSION BATCHES / SAMPLES OF ALL SUBMISSION BATCHES SHOULD HAVE SIMILAR IN VITRO PERFORMANCE

Q How can one establish batch-to-batch consistency?

ANSWER

The first choice to show batch-to-batch consistency is to use a single pH (Quality Control-QC) relevant medium multiple points dissolution testing in view of the assessment of similarity of the batch used in the bioequivalence study to other submission batches and the first production batches.
Depending on the objective sought, it can however prove of interest to show, in specific instances, that there is no difference observed in dissolution at different pHs.

6. ASSESSMENT OF FIRST THREE PRODUCTION BATCHES / COMPARATIVE IN VITRO TESTING OF FIRST 3 PRODUCTION BATCHES

Q Comparative in vitro testing of the first 3 production batches is now required prior to release onto the market. Assuming concurrent validation – is it possible to market the first batch (1 of 3)?

ANSWER

It should be possible to market the first production batch after completion of the relevant dissolution testing for this batch and on the basis of satisfactory results. Applicants/Marketing Authorisation Holders should however carefully evaluate the consequences of (risks associated with) a possible failure of subsequent validation batches to meet this criterion.

7. BIOWAIVER OF OTHER STRENGTHS – BRACKETING

Q For biowaiver of other strengths, a number of conditions need to be met. Is bracketing considered suitable when products differ by more than one criterion (e.g. composition and dissolution)?

ANSWER

The use of bracketing when more than one condition for biowaiver of other strengths is not met could be considered possible provided comparable dissolution data are available. This requires a case by case assessment as generally applicable criteria cannot easily be defined.

Q For modified release products (single unit formulations) single dose fasted studies are required for each strength. Is bracketing considered applicable to modified release products?

ANSWER

Single dose fasted studies on each strength are currently required for prolonged release formulations. The use of bracketing for biowaiver of other strengths for single unit, modified release formulations is considered possible. Details will be outlined in the upcoming revision of the bioequivalence guideline for Modified Release (MR) products.

8. FORMULATION/MANUFACTURING VARIATIONS AND BIOWAIVER

Q For formulation/manufacturing changes that may impact on bioavailability, a BCS-biowaiver or IVIVC level A is required. Level A IVIVC is rarely established for immediate release oral dosage forms. Clarification on requirements for low solubility drug substance is sought

ANSWER

For formulation and manufacturing process changes that may affect bioavailability level A IVIVC or in vivo bioequivalence could be considered acceptable based upon appropriate justification.

Q For some type I variations, e.g. replacement of a single excipient with a comparable one, comparative dissolution testing is required (reference to the Bioequivalence guideline)

ANSWER

A single pH (QC) relevant medium multiple point dissolution testing could be considered sufficient for assessment of similarity between the new and old product.

9. DISSOLUTION TESTING - SINK CONDITIONS

Q Sink conditions may not be achievable in 3 media
- Should results of such testing be reported?
- Is similarity to reference required in such a situation?
- Is similarity between e.g. 2x5 vs 10mg required?

ANSWER

Results from comparative dissolution testing in 3 media should preferably be presented in Marketing Authorisation Applications regardless of whether sink conditions have been achieved. Possible differences observed between different strengths of test product should be justified based on the behaviour of the corresponding strength of the reference product which may confirm that the differences are drug substance related.

10. OTHER QUESTIONS

Q Can BCS Biowaivers be foreseen for Narrow Therapeutic Index (NTI) drug substances?

ANSWER

BCS based biowaiver is not acceptable for NTI drugs. It cannot be said upfront whether a drug substance is an NTI as there is no list of NTI drug substances agreed upon at EU level so far. Scientific Advice (EMA or National Agencies) is the appropriate tool to reach a decision. In the near future, such NTI drug substances will probably be identified one by one through questions raised at CMD(h) or CHMP levels on individual substances. Final EMA position on each substance (developed by the Therapeutic Working Parties) will be published on the EMA website.

Session 2

Study Design

KEY WORDS

- *High Fat Meal*
- *Timing of Administration*
- *Enhanced Formulation Characteristics*
- *Patients*
- *Racemate*
- *Achiral Method*
- *Interconversion Rate*
- *Linearity*
- *Inactive Compounds*
- *Fixed Dose Combination*
- *Replicate Design*
- *Pre-dose Concentration*
- *Number of Studies*
- *Study Population*

1. FED STUDIES

Q If the fed study is required due to safety reasons, should the meal be high fat or normo-caloric (standard)?

ANSWER
The guideline recommends the use of a high fat meal even in cases where the fed study is required for safety reasons.

Q For Modified Release products, is it still recommended to dose the tablet 30 minutes after a high fat high calorie meal, even if this is not in line with the timing of administration according to the SmPC?

ANSWER
For Modified Release products, the dosing of tablet should take place after 30 minutes so as to mimic a 'worst case situation', regardless of potential other SmPC recommendations.

Q Are two studies needed for specific (enhanced) formulation characteristics (if the originator allows both fed and fasting dose administration) although the qualitative and quantitative composition of test and reference products is similar?
If yes which criteria should be applied to claim similarity of two products?

ANSWER
Even in cases where the qualitative composition of test and reference products is similar, differences in the manufacturing process can influence the release characteristics of the medicinal product. Therefore, both fed and fasting studies should be carried out.

Q When the summary of product characteristics require that the bioequivalence studies are performed in patients, and the pathology in question does not allow the patient to tolerate a high-fat meal, how should the meal composition be assessed and justified?

ANSWER
If patients cannot tolerate a high-fat meal, which is an extremely rare situation, another type of meal can be used however this depends on the patient group and the study. This should be justified and pre-specified in the study protocol.

Q Again, in the case of patients who cannot tolerate a high fat meal, would another meal composition (other than a high fat & high caloric breakfast), be acceptable?

ANSWER
As a general rule, fed study should be conducted using high fat high caloric meal unless the SmPC recommends intake with a specific type of meal.

2. ENANTIOMERS

Q The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:
- the enantiomers exhibit different pharmacokinetics
- the enantiomers exhibit pronounced difference in pharmacodynamics
- the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

Does the rule apply for racemate or optically pure isomers or both?

ANSWER
The rule applies to the racemate. For the isomers, applicability depends on the situation (see subsequent questions & answers for details).

Q Is an achiral method appropriate for products containing single enantiomers?

ANSWER
In principle, an achiral method would be appropriate if there is no interconversion.

Q If a single enantiomer is used but there is no information available regarding interconversion with other enantiomer: How should the choice of the method be assessed?

ANSWER
If the relationship to the pharmacodynamics and pharmacokinetics cannot be substantiated then this would therefore imply the use of a chiral method for both enantiomers.

Q In the case of a racemate where 1)[2], 2) and 3) are unknown but there is literature information that the enantiomers are functionally indistinguishable (eg, due to rapid inter-conversion in vivo), is it acceptable to use an achiral method?

ANSWER
Rapid interconversion likely implies similar pharmacokinetics given the continuous compensation between the 2 enantiomers. In such a case, an achiral method can apply.

Q Does condition (3)[3] refer to a change in the rate of absorption induced by factors such as the presence of food, which may cause different exposure (AUC)?

ANSWER
Yes, if there is a difference in the rates of absorption with or without food whereas the ratio between enantiomers is constant.

3. STRENGTH TO BE INVESTIGATED

Q If for a drug substance no data regarding linearity of either parent drug or its metabolites are published eg, due to a lack of sensitivity of the analytical method in the respective dose range, which strength should be investigated in the bioequivalence study (lower or higher strength)?

ANSWER
In the absence of clear evidence of the linearity of a drug, the default assumption is that the pharmacokinetics are non-linear (conservative approach). In cases where the non linearity is known, however the exact type of non-linearity is undefined, then both the lower and the higher strengths need to be investigated. (Bracketing approach could be foreseen in cases where there are more than 2 strengths).

Q How to proceed if the originator claims that the pharmacokinetics are linear and that there is data available in the public domain, but it does not support this claim according to the criteria in the guidelines?

ANSWER
When literature data and SmPC/(E)PAR information related to the linearity of pharmacokinetics differ, the information present in the SmPC/(E)PAR prevails. However, more recently published new data is taken into account during assessment and decision is made based on the quality and extent of the data.

[2] (1) the enantiomers exhibit different pharmacokinetics
(2) the enantiomers exhibit pronounced difference in pharmacodynamics
(3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.
[3] the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption

4. FIXED DOSE COMBINATION

Q If one compound of the fixed combination has no activity in common use, but only acts e.g. to counteract abuse of narcotic drugs, is bioequivalence for the «inactive» compound for such example required? Bioequivalence requirements are covered in the "Guideline on Clinical Development of Fixed Combination Medical Products". But this guideline does not stipulate if both combination drugs always have to meet bioequivalence criteria.

ANSWER
In principle, the bioequivalence should be established for both compounds.

Q In the case of a fixed dose combination product, when one of the components has a significantly lower ISCV when compared to the other, is it possible to measure the less variable component with a portion of the subjects dosed in the study, as long as it is properly pre-specified and pre-defined in the study protocol?

ANSWER
In general, the use of a subset of patients for the low variability drug would be acceptable. This approach should be clearly pre-specified in the study protocol ie, which subjects will be involved in which part of the study and how they will be handled accordingly.

Q Considering a Fixed Dose Combination product composed of a of high variability drug substance (ISCV>30%) and a low variability drugsubstance (ISCV<10%) would a 3-way replicate design (replication for reference only) be appropriate?

ANSWER
A 3-way replicate design is one of the possible options.

Q Is it acceptable to determine pharmacokinetic profile of the low variability drug in the first two periods (standard 2x2 evaluation), whereas the pharmacokinetic profile of the highly variable drug would be determined in all three periods to enable the replicate crossover evaluation?

ANSWER
A preferable approach to excluding a particular period would be to pre-specify in the protocol that for the low variability drug, a subset of subjects will be used rather than all subjects. This would allow preserving all possible sequences.

Q Would it be appropriate, in addition, to design a study in such a way to collect and measure the low variability drug in a smaller group (i.e. in the first N subjects in the study)? (N adjusted to the ISCV of low variability drug)

ANSWER
Yes, this would be acceptable provided it is very clearly defined in the protocol.

Q Pre-dose concentrations
- When pre-dose concentration is more than 5% of the C_{max} value for the subject in that period, we understand that this applies to all periods including the first one. Is our understanding correct?

ANSWER
If in period one, a pre-dose concentration of more than 5% of C_{max} is observed, then in principle, the subject concerned can be excluded from the statistical analysis. The validity of the study design might be questionable in the presence of a subject showing measurable concentrations pre-dose in period 1.

Q

Physico-chemical characteristics
The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly.
What physico-chemical characteristics are critical? How is it possible to demonstrate similarity between test and reference products of the same active substance?

ANSWER
Solubility and chirality are the critical characteristics to be taken into account for study design.

Q

Study Population
Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. Is it understood that mild smokers can still be enrolled into the study if smoking does not have any impact on drug pharmacokinetics?

ANSWER
The enrolment of mild smokers could be acceptable provided there is evidence on the absence of impact of smoking on the drug pharmacokinetics (e.g. drug which is not metabolised or metabolised by a different route).

5. OTHER QUESTIONS

Q Are previously issued EMA Q&A on specific drugs (eg, paroxetine) superseded by the present guideline or not?

ANSWER
Yes, except for those medicinal products not in the scope of the present guideline i.e. immediate release medicinal products with systemic effect. The EMA Q&A documents will either disappear (redundant to the guideline) or be adapted to reflect the approach and recommendations of the new bioequivalence guideline. This will be done by 1 August 2010, time of entry into force of the guideline.

Q If the parent compound AUC cannot be measured accurately but C_{max} can be measured, the AUC of the metabolite can be used. What is the preferred approach?

ANSWER
The information on the parent is the preferred choice. If it can be substantiated that the parent compound AUC cannot be measured accurately, then it is acceptable to measure the metabolite only. Variability of the parent compound alone is insufficient to limit the study to the metabolite.

Q Would a pharmacokinetic approach be acceptable in line with the new guideline for oral immediate release drugs having a local effect (locally applied locally acting) yet leading to measurable plasma concentrations?

ANSWER
The scope of the guideline does not include such products. There is no consensus on the acceptability of the pharmacokinetic approach for locally acting drugs.

Q Regarding the demonstration of the linearity/non-linearity of the pharmacokinetics, what kind / quality of data from the public domain (different trials, different doses, or different volunteers) should be provided in the absence of any statement in the SmPC?

ANSWER
No general answer can be formulated. All available data should be submitted and taken into consideration.

Q For highly variable drugs, information is obtained from a replicate design (ISCV>30%). For Cmax a widening of the acceptance criteria is foreseen however not for AUC, could a multiple dose approach be acceptable for AUC in this case?

ANSWER

No, although this situation can occur, this approach would not be acceptable as it implies the use of a single dose study with additional subjects. The study should be powered accordingly to the variability observed for AUC. Scaling is only applicable to Cmax. AUC is essential in the determination of efficacy and safety and therefore cannot lead to any widening of the acceptance criteria regardless of high variability.

Session 3

Exclusion of Data, Evaluation of Results and Acceptance Criteria of Studies

KEY WORDS

- *Reanalysis*
- *Drop-out Subjects*
- *Exclusion of Data*
- *Reasons for Exclusion*
- *AUC 5% Criterion*
- *Parameters*
- *Acceptance Limits*
- *Highly Variable Drugs*
- *Multiple Dose Studies*
- *Statistical Analysis*
- *Two-Stage Design*
- *Narrow Therapeutic Index Drug Substances*
- *Truncated AUC*
- *Sampling Times*

1. STUDIES TO BE PRESENTED

Q Do all earlier bioequivalence studies including those with different formulations have to be included or only exploratory / pilot studies with the same (or similar) or final "to be marketed" formulation(s)?

ANSWER

A study report synopsis for bioequivalence or comparative bioavailability studies conducted during formulation development should be included in Module 2.7. All studies conducted with final formulation must be submitted. The final reports should be available upon request of an agency.

2. BIOANALYTICAL METHODOLOGY - REANALYSIS

Q Could individual implausible values in a plasma profile trigger an investigation? Can they be considered "rogue" and under which circumstances would a particular value be selected?

ANSWER

Any potential plan for reanalysis of study samples should be predefined in the study protocol (and/or SOP) before the actual start of the analysis of the samples. Normally reanalysis of subject samples because of a pharmacokinetic reason is not acceptable. This is especially important for bioequivalence studies, as this may bias the outcome of such a study. There can be no Pharmacokinetic or Statistical based reason for analysis in order to avoid the introduction of bias. "Good/plausible" values are not reanalysed so why would the "bad" ones be? The power of the study should be sufficient to cover these random effects and they should not alter the outcome. If they are very frequent, it will create concern over the quality of the study. In cases where the pharmacokinetics of the drug are well described and the "rogue" data contradicts the known data, investigation can be undertaken. If re-analysis does not confirm the original value then the choice of value to be reported must correlate to the values pre-specified in a Standard Operating Procedure (SOP) and cannot be based on pharmacokinetic or statistical reasons.

3. EVALUATION – SUBJECT ACCOUNTABILITY

Q Do all available plasma samples of drop-outs have to be analyzed even if the reason for drop out was not safety (i.e. no adverse event–AE) or because the subject cannot be in included in statistical analysis (e.g. if only samples from one period are available)? What about the use of "spares"?

ANSWER

It should be planned that all treated subjects should be included in the analysis, even if there are no drop-outs. That rules out the concept of 'dosed spares'. The applicant should analyse and statistically include all 'spares' as it is unethical to generate yet not use collected data. The drop-out and withdrawal of subjects should be fully documented. If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, but do not need be included in the summary statistics.

[Further information from EMA/CHMP/EWP/26817/2010: All samples should be bio-analysed. This is useful if there is disagreement between Member States over an exclusion as it enables the statistical analysis to be repeated]

Data from all subjects who have completed both phases (full set of data) in a 2-way or even two phases of a 4-way- study should be evaluated.

If the subject did not enter the period two (incomplete data set: subject withdrawn during wash-out period or in the beginning of period 2), there is no need to bio-analyse these subjects regardless of the reason for withdrawal (safety or personal reasons). However, if it is for a clinical reason and the subject was withdrawn from the study but presents a complete set of data, then bio-analysis should be carried out.

In any case, the decision to exclude data from this subject from the statistical analysis must be made before performing the bio-analysis, in order to avoid bias. Any reason to exclude data is acceptable provided it is pre-specified and a decision taken before the bio-analysis.

4. EVALUATION EXCLUSION OF DATA IN STUDIES WITH MORE THAN TWO ARMS

Q In the case of a 3-arm study with two reference products what does "excluding the data" mean?
If the data from one (or more) treatment arm(s) is (are) removed from ANOVA (eg, removing the data for a USA comparator product) and thus effectively considering it as a two arm study then the true sequences and periods are modified.

ANSWER

In studies with more than two treatment arms (eg, a three period study including two references, one from the EU and another from the USA; or a four period study including test and reference in fed and fasted conditions; or 2 test products and one reference provided one of the test products is the final 'to be marketed' formulation), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant to the comparison in question. However, the treatment, groups, sequences and periods should have their original values maintained in the analysis, and not have the values modified. For example an observation made in period 3 should still be coded as period 3, not have the period changed to "2" because the results for that subject in one of the earlier periods has now be removed.

5. EVALUATION EXCLUSION OF DATA, REASONS FOR EXCLUSION

Q Does the wording "alone" imply that implausible individual data in a plasma profile may be excluded if, in addition to an unexpected value in a plasma profile, other reasons (eg, potential mix-up) are identified?

ANSWER

As stated above the exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics. The agency may be interested in the effect of a "potential" correction of the data to evaluate if it has a large effect on the final outcome but the original data set would be considered the only valid data set.
Should implausible individual values occur more than once, the quality of the study might be subject to further investigation by inspectors.

CLARIFICATION

If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the Cmax value for the subject in that period, the statistical analysis should be performed with the data from that subject for that period excluded.
In a 2-period trial this will result in the subject being removed from the analysis.
The trial will no longer be considered acceptable if these exclusions result in fewer than 12 subjects being evaluable.
This approach does not apply to endogenous drugs.

Q The current "AUC 5% criterion" does not take into account the inter-subject variability of AUC for a specific drug. Would, in case of low inter-subject variability, higher limits than 5% also be acceptable?

ANSWER

A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product can be excluded under certain circumstances.
A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject).
The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.
This exclusion is allowed only for the reference product, the test may not be excluded as it is unproven and this low level may be a result of quality issues.
The 5% limit is arbitrary and only applicable in exceptional cases and applies irrespective of intra subject variability, there will be no adjustment for variability in the data.

6. EVALUATION – PARAMETERS TO BE ANALYSED AND ACCEPTANCE LIMITS

CLARIFICATION

For AUC and Cmax parameters, the 90% CI for the ratio of the test and reference products should be contained within the acceptance interval of 80.00-125.00%.
To be inside the acceptance interval the lower bound should be ≥ 80 00% when rounded to two decimal places and the 80.00% upper bound should be ≤ 125.00% when rounded to two decimal places.

7. HIGHLY VARIABLE DRUGS

Q How should a company proceed if outlier values are observed for the reference product in a replicate design study for a Highly Variable Drug Product (HVDP)?

The outlier cannot be removed from evaluation (as stated above) but should not be taken into account for calculation of within-subject variability and extension of the acceptance range.
Such a procedure does not seem to be adequate as removal of an outlier may take the drug from being HVD to low variability. (eg, removal of outlier reduces ISCV drops from 40% to 10%). The sponsor can neither exclude the data nor extend acceptance range

ANSWER

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to:

$[U, L] = \exp [\pm k \cdot S_{WR}]$,

Where:
U is the upper limit of the acceptance range,
L is the lower limit of the acceptance range,
k is the regulatory constant set to 0.760, and
S_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product.

This approach is only acceptable for Cmax, and as long as it is pre-defined in the protocol and that the ISCV (Intra Subject Variability) observed within this particular study is used. The ISCV value is limited to 50% as values above this are very rare and it would be concerning to widen the intervals beyond 70-143 regardless of variability.
For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for C_{max} of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.
To minimise the patient risk in the question above, the more conservative outcome of this approach does result in an actual "penalty" to the company but this is the preferred outcome rather than to increase patient risk unnecessarily. In the question of the extreme situation, where the variability drops to 10% without the outlier, this seems unrealistic; unless this result is very different from peer reviewed literature data then the applicant would have not performed a four way replicate design as the high variability is unexpected.
On a case by case basis, a study could be acceptable if the bioequivalence requirements are met both including the outlier subject (using the scaled average bioequivalence approach and the within-subject CV with this subject) and after exclusion of the outlier (using the within-subject CV without this subject).
An outlier test is not an expectation of the medicines agencies but outliers could be shown by a box plot. This would allow the medicines agencies to compare the data between them.

8. EVALUATION OF MULTIPLE DOSE STUDIES

CLARIFICATION

The cases where it is needed to perform a steady state study rather than a single dose study are rare under the new guideline principles.
However, in steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).
For studies to determine bioequivalence of immediate release formulations at steady state, $AUC_{(0-\tau)}$ and $C_{max,ss}$ should be analysed using the same acceptance interval as stated above.
Cmin is considered irrelevant in these instances for immediate release preparations.

9. EVALUATION – STATISTICAL ANALYSIS

Q

According to statisticians of EGA member companies "subject" and "subject within sequence" should be considered as random effects - Which procedure should be used?
For replicate design studies mixed effect modelling seems to be necessary in order to get unbiased and separate results for intra-subject variability of test and reference

ANSWER

Fixed or random models can be used as long as they are pre-specified but fixed is the preferred approach mentioned in the revised guideline. Both approaches should be acceptable and it is unlikely the agency would refuse an application based on the choice of fixed or random. There will be further discussions on the statistical guidance on these models.
The guideline requires subject and subject within sequence as fixed effects and, in practice, this should not make much difference.
Mixed effects-modelling is not considered absolutely necessary for replicate designs.
Applicants should model with terms for sequence, subject (sequence), period and formulation which are deemed appropriate for replicate design (no need to fit eg, interaction term).
Intra-subject variability for the reference product can be estimated by removing test data from data-set and fitting model with sequence, subject (sequence) and period.
There is an inherent risk if the applicant uses PROC Mixed and does not remove the missing data prior to evaluation as there will be a fitting of data and this will lead to a difference between PROC Mixed and other SAS models.
Medicines agencies will accept the use of PROC Mixed or other PROC as long as the handling of missing data is pre-defined. Its use will not result in arbitration. Replicates may be analysed without ANOVA but if the applicant pre-defines the use of PROC Mixed then this will be acceptable.

10. EVALUATION - TWO STAGE DESIGN

Q

In the Overview of comments received on draft guideline on the investigation of bioequivalence (EMA/CHMP/EWP/26817/2010, p. 158) it reads "In practice the company could essentially do this (blinded interim CV analysis and subsequent adjustment of sample size) under the current draft, by specifying an extreme alpha level at the first analysis, thereby taking almost no penalty. We prefer to stick to having some alpha penalty for any interim analysis, especially as it can be difficult to establish whether data are truly blind in a bioequivalence trial."
If at the first stage, an extreme alpha level is used (with almost no penalty), although not preferred, is it necessary to perform the interim analysis blinded? How should "not preferred" be interpreted? Is there a minimum recommended alpha error to be spent at the first stage?

ANSWER

If this approach is adopted, appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study.
The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%).

For example, using 94.12% confidence intervals for both the analysis of the first stage and the combined data from the first stage and the second stage would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion.
As in other types of trial it is possible to adjust the number to be studied in the second stage based on the first stage results (adaptive design), but it must be shown that the type I error is controlled.
Procedure for adaptation must be pre-specified. Blinding is not important. Any procedure to control type I error is acceptable but the EMA adaptive designs guideline outlines possible approaches. Reduction of subject numbers in the second phase is unlikely to preserve the alpha level.
It is acceptable to adapt the sample size for the second stage after evaluation of the first stage.
It is not acceptable to reduce the number of subjects in the second stage if at the first stage the data set fails a CI range but would pass the criteria if the 'end of the second stage' confidence intervals (CIs) were applied as this would not preserve the type 1 error.

11. NARROW THERAPEUTIC INDEX DRUGS

Q Intra-subject variability has not been taken into consideration for definition of the acceptance range for Narrow Therapeutic Index (NTI) drugs or drug products. Is it possible to use high Intra-Subject Variability (ISCV) as an argument that C_{max} is not of particular importance for safety, thus applying the tightened acceptance interval for AUC only?
Would high Intra-Subject Variability (ISCV) for AUC negate the use of narrower Confidence Intervals (CIs)?
What if under fed conditions we see high Intra-Subject Variability (ISCV)s rendering it impossible to perform successful studies with the tighter CIs?

ANSWER
Medicines agencies will consider individual drugs case by case, based on clinical considerations and there will be no general definition (or fixed general criteria) of an NTI as the interpretation varies across member states. There may be a list of NTI drugs published by the EMA Therapeutic groups (former Efficacy Working Party – EWP) further to specific questions raised by the CHMP or CMD(h).
In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00- 111.11%.
Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter.
In principle:
- It is acceptable to use a high ISCV as justification for widening acceptance range for C_{max}.
- It is acceptable to consider the widening of the acceptance range for C_{max} in fed conditions.
In both instances however, it has to be demonstrated that C_{max} is not the main pharmacokinetic parameter which correlates to safety and efficacy based on the available clinical data. It remains a case-by-case decision.
Drug substances will generally not be classified as NTI drug substances solely in connection with the therapeutic class they belong to.

12. CHARACTERISTICS TO BE INVESTIGATED - TRUNCATED AUC

Q What percentage of unquantifiable samples at 72 hours would still be acceptable for valid use of truncated AUC?

ANSWER
In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{(0-\infty)}$ and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$.
A mixture of AUC_t and AUC_{72} is acceptable as long as the sampling period allows for an adequate characterisation of AU_{Ct}.
Of course, in the event samples were absent because of protocol violations on a mass scale then this would affect the acceptability of the study.

13. CHARACTERISTICS TO BE INVESTIGATED - SAMPLING TIMES

Q

No requirement similar to that described for multiple-dose studies is given in the guideline for acceptable time deviations of the last sample. Is it required?
Would "within 30 minutes" or "within 1 hour" be adequate considering the larger time interval compared to multiple-dose studies? Is adjustment needed also in case of small deviations from the planned sampling time?

ANSWER

The actual time of sampling should be used in the estimation of the pharmacokinetic parameters.
In multiple-dose studies, the pre-dose sample should be taken immediately before (within 5 minutes) dosing and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0-\tau)}$.
These are recommendations and not an absolute requirement, it is preferred to use actual sample times and if required to pre-define acceptable deviations from sampling times in the protocol.

Session 4

Ask your questions to the regulators

KEY WORDS

- *Implementation*
- *Repeat Use Procedures*
- *Spare Subjects*
- *Steady State*
- C_{min}
- *Reference Product*
- *Locally Acting Products*
- *Oral Solutions*
- *Suspension*
- *Study Quality*
- *Sensitivity of Analytical Method*
- *Medicinal Product Packaging*
- *Study Report*

1. IMPLEMENTATION ISSUES Q&A DOCUMENT.

Q Once the new guidance is implemented, will the Q&A 2006 and 2009 and various position papers remain valid or will they be entirely superseded by the new guidance?

ANSWER

The EMA Q&A and position papers will be considered superseded by the revised guideline, from the entry into force of the guideline (i.e. 1 August 2010 onwards), except for those products not in the scope of the present guideline i.e. immediate release medicinal products with systemic effect.

The EMA Q&A documents will either disappear (because they are redundant to the guideline) or be adapted to reflect the approach and recommendations of the new bioequivalence guideline. There will be further clarification issued on the web site.

For specific issues, scientific advice should be sought in the interim.

CMD(h) approach is in line with the approach of the EMA.

It is expected that all new applications should comply with the new guideline if submitted after 1 August 2010. The applicant can apply the guideline now but the competent authority should wait for 1 August 2010 to implement

2. IMPLEMENTATION ISSUES REPEAT USE PROCEDURE (RUP)

Q If a company runs a first wave of DCP procedure in 6-year Data Exclusivity (DE) countries and then, the applicant wants to carry out a repeat wave in 10-year DE countries later on,
Would the initial studies supporting the applications be accepted for Repeat Use Procedure (RUP)?
Would all bioequivalence studies be re-evaluated to the new guidance?
Can medicines agencies offer any clarification on how to deal with any RUP after 1 August?

ANSWER

This will be dealt with on a case-by-case basis and it is recommended to closely liaise and discuss with the RMS before starting a new MRP.

Medicines agencies will honour previous CMD(h) referral decisions but whilst the dossier is being updated for this RUP, consideration should be given to the bioequivalence study and a discussion with the RMS is recommended.

Additonal bioequivalence studies may be required as a result of this consultation. Old bioequivalence studies will not necessarily be adequate going forward.

3. IMPLEMENTATION ISSUES - SPARE SUBJECTS

Q In the revised guideline, it is no longer acceptable to have "spare subjects" which will only be included in the analysis if required as replacements. Given that it is considered current practice and therefore may affect studies in current assessment, it does not seem reasonable to repeat studies for this reason alone during the transitional phase. What is the medicines agencies' position on this point?

ANSWER

Aspects of this have been covered in other sessions. However, if a study is already reported and spare subjects were recruited but not used, this will not warrant a rejection or repeat of the bioequivalence study based only on the "spares" issue.

4. STUDY DESIGN STEADY STATE

Q Steady state studies as an addition to a single dose study are no longer stipulated as the request for steady state studies in case of dose or time dependent pharmacokinetics has been removed. Is our understanding correct that even for drugs with time-dependent pharmacokinetics such as Omeprazole or other Proton Pump Inhibitors (PPIs), steady state studies are no longer required?

ANSWER

Yes this is correct. Steady state studies are no longer required for the likes of omeprazole.
Multiple dose studies for immediate release formulations are therefore no longer required.

Q Is the C_{min} definition as C_{trough} still valid for Modified release cases? The modified release guidance (CPMP/EWP/280/96 Corr) has no such definition.
Could C_{min} data be considered for scaled CIs like C_{max} data?

ANSWER

Whilst the current guideline for Modified Release products is applicable there is no scope to widen CIs for C_{max}. This will be reviewed for the Modified Release products guidance when it is revised.
There is still a requirement for C_{min} in the Modified Release products guidance and this has not changed either. The definition of C_{min} will be further reviewed for the Modified Release guideline.

5. STUDY DESIGN

Q In studies with more than two treatment arms, the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question. Will this approach be also applicable for studies with studies including 2 test products vs. one reference product?

ANSWER

In principle, in specific circumstances and unusual situations, recommendation is to seek scientific advice.
A 3-way study with 2 test products (alternate lead formulations) may raise some questions with some medicines agencies. This may lead to alpha adjustments.
A more appropriate solution would always be to run 2 separate bioequivalence studies.
If there were 2 test products and the other formulation was for exploratory purposes eg, solution or different form, then it may be acceptable to perform the study and remove this arm from the calculation.

Q Highly Variable Drug Product: Is it acceptable to perform a 3 period crossover scheme replicate design where only the reference formulation is replicated (ie, TRR and RTR sequences)?

ANSWER

Yes, the guideline allows this approach.

6. STUDY DESIGN REFERENCE PRODUCT

Q More than two treatment arms (e.g. a three period study including two references, one from EU and another from USA, or a four period study including test and reference in fed and fasted states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison. We assume that all European Agencies will accept these trial designs: a three period study including two references, one from EU and another from USA?

ANSWER

This will be acceptable

7. LOCALLY ACTING PRODUCTS, IMMEDIATE RELEASE

Q

Is it meaningful to perform a clinical efficacy study to measure differences between a test and reference product which are composed of the same amount of active ingredients and the same excipients? This kind of study usually does not have enough sensitivity to measure small differences.
Are pharmaceutical characteristics not more meaningful than clinical testing?

ANSWER

In principle the EMA Pharmacokinetic subgroup agrees that therapeutic studies may be insensitive.
There is a need to revise the guidelines for locally acting locally applied products. Although the revised bioequivalence guideline comprises a small paragraph on locally acting products, there are important differences between different forms of locally acting products and therefore this should be addressed separately as it is not possible to give detailed guidelines on such different formulations in the context of the revised bioequivalence guideline

8. LOCALLY ACTING PRODUCTS, CHANGE FROM DRAFT TO FINAL GUIDANCE

Q

The draft guideline stated that "If the extent of absorption and the bioanalytical method are such that a pharmacokinetic approach is reliable, then a bioequivalence study might provide the best data for the approval of a locally applied/locally acting generic medicinal product". This sentence has been removed in the final version. Has this sentence has been deleted because it refers to locally acting products which follow a specific guideline or because pharmacokinetics in locally acting drugs is no longer acceptable for European Agencies?

ANSWER

The main reason for the removal of this statement was because of the complexities of the issues. Pharmacokinetics remains applicable mainly for safety concerns and has the upper limit of 125%.

9. ORAL SOLUTIONS

Q

If the test product is an aqueous oral solution containing an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect either the transit, the absorption, the in vivo solubility or the in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers (see Appendix III, Section IV.2 Excipients).
If however the aqueous solution formulations are identical (Test/Reference) but contain one of these Gastro-Intestinal (GI) transit modifiers, can a bioequivalence study be waived?

ANSWER

If the specific excipients are present in the same amounts (i.e. identical formulations) then it could be waived. If critical excipients differ, a thorough justification should be provided, including evidence that absorption is not affected. Final decision is made case by case.

Q

Could a bioequivalence study on a suspension be waived based on in vitro criteria (eg, dissolution, etc.) that are applicable to solid oral dosage forms? It is effectively only a wet tablet?
Could a bioequivalence study on a solution or suspension comparing it to a solid oral dosage form (no liquid innovator available) be waived based on the same in vitro criteria?

ANSWER

If the reason for the suspension is that the drugs are not BCS class I or class III, then there cannot be a biowaiver.
If the drug substance is either class I or III and the suspension was selected as pharmaceutical form for purposes other than lack of solubility, then the applicant should establish that the drug substance is in solution as justification for the

biowaiver which might be granted.
It is not possible to waive a bioequivalence study in the case of comparing a solid oral dosage form to a liquid form as the release from the stomach will be different.

10. PRESENTATION OF DATA - COMBINING DATA FROM MULTIPLE STUDIES

Q With regard to the combined analyses of the studies, additional clarification and/or examples would be appreciated on how to present the data

ANSWER
Individual study reports should be presented together with a separate combined study report.
It would not be possible to put two underpowered studies together to pass. One component study must have passed and be of adequate power.
The assessor will still need to be convinced as to why he should accept the studies and that the individual studies do not contradict conclusions of equivalence.

11. STUDY QUALITY AUDIT/ MONITORING

Q It is understood that study site audits are not monitoring visits. The sponsors will perform their own audits and monitoring visits under their own risk management plan but given that the sponsors may see different issues to inspectors, will the medicines agencies issue GCP/audit reports of CROs?
Would medicines agencies inspect on request?
Would there be inspection certificates for CROs and will these be considered in the review of bioequivalence studies?
Could there be a qualification of supplier systems?

ANSWER
There is a joint CMD(h) and EMA GCP inspectors Working Group.
These questions will be taken back to this sub-group and there will be feedback in due course.
There is however no current plan for medicines agencies to issue inspection certificates for individual CROs.

12. SENSITIVITY OF THE ANALYTICAL METHOD

Q In some cases, the volunteer may receive up to or more than double the highest dose indicated in the SmPC. How can a generic medicines company check the tolerability of the product in healthy volunteers?

ANSWER
Safety of the study subjects should be considered first. However, when a generic application is submitted, the product has been on the market at least for 10 years. This means there is substantial evidence in the public domain with regard to safety. In most instances this includes data on doses higher than approved by the regulators. Therefore, whether it is acceptable to administer a higher dose to healthy volunteers is based on the safety profile of the product and on the evidence available.
For the generic medicines industry, there is usually a significant amount of clinical experience with the reference product at high levels and as the preferred design is a single dose study, this is seen as a very rare issue. The guideline is certainly not proposing this approach to become common practice.
The safety of the study subject is of paramount importance

13. SENSITIVITY OF THE ANALYTICAL METHOD PRO DRUGS

Q

The current EMA guidance states "Demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured. However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound.
In this situation, is it acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound? In the context of this guideline, a parent compound can be considered to be an inactive pro-drug if it has no or very low contribution to clinical efficacy."

ANSWER

There cannot be a general answer as it depends on the drug itself. It will be considered on a case-by-case basis as criteria to establish that plasma concentrations are low and elimination rate is rapid are not evident.

Q

Could criteria to establish low plasma concentrations and rapid elimination rate be clarified?
Some drugs are not identified as pro-drugs in their monograph if they exhibit these criteria: could this paragraph apply to these drugs?
Could this section of the guideline be considered applicable to a product that is not identified as a pro-drug but which has very low plasma levels and is rapidly metabolised?
Thus in this situation, is it acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound?

ANSWER

If variable plasma concentrations are observed, the answer will depend on the nature of the drug itself and should therefore be addressed on a case-by-case basis.
A possible justification would be if the variability is so high that it would imply the enrolment of a huge number of subjects. In such instances, it would be acceptable to evaluate bioequivalence based on the metabolite.
There are inactive pro-drugs that can be easily measured (e.g. enalapril). In these cases the medicines agencies will ask for the parent compound to be measured.
The demonstration of bioequivalence only on the main active metabolite (and not on the parent compound) would be rather exceptional (e.g. betahistine, for which the parent data is variable and unreliable).

14. PACKAGING OF STUDY PRODUCTS

Q

Is dispensing of study medication acceptable if it is done by a Clinical Research Organisation (CRO) according to local laws and internal SOPs, but the CRO cannot confirm that it is done according to GMP Annex 13?
Can products be "manufactured" under Annex 13 by the sponsor but "dispensed" at the CRO?

ANSWER

The direct answer from the inspectorate is: If the site is located in the EU then GMP has to be followed as outlined in annex 13.
If the site is located in a third country, then the site must demonstrate it uses standards equivalent to these EU GMP requirements and it has performed the study in compliance with local requirements.
Other laws, guidance or SOPs can be followed as long as the standards are of the same level.
Further clarification is available and can be found on the EMA website.

Q

"Reference and test products packed in an individual way for each subject and period". Does this mean that they need to be pre-dispensed and that such activity performed at an EU GMP certified manufacturing site (andshipped to the clinical site with the accompanying randomization code)? If yes, will the current version of the Guidance be modified accordingly to withdraw the option for the clinical sites to perform such procedure?
Alternatively, how can a foreign clinical CRO (e.g. North America) comply with the guidance if not EU GMP certified?

ANSWER

It is not the certification or inspection of the site that assures EU GMP compliance but it is the internal quality systems of the site and sponsor.
Reference and Test products can be pre-packaged (eg, at the manufacturer's site) and then sent to the CRO. Or it can be shipped in bulk (eg, the reference product in its commercial packaging and the test in, for example, blisters or bulk container) and then packaged locally.
GMP certification will only be required based on local legislation (i.e. if the local law does not call for specific authorisation or a local GMP certificate then it is not needed).The packaging will however have to be performed at that site to the principles of EU GMP.

15. BIOEQUIVALENCE STUDY REPORT

Q The study report should include evidence that the choice of the reference medicinal product is in accordance with Art.10(1) and Art. 10(2) of Dir 2001/83/EC as amended. This should include the reference product name, strength, pharmaceutical form, batch number, manufacturer, expiry date and country of purchase. Is it acceptable to report the Marketing Authorisation holder of the reference product in the country of purchase instead of manufacturer?

ANSWER

This is not acceptable. All the requirements listed in the guideline have to be complied with and corresponding data submitted.

Q There is a statement that composition of the test product(s) used in the study should be provided. Since the studies are conducted in CROs which write the study reports as well, and the qualitative composition is at the time of the conduct of the study or the report writing still confidential information. Is it really mandatory to include the composition of the test product in the bioequivalence study report?

ANSWER

There is no requirement that this has to be part of the final study report as long as the data is included somewhere in module 5 together with other documents relevant to the bioequivalence study.

Q A signed statement regarding the composition and manufacturing of the test product is requested. In what part of the dossier should this statement be included?

ANSWER

It would be in Module 2.5. ICH guidelines provide clear information on where to put this data.

16. FURTHER MISCELLANEOUS CLARIFICATIONS

- Use of non EU reference product is not allowed even if reverse engineering is available to show similarity to EU originator product.
- Analysis if more than one study is combined into a final data set requires an extra term for 'study' to be included in the statistical analysis (ANOVA).
- Generally Cmin for Modified Release products has to fit the 80-125% criteria.
- A study cannot be refused upfront on the basis that a number of subjects present an extrapolated AUC which is outside 20%. As a general rule, an extrapolated AUC > 20% is acceptable in no more than 20% of study subjects. The applicant must support the fact that the extent of absorption is complete. The applicant should demonstrate that the data available on the rate and extent of absorption is appropriate. Based on sound justification, this might be acceptable.
- If a particular dose cannot be given because of safety reasons then it is acceptable to use the lowest dose. If this is not possible then the study will have to be carried out in patients.

LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance (statistical model)
AUC	Area Under the Curve
BCS	Biopharmaceutics Classification System
CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
Cmax	Maximum (Peak) Concentration
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures (human medicines)
Cmin	Minimum Concentration
CRO	Clinical Research Organisation
CTD	Common Technical Document
DCP	Decentralised Procedure
DE	Data Exclusivity
EGA	European Generic medicines Association
EMA	European Medicines Agency
(E)PAR	(European) Public Assessment Report
EWP	Efficacy Working Party
FDC	Fixed Dose Combination
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
HVD(P)	Highly Variable Drug (Product)
ICH	International Conference on Harmonisation
(IS)CV	(Intra-Subject) Variability
IVIVC	In vitro in Vivo Correlation
MRP	Mutual Recognition Procedure
NTI(D)	Narrow Therapeutic Index (Drug)
PK	Pharmacokinetics
PPI	Proton Pump Inhibitor
PROC mixed	Statistical analysis tool
SAS	Statistical analysis tool
QC	Quality Control
SmPC	Summary of Product Characteristics
SOP	Standard Operating procedure

EGA | European Generic Medicines Association

The EGA is the official representative body of the European generic and biosimilar medicines industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

www.egagenerics.com.

EGA QUESTIONS & ANSWERS

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