European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE CPMP/EWP/QWP/1401/98 REV. 1

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA	
2	European Generic medicines Association (EGA)	
3	EUFEPS Network on BABP	
4	FIP Special Interest Group on BCS and Biowaiver	
5	BPI-German Pharmaceutical Industry Association	Germany
6	The Association of the European Self Medication Industry (AESGP)	
7	European Federation of Statisticians in the Pharmaceutical Industry	
8	European Quality Assurance Confederation	
9	International Association for Pharmaceutical Technology	Germany
10	BEBAC-Consultancy Services for bioequivalence and Bioavailability Studies	Austria
11	CIPLA LTD. INDIA	India
12	Pharmascience Inc. Montreal, Canada	Canada
13	Anapharm	Canada
14	Lupin Bioresearch Center	India
15	MANEESH PHARMACEUTICALS, LTD	India
16	MDS PHARMA SERVICES	
17	POLFA TARCHOMIN S.A	Poland
18	PHAST GmbH	Germany
19	Jenson Pharmaceutical Services Ltd	
20	Douglas Pharmaceuticals Ltd	New Zealand
21	Ratiopharm GmbH	
22	Ranbaxy	
23	Orion Corp. Orion Pharma	
24	Gilead Sciences International Ltd	
25	CEPHA s.r.o.	Czech Republic
26	H.L. Lundbeck A/S	
27	Combino-pharm	Spain
28	Bayer Schering Pharma AG/Clinical Pharmacology and Global Pharmacometrics	
29	Quinta Analytica-s.r.o.	Czech Republic
30	Hexal AG	Germany
31	Synthon BV	The Netherlands
32	UCB Pharma S.A.	
33	Merck Sharp & Dohme (Europe) Inc	
34	ACC GmbH, Analytical Clinical Concepts	Germany

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35	Slovak National Accreditation Service	Slovakia
36	Good Laboratory Practice Monitoring Authority	UK
37	Norwegian Accreditation	Norway
38	Eye- Care Industries European Economic interest grouping	
39	Dr. Nasir Idkaidek	Jordan
40	Patrick Nicolas	France
41	Atholl Johnston	UK
42	Laszlo Endrenyi	Canada
43	Aldo Rescigno	
44	Carla M Catsmella	Italy
45	Salvador Fudio	
46	Dr. Kamal K. Midha and Dr. Gordon McKay	
47	Swissmedic	

Table 2:Discussion of comments

GENERAL COMMENTS	Outcome
1) There is a general confusion about the implementation of new guidelines now that interim advice has been issued. In particular, companies appear to be concerned about the fate of applications entering the system before finalisation. An explicit statement of the date (a) when agreed guidelines will come into force and (b) that regulations will not be applied retrospectively, would be useful. (2) Although there is a wish to examine as much data as is available, it should be stated that submissions for non-EU submissions can be omitted. (3) In the document there is use of general terms such as "same", "similar" and "major" which have a wide range of interpretation. Where ever possible, a numerical guide should be used. For example, a major metabolite might constitute **30%** of the dose etc. (4) General definitions, e.g. of bioavailability, bioequivalence, generic medicinal products, pharmaceutical equivalence etc. should also be included in the new guideline.	1) Once the final guideline has been adopted by CHMP it will be published for 6 months before coming into operation. The revised guideline should be applied to all applications submitted after the guideline has come into operation, regardless of when the BE studies were conducted. The present guideline and Q&A document are relevant for applications submitted until the new guideline comes into operation. See also EMEA/P/24143/2004. Items 2, 3 and 4) are covered by responses to specific comments.
Over 80 pages of detailed comments from over 16 companies were consolidated into this document. In general, this revision is welcomed and considered to be well written. In particular we welcome the principle of applying 'scientific reasoning ' to guide the choice of design, dose, analysis and acceptance criteria. A few general comments, before line by line specifics are given in the rest of the document. Several companies asked for additional clarification regarding exactly when the scientific principles of BE described in the guidance apply to generic substitution (or do not apply). Please consider adding clarification to various sections as to applicability of scientific principles of BE to formulation development versus generic substitution. Could you make reference to the fact that the new document does not cover the topic "bioavailability" and from where guidance on this topic is intended to come? Furthermore, the current NfG on the Investigation of Bioavailability and Bioequivalence includes a number of definitions (e.g. pharmaceutical equivalence, essential similarity of products, etc.), which are missing in the new draft. Will these definitions be included in another guideline? There was the typical dichotomy of comments asking for more detail and those asking for less 'prescriptive' guidance. However, in a few specific places, most companies thought that the draft guidance note is overly prescriptive in several areas where there are proposals for alternative approaches, which could be appropriately taken with adequate scientific rationale provided by sponsors, in particular Line 195 (requirements for reference and test product packaging) and Line 989-998 (detailed provision of analytical method parameters). Proposals for alternative wording are made below within the detailed comments.	Generic substitution is a national legal issue and is not covered in this EU guideline. The other issues are covered by responses to specific comments.

We welcome the clarification provided on the definition of 'complete absorption' and feel that the appropriate threshold for complete absorption is a topic worth further exploration for consideration in future guidance revisions. The draft guidance note requests proof of dissolution profile similarity by generation of dissolution data in 3 buffer systems (e.g. pH 1.2, 4.5 and 6.8). We propose that if changes in formulation and manufacturing process are made within a pre-defined design space, there should be no requirement for confirmatory dissolution testing beyond the specified dissolution test. We seek greater clarity on the value added by the 3 pH point dissolution test in the case of an enhanced product/process understanding and control strategy.	
We recommend greater incorporation of the principles of enhanced product specific understanding in the selection of dissolution methodology. We believe that once the critical quality attributes impacting drug product performance are identified, monitoring these parameters utilising a discriminatory or biorelevant dissolution test, would provide a viable alternative to a 3 point dissolution testing in support of biowaiver applications. We are concerned by the apparent constriction in dissolution criteria applied to biowaiver applications. In the original guidance note (CPMP/EWP/QWP/1401/98) it was stated that "in case of exemption from BE studies, in vitro data should demonstrate the similarity of dissolution profile"… and "in cases where more than 85% of the active substance are dissolved within 15 minutes the similarity of dissolution profiles may be accepted as demonstrated" i.e. without further mathematical testing. The current draft guidance indicates that BCS based biowaivers will only be accepted for very rapidly dissolving drug products (lines 917 & 923), i.e. > 85% dissolved within 15 minutes. This is considered overly conservative with respect to scientific understanding of pharmacokinetics and typical gastric emptying times. For biowaiver applications we strongly recommend consideration of drug products with rapid dissolution where ≥85% dissolution occurs in 30 minutes (as discussed in lines 792 through 797). In these cases mathematical testing should be performed to demonstrate similarity in dissolution profiles. This approach would provide greater scope for alignment with regulatory guidance for other regions. We recommend keeping mathematical methods used to demonstrate dissolution profile similarity as simple as possible so that the key aspect, i.e. what magnitude of difference is important, can be defined in a manner that is readily understood by all and may be related to the practical consequence of failing to meet this requirement. Complex multivariate distance based approaches provide a challenge in interpretation of what constitutes a meaningful difference. We suggest that this is a complex topic requiring further discussion.	

Marketed highly variable drugs have been demonstrated to be safe and effective indicating that individual subjects as well as the general patient population receive benefit despite the large day to day fluctuations in their exposure. While the proposed criteria recognize this for Cmax, they do not address the same problem for AUC. Thus, we recommend consideration of a scaled approach to BE criteria (Cmax and AUC) as described in Haidar SH, Makhlouf F, Schuirmann DJ, Hyslop T,We Davit B, Conner D, Yu LX. Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs. AAPS J. 2008 Aug 26. This method avoids unnecessary exposures to subjects in BE studies who receive no therapeutic benefit while adequately ensuring acceptable product performance. Plasma/serum can be used throughout the guidance or a footnote/comment that for plasma also serum may be read.	
In general the guidance lacks any information on how to evaluate the results of a chemical entity displaying double peaks in the concentration time profile.	For immediate release products double peaks is expected to be a rare phenomenon. In the context of this guideline, bioequivalence for immediate release products, Cmax (the highest concentration, regardless if this is reached with the first or second peak) is considered appropriate. No change to the guideline is needed.
The EGA welcomes the release of the draft revision of the bioequivalence guideline as a great step forward. Generally, the presence of greater detail and more flow charts achieves the clarification level which was deemed necessary by both generic medicines companies and assessors. The EGA also welcomes the perspective of a harmonised approach to BCS-biowaivers applications. This approach will certainly limit the degree of variation in interpretation of bioequivalence requirements in Europe. Member states will need to show political will to implement these provisions harmoniously. In spite of this notable progress, the EGA would qualify this guidance document as very demanding in light of the prescriptive requirements it contains and of the number of new acceptance criteria it introduces. In addition, the EGA has identified a number of topics which would still deserve additional clarification or information. The EGA would generally note that, contrary to other initiatives in the world, European regulators are moving in the introduction of additional requirements for steady-state studies in the case of immediate release dosage forms. The EGA is of the opinion that this does not contribute significantly to better proof of bioequivalence. This move must have its roots in an overestimation of the added value of steady-state studies in those cases. Additionally, the guideline is rather extensive and tends to cover numerous topics and issues. The	The present guideline is interpreted differently by different member states with some member states considering bioequivalence as a “quality” issue and are very reluctant e.g. to accept widening of the acceptance criteria based on justification that this does not affect efficacy or safety, while others are more open to this and have a more “clinical relevance” approach. This has lead to a large number of applications being referred to CMDh/CHMP. One aim of the revision of the guideline was to provide more clear guidance with less risk for different interpretation and fewer application procedures leading to CMDh/CHMP referrals. Hence, before the revision was initiated it was agreed between member states to revise the guideline towards a “quality” approach and leave less room for justifications from clinical efficacy and safety perspective. The development of the draft guideline therefore focused on providing recommendations for design and conduct of bioequivalence studies that would assure essentially similar biopharmaceutical quality between test and reference. At the

EGA would require that those chapters which remain general in nature and do not particularly add any new information be removed in order to improve readability. Although in general the requirements seem well defined, the clarity of the text is undermined by the use of non-specific and undefined terms and phrases such as 'markedly high', 'may be acceptable' or 'sufficient'.	same time, the draft guideline was written with the ambition to cover all clinically relevant situations where a simple design evaluating parent compound after single dose administration would potentially not be sufficient to conclude bioequivalence between test and reference products. Hence, the request for e.g. multiple dose studies in certain cases of dose-and time dependent pharmacokinetics or the evaluation of active metabolite that contributes significantly to the efficacy when use of metabolite data may be more sensitive to detect differences between formulations. It has become evident from the comments received that the draft guideline is difficult to interpret and may lead to new situations with different interpretation between industry and regulatory agencies and also between different member states. Hence, there is a clear need for simplification of the guideline. As described in responses to the comments below, a major revision of the guideline has been made, with the ambition that the guideline will be easier to interpret.
There is no precise indication of how the guideline is to be implemented once it has been adopted. As it contains several changes in terms of strategy and approach to demonstrating bioequivalence, it is important to consider the practical aspects of implementation. Will the date of the protocol sign-off or the date of the study be taken into account (ie, study was carried out before or after publication of the new criteria)? This point is particularly important for the generic medicines industry where licensing in or out is common business practice. In order to avoid delays in assessing new or pending applications, clarification as to which guideline should be referred to while the revised guideline is not yet final should be discussed, ie, the guideline in force or the unapproved draft? Formal guidance in this regard should be provided to assessors throughout Europe in order to promote harmonised implementation and to ensure consistency and predictability in registration procedures.	See comment above
A list of SmPC reference terms should be introduced in order to describe more systematically, for example, the need and timing for water intake/restriction, or the food effect, and the definitions of "before", "with" and "after" food, according to the available supportive clinical evidence. This could contribute to optimising study designs and to limiting the unnecessary enrolment of subjects.	These issues are covered by responses to specific comments
The EGA believes that bio-analytical requirements should be addressed specifically, more in depth and, preferably, in a separate guideline. The EGA welcomes the recent news that the EMEA EWP concurs with the need for a separate guideline on bio-analytical method validation. The EGA will	A separate guideline for validation of bianalysis methods is being written.

actively contribute to the drafting process of such a guideline.	
Even if defined in the glossary, the term SPC should preferably be changed to SmPC throughout the text of the guideline.	Agreed.
Even though this guidance' ultimate goal is to clarify some previous rules and requirements and to add some new, some of the included recommendations may be challenging to achieve for the generic industry aiming into EU submissions. Some new items such as the need of submitting ALL studies which it is not clear if this would concern pilot and failed studies as well, what would be the added value of combining Fasted and fed testing conditions within the same study, or the use of on pharmacokinetic parameter (Cmax) of the parent drug along with others for the metabolite (AUC) in case of low parent concentration, etc. would definitely need some clarification as these would open the door to some different interpretation and assessment!	These issues are covered by responses to specific comments
The pharmaceutical products are manufactered in conditions of GMP – **which are inspected and certified**. The bioequivalence trials of those products are realised in GCP conditions, **which are inspected**. So bioanalytical part of bioequivalence trials **must be realised in the same quality conditions according to the GLP Principles which must be inspected and certified**.	These issues are covered by responses to specific comments
My general comment concerns the evaluation of tmax. On lines 45-46, it is said that Cmax, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, tmax, are parameters that are influenced by absorption rate. This is in line with all the previous texts on bioequivalence. However, on lines 504-505, it is said that a non-pametric analysis is not acceptable. Indeed, the statistical analysis of tmax, while always considered as relevant parameter for the rate of absorption, has almost disappeared from the generic files because of its statistical analysis. I do not understand why non parametric analysis is not acceptable but I take this fact as it is. This probably explains the possibility to use partial AUC (lines 313-317) instead of tmax for products where rapid absorption is of importance. To me, this is a false "good idea" because the variability attached with partial AUC will likely prevent from obtaining 90% CI contained within the regulatory limits, e.g. 80.00 – 125.00%. My suggestion could a decision tree (not drawn here) based on Cmax and tmax : a) if Cmax bioequivalent within the acceptance limits and tmax not different with a non parametric test (sorry, I maintain the use of such test for tmax), then we can accept the bioequivalence for the rate of absorption b) if Cmax bioequivalent within the acceptance limits and statistical difference on tmax, then consider to test Cmax of the reference versus the concentration of the Test observed at the corresponding tmax. For illustration, if for a subject Cmax of the Reference occurs at time 2 h post dose (so tmax = 2h), then consider for the Test, the concentration obtained at 2 h post dose (even if 2h is not the tmax of the Test for this subject). So, if Cmax Rf is bioequivalent to Ctest at Tmax Ref, then we can accept the bioequivalence for the rate of absorption. If Cmax Ref not bioequivalent with C at Tmax Ref, case-by-case discussion.	These issues are generally covered by responses to specific comments. The suggested decision tree for Cmax and tmax is interesting but has not been implemented. As an evaluation of tmax is only needed in rare situations, the proposed decision tree is not considered needed.

c) if Cmax not bioequivalent and tmax statistically different, then we can reject the bioequivalence for the rate of absorption d) if Cmax not bioequivalent and tmax not statistically different, case-by-case decision. This approach has still the inconvenient of the case-by-case decision but it keeps the inclusion of tmax in the assessment, without the use of non parametric confidence intervals. I am convinced that this rule should perform better than the use of partial AUC.	
On page 24/29 it is stated that the BCS-based Biowaiver system is not applicable to orodispersible formulations. This blanket approach to the ineligibility of orodispersible formulations is not logical. Orodispersible formulations are designed to release their drug substance more rapidly than a conventional release tablet, yet it is possible that a biowaiver could be accepted for a conventional release, film-coated tablet whilst an applicant could not apply for a biowaiver for a non-buccally absorbed orodispersible tablet containing the same drug substance.	This is covered by responses to specific comments
The overall impression of the document is that it tightens the requirements for bioequivalence studies to an extent where huge additional efforts have to be undertaken by generic companies to comply with sometimes over-discriminating bioequivalence criteria compared to clinical parameters. This development is in contrast to the situation in other parts around the world and is hardly understandable considering the low incidence of clinical issues with generic products in the previous years. Even if quality is given a higher priority than clinical relevance in the current draft guideline, the main task of a bioequivalence study remains to demonstrate a similar efficacy and safety profile compared to the originator product. The topics of our main concern in the draft guidance are the planned restrictions in the extension of the acceptance range, restrictions in the elimination of subjects with anomalous values, the introduction of a new parameter (partial AUC) for evaluation in some cases, and the need for additional multiple dose studies.	See comment above.
This guideline is an improvement on the current document and makes many issues clearer. However, there are several issues that still lack clarity and these need to be addressed before the document is finalised.	
Conditions and expectations for the determination of bioequivalence should depend on its principal purpose. The conditions and procedures could be different if the primary goal is either quality control or to serve as a therapeutic surrogate. A freshly revised guideline would provide an outstanding opportunity to clarify definitions and make distinctions between the corresponding, relevant approaches.	The guideline has been updated and is hopefully now more clear on this issue.
This new guideline represents a significant step forward in the evaluation of bioequivalence of drug products taking into consideration well accepted principles and recent scientific findings into this regulatory document. It is also appreciated that the document focuses solely on bioequivalence and separates these from a general discussion of bioavailability as in the previous Note for Guidance	

1. In situations where the drug is therapeutically administered with a PK enhancer (eg ritonavir) and a steady-state BE study is required, the PK enhancer should also be administered similarly to the situation where food is required. 2. Section 4.1.5 Parent compound or metabolites. This section could perhaps be written more simply 3. Section 4.1.7 Chemical analysis. The amount of detail of automatically integrated versus manually integrated chromatograms (lines 478-481) requested to be discussed appears appropriate for raw data records but somewhat excessive for the study report.	Comment 1: The guideline now include a section on medicinal products which according to the originator SPC are to be used explicitly in combination with another product. Steady state studies are no longer required so that part of the comment is now irrelevant. Comment 2 and 3. These issues are covered by responses to specific comments
There is, at least, one active parent compound that "*has low plasma concentrations, be quickly eliminated and have high variability, resulting in difficulties in demonstrating bioequivalence for the parent compound in a reasonably sized bioequivalence study"*, while exposure to its **inactive** metabolite "*is very much higher"* and easily measurable. Attending to this draft that, under certain circumstances, allows evaluation of bioequivalence just with main active metabolites, there are no chances to perform a bioequivalence study with this kind of drugs. In order to make possible bioequivalence studies with drugs that may show this pharmacokinetic profile, we suggest the change shown below.	This is covered by the revised recommendations in section 4.1.5.
The new document is intended to replace the current NfG on the Investigation of Bioavailability and Bioequivalence. However, the new document does not cover the topic "bioavailability".	The guideline focuses on bioequivalence. Recommendations for e.g. suprabioavailability may be included in the PK EWP position paper (EMEA/618604/2008).
Furthermore, the current NfG on the Investigation of Bioavailability and Bioequivalence includes a number of definitions (e.g. pharmaceutical equivalence, essential similarity of products, etc.) which are missing in the new draft. Will these definitions be included in another guideline?	The guideline has been revised to include some additional definitions
The draft guideline deals only with average bioequivalence. Population and individual bioequivalence approaches are not mentioned anywhere, therefore it is not clear as to whether these approaches are acceptable.	The average bioequivalence approach is the recommended method to establish bioequivalence.
The FIP Special Interest Group welcomes a specific guideline on the evaluation of bioequivalence of drug products, disconnecting this topic from the guidance on bioavailability. However the draft Guideline restricts the applicability of the BCS concept significantly compared to the present Note for Guidance on BA/BE, which itself was largely in line with FDA`s Guidance: Waiver of In Vivo BA and BE etc. As these two Guidances were issued in 2001 and 2000, respectively, the present concepts of BCS and biowaivers have already been in use for nearly a decade. Up to now, not one single example has been presented where a drug product, approved under the present regulations using a biowaiver approach, later proved to be bio*in*equivalent. Hence a more restrictive approach to biowaiving lacks scientific justification.	This is covered by responses to specific comments

A major problem is based on the requirement of testing bioequivalence with the highest strength and dose unless the drug substance is highly soluble. If the dose is not tolerated by healthy volunteers patients should be included. Patients need the medication so a steady state study must be done in certain cases. Steady state studies are less discriminatory than single dose studies so the value of doing the highest dose is lost. Hence: Will performing a steady state study in patients really reduce the consumer risk when compared to doing a single dose study with a lower strength? It would be helpful to clarify the position of the competent authorities in this case.	The comment is acknowledged. The revised guideline focuses on strength and not dose. In cases where evaluation of the highest strength is recommended and this is not tolerated in healthy volunteers, the highest tolerated strength may be selected.
The efforts revising the current guideline following new developments since the Q&A document are highly appreciated.	
AESGP represents the manufacturers of non-prescription medicines in Europe. AESGP welcomes this revision and consider the guideline to be well written. In particular we welcome the principle of applying 'scientific reasoning' to guide the choice of design, dose, analysis and acceptance criteria. We would recommend further details be added on the applicability of the bioequivalence scientific principles to formulation development versus generic application. We have the following general comments to make: 1. There seems to be an apparent constriction in dissolution criteria applied to biowaiver applications. In the original guidance note (CPMP/EWP/QWP/1401/98) it was stated that "in case of exemption from BE studies, in vitro data should demonstrate the similarity of dissolution profile"… and "in cases where more than 85% of the active substance are dissolved within 15 minutes the similarity of dissolution profiles may be accepted as demonstrated" i.e. without further mathematical testing. The current draft guidance indicates that BCS based biowaivers will only be accepted for very rapidly dissolving drug products (lines 917 & 923), i.e. > 85% dissolved within 15 minutes. This is considered overly conservative with respect to scientific understanding of pharmacokinetics and typical gastric emptying times. Consideration should be given for biowaiver applications for drug products with rapid dissolution where ≥85% dissolution occurs in 30 minutes (as discussed in lines 792 through 797). In these cases mathematical testing should be performed to demonstrate similarity in dissolution profiles. 2. In addition to using *in vivo* methods to claim a complete absorption, validated *in vitro* methods should also be considered as acceptable to claim high permeability/complete absorption.	Point 1 and 2 are covered in specific comments. Point 3 is clarified in the revised guideline, App. III.

3. Guidance addressing the instability of test compounds in the GI tract when applying biowaiver should also be included.	
The guideline should introduce the requirement of traceable calibration of equipment to national or international standard of measurement, where it is applicable. The comparability of results is only achieved if the laboratory conducting the analysis has same base for measurement standard. This is practically achieved through traceable calibration of measuring equipment.	This is a basic prerequisite of state-of-the-art manufacturing and testing and beyond the scope of this guideline
The guidelines should consider to introduce the term "measurement uncertainty" instead of precision and fit for purpose/true value instead of accuracy. The term precision and accuracy in terms of physical measurement process carry very little significance. According to ISO the use of term measurement uncertainty give useful information for comparison of results. Due to random error it is not possible to achieve the "perfect true value". The true value of any result lies within the given range of uncertainty at quoted significance level.	The terms 'precision' and 'accuracy' are general well known and widely accepted terms, and are in line with those used in for instance in the FDA guidance. As such these terms will be used also in the to be written Guideline for validation of bioanalysis methods.
A chapter including the definition of all the specific wording used in this guideline should be added e.g. reference product, test product, comparative product, bioavailability, bioequivalence… etc. "active substance" should be defined in a consistent way with lines 60 to 62 (introduction) and lines 933 to 938 (Appendix III).	Some additional definitions have been added. However, it is not agreed that all these well known words need to be defined.
Is dissolution % (> 85% within 15 min.) applicable to individual values or mean value? Would the guidance be clearer using the Q value at level 2 (Q ≥ 80% within 15min.) as in Ph. Eur. method 2.9.3.?	The value refers to the mean however also considering the variability and it is not meant to be a two stage test procedure.
Studies planned and performed prior to the implementation of the final version of the revised guideline should remain valid for regulatory purposes.	See response above
We would like to take to opportunity to highlight potential for harmonisation of BE requirements with other regions and remark that there are some significant differences as compared for example to the current FDA guidance. We would encourage a transatlantic dialogue and potential alignment based on scientific principles.	The comment has been taken into account in the revision of the guideline.
1. This draft guideline is somewhat poorly worded. The draft is at times too wordy without conveying pertinent information in specific terms. The descriptions seem to be vague and in several places lack clarity. It is likely to confuse the user of this guideline, thus defeating its intended purpose. 2. The organization of this document needs some modifications for better understanding of its contents. For example: under section 4.1, special drug class, such as narrow therapeutic index drugs and highly variable drugs and drug products should be separated from the general description of Design, Conduct, and Evaluation of bioequivalence study. It would emphasize on the special consideration for these drugs/drug products under different subheadings.	Some of these comments have been taken into account in the revision of the guideline

3. Different factors and tests for bioequivalence assessment are combined together in many sections instead of making discussion and recommendation for each factor and each test discrete for better understanding of the user of this guideline. 4. This guideline recommends that the sponsor justify several aspects of the bioequivalence study. Different sponsors of the same product may justify in way that might include different approaches. That is inappropriate and would cause a lot of confusion. 5. In summary, this document is written in a manner where the important issues in bioequivalence assessment might get lost. In our opinion it should be revised.	
The term "plasma" is used throughout the guideline although, depending on the active substance, measurement of drug concentrations in another matrix, e.g. serum or whole blood, may also be feasible or even more appropriate.	The comment has been taken into account in the revision of the guideline.
The guideline does not differentiate between drug substances intended for short-term use and those for long-term treatment. The requirement for a multiple-dose study in addition to the single-dose study (cf section 4.1.1) might be of minor clinical relevance for drugs that are usually used only for a short period of time (e.g. 3 days) even if the drug's pharmacokinetics are not linear as steady-state will not be reached in clinical practice. In this case, a single-dose study should be sufficient to ensure the generic product and the originator product are interchangeable.	The comment has been taken into account in the revision of the guideline. See also responses to specific comments on line 153-159.

SPECIFIC COMMENTS ON TEXT			
EXECUTIVE SUMMARY (line 33-36)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Title & Scope	We recommend greater clarity in the title of the guideline where this is currently no reference. Specifically, it may be helpful to specify in the title that the guidance applies to Oral Immediate Release drug products.	Add reference to Oral Immediate Release drug products with systemic action to the Title of the document. Add language which specifies whether this guidance applies equally to of both low and high molecular weight pharmacotherapeutics	The scope clarifies that the guideline applies to immediate release formulations with systemic action (not only oral formulations) and that it does not apply to biological products.

	Also, could you provide clarification whether this guidance applies equally to of both low and high molecular weight pharmacotherapeutics?		

1 INTRODUCTION (line 37-80)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
1. Intro-duction	To improve clarity of section 1/Introduction, we suggest subdividing this section into two distinct subsections “1.1 Background” (lines 37 to 49) and “1.2 Basis for Approval of Bioequivalence” (lines 50 to 80) and other suitable subtitles: “1.2.1 Generic Applications” (lines 53 to 66), “1.2.2 Hybrid Applications” (lines 67 to 69), “1.2.3 Applications for Extensions” (lines 70 to 72), “1.2.4 Applications for fixed-dose combination products“ (paragraph to be added - see rationale below), 1.2.4 Variation Applications” (lines 73 to 74), and “1.2.5 Formulation Development for New Chemical Entities” (lines 75 to 80).	For clarity, please consider subdividing section 1/Introduction.	Partly agreed. The structure of the introduction has been revised and now includes different sub-headings.
38	We note that the definition of bioequivalence no longer includes a requirement for demonstration that the new product is either pharmaceutically equivalent or a pharmaceutical alternative to the reference product. Please clarify why these changes have		The definition of bioequivalence in the introduction has been revised.

	been made.		
Lines 38-40	"Two medicinal products containing the same active substance are considered bioequivalent if their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits." If two concentration vs. time curves are superimposable, we don't need to measure rate and extent of absorption separately.	Delete "**rate and extent**" from line 39	The rate and extent of bioavailability is important and we want to emphasise that. If the rate and extent of absorption are the same the concentration vs time profiles will be superimposable for the two tested products. No change made.
Line 39	Section 5.5 in the current NfG on the Investigation of Bioavailability and Bioequivalence discusses how two medicinal products can be bioequivalent in spite of different molar doses if the test formulation is suprabioavailable. The current guidance leaves out this possibility. We agree with the omission, but would request that that text would state that the concept of suprabioavailability is 'out of scope' of the current guidance.	Please state that the concept of suprabioavailability is 'out of scope' of the current guidance and refer the reader to an appropriate different guidance to discuss the recommended approach for suprabioavailability?	Recommendations for suprabioavailability may be included in the PK EWP position paper (EMEA/618604/2008).
39, 1	The previous version of this guideline contained a paragraph on suprabioavailability which is not part of this revised draft version. Of note, drugs are marketed for which a second formulation was approved which demonstrated higher bioavailability ('suprabioavailability') in comparison to the initially approved formulation e.g. glibenclamide. In general, higher bioavailability of an oral formulation translates into reduced variability and less pronounced effects of concomitant	It is proposed that the respective section 5.5 in the current NfG on the Investigation of Bioavailability and Bioequivalence should be maintained in the new draft or modified in order to give guidance for the clinical development of suprabioavailable formulations. Given the above, the statement *'after administration in the same molar dose'* should be deleted or modified to take into account suprabioavailable formulations.	Recommendations for suprabioavailability may be included in the PK EWP position paper (EMEA/618604/2008). The definition of bioequivalence including *'after administration in the same molar dose'* is the same as in FDA, Canada and WHO guidelines and has not been changed.

	food. It would be appreciated if guidance could be given for this situation i.e. under which circumstances a bioequivalence study can serve as basis for approval of a suprabioavailable formulation containing a different molar dose as compared to the reference.		
Line 42 Minor Comment	Please change following sentence: "In bioequivalence studies, the plasma concentration time curve…"	Suggested rewording: "In bioequivalence studies, the plasma, serum or blood concentration time curve…"	The text has been revised.
Lines 42-46	"In bioequivalence studies, the plasma concentration time curve is used to assess the rate and extent of absorption. Meaningful pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products. AUC, the area under the concentration time curve, reflects the extent of exposure. C_{max}, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, t_{max}, are parameters that are influenced by absorption rate." As above, if two concentration vs. time curves are superimposable, all direct and indirect parameters are equal.	**In bioequivalence studies, the plasma concentration time curve is used to assess the bioavailability. Two medicinal products are bioequivalent, i.e., they have the same bioavailability, if their plasma concentration curves are almost superimposable. In other words, the "distance" between the two *c*(*t*) curves must be smaller than a preset value**	The concept is interesting. However, this is not a validated method with a defined value for an acceptable difference. No change made.
1. Intro-duction Line 50	"*The concept of bioequivalence forms the basis for approval of generic application, (...)"* It is an important prerequisite for approval of generic applications, but not the only one.	The sentence should be reworded avoiding the simplistic impression that bioequivalence is more or less the only prerequisite for approval of generic application. Perhaps, "The concept of bioequivalence plays an important role in approval of a generic application, (…)"	Agreed

Line 50-80	The applicability of the scientific principles of bioequivalence to extension, variation, formulation development or generic application should be made clear in each section of the guidance	We suggest that the various paragraphs of the introduction be differentiated and titled (e.g. paragraph from line 53-66 "generic applications", paragraph from line 67-69 "hybrid applications", etc.) and that the same concept be applied to the remainder of the guidance	Section 1 has been revised. The scope of the guideline is to specify the requirements for design, conduct and analysis of bioequivalence studies. It is out of the scope of this guideline to provide specific recommendations on all situations when bioequivalence studies may be applicable. When there is a need for in vivo bioequivalence studies to support different applications, e.g. variations, fixed-dose combinations, extensions and hybrid applications that are based exclusively in bioequivalence demonstration, the bioequivalence study should be conducted according to this guideline. The recommendations for design and conduct of bioequivalence studies given in this guideline can also be applied to comparative bioavailability studies that may be used in support of e.g. hybrid or extension applications or applications for NCEs where also additional clinical data are available. It is out of scope of this guideline to provide recommendations on the extent of additional data that may be needed to support any deviation from bioequivalence that may be found in comparative bioavailability studies.
1. Intro-duction Line 51	The concept of bioequivalence may also be applicable to fixed-dose combinations application as mentioned in section 3/Legal basis.	Please change as follows: "…, but it may also be applicable to hydrid application, extensions, **fixed-dose combinations** and variations applications,(…)"	Agreed
Line 51	"Fixed combination" referred to in section 3 is missing here	Add 'fixed combination'	Agreed
Line 51 –	"hybrid application" should be better explained		It is out of the scope of this guideline to define "hybrid applications". Additional information can be found in Directive 2001/83/EC, Article 10(3) and in Notice to Applicants Chapter 1.
Line 53 – 66:	This paragraph describes too many concepts. The reader is likely to be confused. Each concept should be		Not agreed. This paragraph describes the definition of generic product according to Directive 2001/83/EC, Article 10(2)b. To provide the full definition of a

	properly described.		generic product all aspects needs to be covered.
Intro-duction Line 54	We suggest including a clearer description/definition of "biopharmaceutic quality" or change to an alternative term.	We would suggest suitable alternative wording such as "rate and extent of systemic exposure"	This is a widely used scientific term and does not need to be changed or explained it in more detail
60	Re the statement: "By definition it is considered that different salts, esters, ethers, isomers, mixture of isomers, complexes, derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy." There are several examples of compounds currently marketed for which the safety and efficacy of different isomers or different salts are clinically significantly different. This statement suggests that the default assumption will be that there are no differences between these different active substances. How will this approach ensure that patient safety and clinical efficacy are maintained?		The statement is in line with the definition of a generic product in Directive 2001/83/EC, Article 10(2)b, where additional information regarding the need for pre-clinical tests and clinical trials is given.
Line 60	Please clarify if "same pharmaceutical form" can be claimed if there is a different crystal form between test and reference products. If considered different forms, please indicate what requirements are needed to establish BE of products that are not considered "the same pharmaceutical form".		The same pharmaceutical form is referring to the formulation and may be claimed if the API has different crystal forms. However, this could have little effects in case of highly soluble APIs but is relevant in case of APIs with low solubility.
Lines 63-64	Oral solutions, tablets and capsules can be considered one and the same. This is because all achieve systemic	Add sentence in line 64, after…….to be one and the same formulation: "This does not apply to orodispersible or sublingual formulations, where	This is clarified in Appendix II and III

	exposure via GI tract absorption. Sublingual formulations are absorbed primarily via the buccal mucosa avoiding the first pass effect and therefore should NOT be considered one and the same as other oral presentations.	absorption is via the buccal mucosa and not the GI tract, where there is a significant first pass effect.	
63	The statement that "…various immediate-release oral pharmaceutical forms are considered to be one and the same pharmaceutical form." is not consistent with subsequently stated BE requirements, including PK studies for immediate release oral forms such as orally dispersible tablets.	The statement on line 68 should be consistent with the BE requirements subsequently listed in the guidance document.	This is clarified in Appendix II and III
Line 63-64	It should be made clear that sublingual or orodispersible formulations are distinct from oral formulations (e.g. solutions, tablets, capsules, etc)	We suggest adding "this does not apply to orodispersible / sublingual formulations which absorbed through the buccal mucosa"	This is clarified in Appendix II and III
Intro-duction Line 66	We would recommend that a reference for the definition of the term "biowaiver" is included	For example, "BCS-based Biowaiver (Appendix III)"	The text has been revised based on this and other comments.
Lines 67-69	Multiple companies asked for additional detail/ clarification around the term "Hybrid application".	Please add additional detail around what would be needed to prove BE in a hybrid application. For example, could such an application include a BE study in animals + dissolution profiles?	Although bioequivalence studies may be part of a hybrid application, additional details on requirements for Hybrid applications is out of the scope of the current guideline which focuses on the design and conduct of bioequivalence studies.
Line 67-80:	Application of bioequivalence concept to different situation and conditions could be described with clarity or presented in a tabular form.		Not agreed.
Line 71	Clarify the sentence "Also applications for extensions…often need support of bioequivalence in order to bridge…."	Modify text to "Also applications for extensions…often need support of bioequivalence <u>studies</u> in order to bridge…."	The paragraph has been changed based on other comments

Lines 72-73	We suggest adding a specific paragraph on fixed-dose combinations application as was included for the other applications (hybrid, extensions, variations).	Please change to the following: "Also applications for extensions such as additional dosage forms, new strengths, new routes of administration often need support of bioequivalence in order to bridge data from the authorized reference medicinal product. Some fixed-dose combinations applications also need bioequivalence studies in order to bridge data from the authorized mono-component reference products or originator fixed-dose combination product."	Fixed dose combinations is now mentioned in this section
Lines 73-74 Paragraph 1	***"Variations for a change in composition or for significant manufacturing changes which may affect drug bioavailability may also require support of bioequivalence studies."*** As variations are often in support of a global regulatory submission, it is recommended that EMEA and other authorities reach consensus on what is defined as a significant change during up-scaling or post approval. Further, To clarify which type of pharmaceutical modifications is concerned by a new bioequivalence study, we suggest to add a cross-reference to the guideline on dossier requirements for type IA and IB notifications.	Please add examples, which could help to clarify what is considered as a significant or insignificant change in composition or in manufacturing. Please change as follows: "Variations for a change in composition or for significant manufacturing changes which may affect drug availability may also require support of bioequivalence studies **(see also guideline on dossier requirements for type IA and IB notifications).**"	This paragraph has been removed. Reference to the variations regulation is given in section 3.
73	Re manufacturing or formulation changes that may require BE studies.	Please consider adopting a more defined approach.	This paragraph has been removed from the introduction. See also comments on section 4.3

1. Line 73:	"Variations for a change in composition or for significant manufacturing changes" should be defined in more detail. Could the corresponding SUPAC-IR guidance be used in this case?	Clarification on section 4.3. Variation is required.	This paragraph has been removed from the introduction. See also comments on section 4.3
Line 75-77, last §, page 3/29	"During development of new chemical entity (NCE), the principles of bioequivalence may be applied in order to bridge data between different formulations e.g. between a formulation used in the pivotal clinical studies and the to-be-marketed formulation." --> To what extend is it necessary to apply the principles of bioequivalence? For example, if various immediate-release oral pharmaceutical forms that are not eligible for BCS-based biowaivers are successively used during the development of a NCE, are bioequivalence studies mandatory or recommended to bridge data from phase I, phase II and phase III studies together? Please specify the requirements during development of a NCE.		Bioequivalence studies are needed if there has been a change between the formulation used in phase III and the final marketing formulation which may affect rate or extent of absorption. Relative bioavailability studies (or comparative bioavailability studies) are recommended between different formulations used during phase I, II and III. See also comment below.
1. Intro-duction Lines 77-78	Multiple companies requested that it be clarified whether the "*wider acceptance limits*" apply specifically to development phase (i.e. to bridge pivotal and/or supportive phase II with pivotal phase III studies)? More generally, what is the requirement for	A description of the rules for widening the acceptance interval in the case of bridging studies should be added (if the rules for bridging studies differ from the general rules given in section 4.1.10). Provide clarification in the text that, if accepted, the wider limits apply to only post-marketing changes or to both post-marketing	This paragraph has been deleted. Section 1 has been revised. The only option for widening acceptance criteria for generics and for post-marketing changes (for all products) is that described in section 4.1.10 (high variability drug products). Regarding comparative bioavailability studies during drug development for an NCE, there is no requirement

	bridging phase II and phase III studies during development to support filing? If a wider acceptance range is accepted during development would this imply automatically that it will apply for post-marketing changes or generics the same way?	changes and generics.	for demonstration of bioequivalence between phase II and phase III formulations. It is assumed that any difference in rate or extent of absorption between these formulations is taken into account in the design of the phase III studies. The clinical relevance of any differences in exposure between formulations used in phase I, II and III studies should be discussed in applications for NCEs in Module 2.5 and 2.7.1 and taken into account in the assessment of pharmacokinetic data in Module 2.7.2. See also comment above.
75-78, 1. Intro-duction	Possibility of widening of the acceptance limits the scope inclusively to bridge data between different formulations during new chemical entity development and in complete applications. This excludes other situations where data are available (including literature data) to support wider acceptance limits such as line extensions and hybrid applications referred to in lines 67-72.	The paragraph should be modified to address all situations when wider acceptance limits can be applied and appropriate supportive data is available.	This paragraph has been deleted. Wider acceptance limits than those defined in this guideline for bioequivalence studies may in certain cases be used in comparative bioavailability studies submitted in support of e.g. extensions or hybrid applications provided that this can be supported by other clinical data (published or in-house). However, it is out of scope of this guideline to address all situations when this may be applicable.
75-80 1. Intro-duction	If wider acceptance limits are acceptable in a complete application (ie, originator product) based on data submitted, this should also be possible with a generic medicine application if sufficient evidence is provided (eg, in literature). It does not appear justified to give the option of a wider acceptance range only in cases of complete applications as other types of applications are allowed to refer to these data and/or may contain appropriate supportive evidence for doing so, eg, in cases where C(max) lacks clinical relevance.	CHANGE: Please delete paragraph or expand the possibility of wider acceptance ranges for applications containing appropriate supporting evidence.	This paragraph has been deleted. The only option for widening acceptance criteria in bioequivalence studies (regardless of application type) is that described in section 4.1.10 (high variability drug products).

75 to 80	A widening of the BE limits is acceptable when the widening will not result in clinically relevant consequences with respect to safety and efficacy of the drug product. This holds true e.g. when an originator's formulation used in the pivotal studies and the to-be-marketed formulation are not identical. In this very case the originator may be in a position to justify the widening of the acceptance range based on clinical data obtained in a few thousands of patients. This same principle should also be applied when the equivalence between a generic and an originator drug product is tested.	The first sentence of this paragraph should be deleted and –in line with the definition of bioequivalence in lines 40 – 41 the second sentence should read "Acceptance limits for bioequivalence decision making should be based on data adequately addressing the clinical relevance from both a safety and efficacy perspective." Alternatively this sentence could be inserted in line 41.	Not agreed. The paragraph has been deleted. The only option for widening acceptance criteria in bioequivalence studies (regardless of application type) is that described in section 4.1.10 (high variability drug products).
75 – 80, 1	It is mentioned that wider acceptance intervals might be used for bridging studies between different formulations. There is no reference to this topic in the rest of the document, with the exception of some general rules (section 4.1.10) for widening the acceptance interval. Will this process with bridging studies be identical for BE studies with generic products?	A description of the rules for widening the acceptance interval in the case of bridging studies should be added (if the rules for bridging studies differ from the general rules given in section 4.1.10).	The paragraph has been deleted. See also comments above.
1. Intro-duction Lines 77-78	Multiple companies requested that it be clarified whether the "*wider acceptance limits*" apply specifically to development phase (i.e. to bridge pivotal and/or supportive phase II with pivotal phase III studies)? More generally, what is the requirement for bridging phase II and phase III studies	A description of the rules for widening the acceptance interval in the case of bridging studies should be added (if the rules for bridging studies differ from the general rules given in section 4.1.10). Provide clarification in the text that, if accepted, the wider limits apply to only post-marketing changes or to both post-marketing	This paragraph has been deleted. The only option for widening acceptance criteria in bioequivalence studies (regardless of application type) is that described in section 4.1.10 (high variability drug products). See also comments above on comparative bioavailability studies.

	during development to support filing? If a wider acceptance range is accepted during development would this imply automatically that it will apply for post-marketing changes or generics the same way?	changes and generics.	
77-80, 1.	For demonstration of bioequivalence, the same criteria should apply for generic and for originator products. Therefore, widening of the acceptance range for Cmax should be allowed for both generic and originator products under the same circumstances. In particular, it would be unfair if an originator application solely based on a bioequivalence study with widened acceptance range would be approvable, but a comparable generic application would not be approvable. E.g. if an originator develops an ODT to an existing marketing authorisation for a tablet and solely performs a biostudy, the same criteria should apply as for a generic company developing an ODT with a biostudy versus the respective tablet.	Please delete: "In such situations however, wider acceptance limits may be acceptable if these are justified based on data provided with a complete application, adequately addressing the clinical relevance of the widening from both a safety and efficacy perspective."	In this specific situation bioequivalence should be demonstrated between the generic ODT and the originator ODT. Hence, widening of the acceptance criteria for the generic for the reasons put forward is not applicable. See also comment above.

2 SCOPE (line 81-93)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Line 86	It needs to be clarified whether this guidance is applicable for both New Chemical Entities (NCEs) and New Biological Entities (NBEs)	Please state explicitly that this guidance is not applicable for New Biological Entities.	The guideline does not apply to New Biological Entities. This has been clarified

Line 87	It would be helpful to provide reference linking to key guideline for biosimilar products		There are a number of comparability guidelines, which cannot be listed in the bioequivalence guideline. The guidelines can be found at http://www. emea.europa. eu/htms/human /humanguidelines /multidiscipline.htm
Lines 89-91	Where bioequivalence cannot be demonstrated using plasma drug concentrations, reference to other endpoints may be needed, however with a clear comment that this is outside the scope of this guideline (and reference to other specific guidelines). Situations may arise where there are no other specific guidelines, it may therefore be helpful to retain some of the wording from the previous guideline version (July 2001) noting that other models etc. may be used in exceptional circumstances provided they are appropriately justified/validated (rather than a blanket exclusion).		Not agreed. The former guideline does not contain any important additional information regarding this that needs to be included in the new guideline.
Lines 92-93	We found the sentence out of place in this scientific guidance	Delete this sentence	It is agreed that this may seem to be out of place. However, as this issue is important for many generic companies it is important to clarify that generic substitution is a separate issue which is subject to national regulation, and is not automatically connected to the approval for marketing authorisation.

3 LEGAL BASIS (line 94-122)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Line 100 to 115 MINOR COMMENT	ICH E9 "Statistical Principles for Clinical Trials" is missing in the list of reference guidelines	Suggest to add ICH E9 in the list of reference guidelines	Agreed.

4. MAIN GUIDELINE TEXT			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
4.1 Design, conduct and evaluation of bioequivalence studies (line 125-144)			
128-133 4.1 Design, conduct and evaluation of bioequivalence studies	The definition of "comparable salts" is not provided. The current wording in the draft guideline is ambiguous and open to interpretation.	CLARIFICATION: Please provide a definition or examples to illustrate what is meant by the expression "comparable salt".	This paragraph has been removed. A clarification on comparable salt can be found in Appendix III.
Line 131	Multiple companies thought that the term 'comparable salts' was ambiguous. Comparable salts could be different salts providing the same rate of solubility or at least comply to the same dissolution limits. Therefore, if a salt form within the same solubility classification with comparable dissolution is presented in a test product the waiver of a BE study should also be justifiable.	We recommend a change to the text to read "However, when the active substance in test and reference products are identical or contain salt forms within the same solubility classification with comparable dissolution, in vivo bioequivalence studies may, in some situations, not be required as described in Appendix II…"	This paragraph has been removed. A clarification on comparable salt can be found in Appendix III.
Line 131	What is meant by comparable salts?	Please specify in more detail. Examples may be helpful.	This paragraph has been removed. A clarification on comparable salt can be found in Appendix III.
Lines 134-141:	Generally the sponsor should be given the option to decide on the approach to conduct bioequivalence study on a drug product with adequate rationale. However it should be considered the responsibility of the regulatory authority to recommend the approach in certain cases. There are special drug products such as cytotoxic drugs and other complex drug that would require special considerations.		It is agreed that there are specific cases such as cytotoxic drugs, where a different design than the standard is needed. General information regarding this is given in section 4.1.3. See also response to comment on section 4.1.3, line 247-249 below.

Lines 134-141	For many low solubility drugs, differences in the particle size range can markedly affect both dissolution rate and bioavailability. There should be a reference to this at this point.	Provide clarification in text.	This is well known and also covered e.g. by the variation regulation. Such a statement is consider to be too detailed in this context
4. Line 139	Low soluble drug substances are now defined as all that are not highly soluble. Could an intermediate situation be defined where the solubility characteristics allow performing studies with lower strengths for volunteer safety reasons if the pharmacokinetics are linear? For example, as implied by Yazdanian et al, 2004, an acidic drug shows high solubility at pHs > 5 for the highest strength and dose and is rapidly dissolving in this context. It cannot be classified as highly soluble because at low pHs the highest strength and dose would not dissolve easily. However, the solubility characteristics cannot be considered low or critical for bioavailability since it is unlikely that the highest dose will have a different bioavailability than the lowest. In these cases could the bioequivalence study be performed with a dose tolerable to healthy volunteers even though the product is not highly soluble?	The company asks for an intermediate situation of the solubility characteristics.	A definition of intermediate solubility as proposed has not been made. See also comments and changes to section 4.1.6.
142 4.1 Design, conduct and evaluation of bioequivalence studies	Clarification should be provided as to the meaning of "all studies". Our understanding is as follows: bioequivalence studies carried out on the same formulation, manufactured according to the same manufacturing process, and supporting the European registration of a medicinal product should be presented in the dossier, regardless of the outcome of the study. Two medicinal products are considered different if one is derived from the other following a reformulation step in the pharmaceutical development process. Studies against non-EU reference products usually do not support a European registration and should therefore not have to be submitted. An outline of studies carried out should serve the transparency purpose sought here. A comprehensive set of data would remain	CLARIFICATION: Please clarify the meaning of "all studies". CLARIFICATION:	It is correct that "all studies" applies to bioequivalence studies carried out on the same formulation, manufactured according to the same manufacturing process, and supporting the European registration of a medicinal product. These studies should be presented in the dossier, regardless of the outcome of the study. Studies against non-EU reference products should not be submitted. Study reports synopses of bioequivalence or comparative

	available on file.	Please specify that a synopsis of the relevant studies would be sufficient.	bioavailability studies conducted during formulation development should also be provided.
Lines 143-144	It is stated "*All bioequivalence studies comparing the product applied for with the reference product of interest must be submitted.*" Could you please clarify the wording "*the reference product of interest*" (or use another appropriate term) and precise which bioequivalence studies have to be submitted: - Do we have to submit all bioequivalence studies performed with the test product, even local bioequivalence studies performed against local comparator products? - Do we have to submit all bioequivalence studies performed in European countries whatever the chosen reference product? - Do we have to submit only bioequivalence studies performed with the same reference product (same dosage form, same formulation and same manufacturer) as the one used for the European registration application? Do we have to submit all previous bioequivalence studies performed on the test product even if changes have been done during the product development (change in formulation, change in manufacture…)	To clarify the wording "*the reference product of interest*" and to add in the proposed annex-glossary.	See comment above. The text has been revised.
143	The guidance states that "*The clinical overview of an application for marketing authorisation should list all studies carried out with the product applied for.*" However, there are cases when studies carried out are of little relevance to the submission and it could become cumbersome to include all studies that are not pertinent to the global submission, such as pilot studies.	"*The clinical overview of an application for marketing authorisation should list **all relevant** studies carried out with the product applied for. **All relevant** bioequivalence studies comparing the product applied for with the reference product of interest must be submitted."*	Agreed. The text has been revised based on this and other comments
4.1 Line 143	All bioequivalence studies comparing the product applied for with the reference product of interest must be submitted. The company considers that the definition of the "product applied for" refers to the drug product as intended to be marketed (final formulation).	Please refine the meaning of "product applied for".	The text has been revised, see also comment above.

	Should these studies be submitted as a summary in the pharmaceutical development section or as a full report as part of module 5?	This needs to be clarified.	
Lines 143-144	It is stated that "*All bioequivalence studies comparing the product applied for with the reference product of interest must be submitted*."	Please clarify "reference product of interest" and add a definition	Agreed. The text has been revised
Line 144	Include reference to CTD section Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods".	Add a sentence at the end of the paragraph "The general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and in vitro dissolution profile database should be included in Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods".	Partly agreed. See also comment above
144, 4.1	It should be further clarified that only the studies comparing the test product with the EU reference product of interest must be submitted. The Health Authorities do not accept biostudies with non-EU reference instead of biostudies with EU reference, therefore submission of such studies should not be required.	Please modify to: "All bioequivalence studies comparing the product applied for with the **EU** reference product of interest must be submitted."	See above.
4.1.1 Study design (line 146-175)			
Line 148 to 151 + Standard design	Randomisation and avoiding bias is mentioned in different places in the document (line 244 to 246 for bias and line 580 for randomisation) but not specified in the standard design section.	Suggest to add the following sentence at the end of Standard design section: Whenever possible, trials should be randomised.	Partly agreed. Text revised based on comment below.
Line 149-151 Paragraph 4.1	*"If two formulations are going to be compared, a two-period, two-sequence single dose crossover design is the design of choice. The treatment periods should be separated by an adequate wash out period."* It is recommended to add "randomised"	"If two formulations are going to be compared, a **randomised**, two-period, two-sequence single dose crossover design is the design of choice. The treatment periods should be separated by an adequate wash out period."	Agreed

149-151 4.1.1 Study Design	The description of a standard study design for bioequivalence studies should mention whether the design is blinded or 'open label'. The bio-analytical part is usually blinded.	CHANGE: Include a reference to the accessibility of the label (eg, blinded design, open label design), for the study and for the bio-analytical part.	It has been clarified in section 4.1.7 that the bio-analytical part should be blinded
149 – 151, 4.1.1	A minimum length for the washout period is not defined. The length of the washout period is the most important measure to prevent a carry-over.	Include a sentence on the minimum duration of a washout period (for example, "the washout period should generally be sufficient to allow drug concentrations to drop below the lower limit of quantification in all subjects").	Agreed. A definition has been added.
149 – 151, 4.1.1	A minimum length for the washout period is not defined. The length of the washout period is the most important measure to prevent a carry-over.	Include a sentence on the minimum duration of a washout period (for example, the washout period should last more than 5 terminal half-lives of the moieties to be measured).	Agreed, see comment above.
152 4.1.1 Alternative design	When steady-state cannot be reached within a reasonable time period (eg, after dosing for 10 days), is there some option to define a study as multiple dose and perform the 90% CI calculations although you have not reached steady-state? For some drugs with very long half-lives, steady state cannot be reached within a reasonable period of time. As this guideline is introducing additional requirements for steady-states studies for immediate release products, multiple dose studies are considered unnecessary when the half-life is so short that no accumulation occurs.	CHANGE: Define a maximum treatment period in multiple dose studies for drugs with a very long half-life even if steady state is not reached. CLARIFICATION: Please specify that multiple studies are unnecessary when no accumulation can be achieved.	The request for steady state studies in case of dose- or time dependent pharmacokinetics has been removed. There is an option to use multiple dose administration if parent cannot be measured after single dose administration. With better analysis methods nowadays, this situation is expected to be rare. A statement regarding maximum treatment period is not considered needed. A multiple dose study in case of no accumulation obviously is not needed. This does not need to be stated.
Line 152-175 + Section	The guidance does not cover other possible designs (e.g multiple test products in a bioequivalence study testing a combination of product or different formulations).	Suggestion: Other alternative design can be considered with rationale for implementation.	It is not understood which other alternative designs the comment refers to. No change made.

4.1.1			
Line 152-175: *Alternate design:*	Bioequivalence is a product quality issue in the broader sense. Single dose studies are sensitive to formulation differences or product performance differences compared to the multiple dose studies. Thus generally single dose studies are ideal. Furthermore, at steady state, the variabilities associated with the formulations are dampened. This is likely to hide true differences between the formulations. Variability is one of the important considerations for documenting bioequivalence. However under certain circumstances multiple dose studies may be preferred. Bioequivalence is generally tested on the highest strength of all drug products including the nonlinear drugs. Furthermore combining the single dose and multiple dose studies would require large volume of blood draw from a subject which could be a safety issue and there seems to be no compelling reason to recommending a steady state study in addition to the single dose study. This seems to be unnecessary human testing and increasing "producer' risk with little public health advantage. There should be good scientific rationale for a multiple dose study. For example, lack of bioanalytical assay sensitivity for the analyte of choice may be one of the reasons to conduct studies at steady state. However, with huge advancements in bioanalytics, the issue of assay sensitivity becomes more often mute. The meaning of "dose or time-dependent" pharmacokinetics is not clearly understood. This needs some explanation. It would be desirable to provide an explanation with example(s) of differences in dose-dependent pharmacokinetics versus time-dependent pharmacokinetics. It is hard to rationalize the recommendation of 90-111% 90% confidence interval for AUC in a single dose study to waive the steady state study. This seems to be very empirical and may not be scientifically valid.		Partly agreed. A steady state study would be more sensitive to detect differences in the amount of absorbed drug in case of dose- or time dependent pharmacokinetics where the exposure is markedly higher at steady state than expected based on single dose PK data. A steady state study would, however, be less sensitive than a single dose study to detect differences in Cmax (given that we only request multiple dose studies for drugs with dose-or time dependent pharmacokinetics resulting in markedly higher concentrations at steady state than expected from single dose data, thus with a marked accumulation). Hence, the request for a steady state study in addition to the single dose study. The request for a 90-111% confidence interval was arbitrary chosen to ascertain that a potential difference after single dose would not exceed 20% at steady state (i.e. 90% CI within 80-125%). It is, however, agreed that the situation where a multiple dose study would be more sensitive than a single dose study is rare and that single dose studies in general are sufficient. It is also difficult to define "dose or time-dependent pharmacokinetics, resulting in markedly higher concentrations at steady state than expected from

			single dose data" in more detail. Hence, in order not to complicate the guideline for these rare situations, the request for additional multiple dose studies has been removed.
153, 4.1.1 Appendix V	A definition for "dose or time-dependent pharmacokinetics" should be added.		See comment above.
153-159 4.1.1. Alternative designs	The paragraph introduces the requirement of an assessment of AUC after multiple dose administration in addition to single dose studies for products with "markedly higher concentrations at steady state". After a thorough literature review, we came to the conclusion that the requirement is based solely on hypothetical assumptions. Single dose studies are generally considered to be more discriminatory than multiple dose studies in the identification of differences between formulations. The general requirement defined in the draft guideline applies to a very broad range of possibilities. In addition the "markedly higher" term is not well defined and is perhaps difficult to numerate. As the primary purposes of bioequivalence studies are designed to assess formulation impact on absorption, situations when non-linearity stems from post-absorption processes should be clearly excluded from this additional requirement.	We believe that the paragraph should be removed. As an alternative, situations when multiple studies can be used to assess differences in AUC in addition to single dose studies should be precisely defined. This will allow identification of the circumstances that would be unambiguous for both the sponsors and the regulators.	The paragraph has been removed, see comment above.
Lines 153-159	Multiple (almost all) companies had significant comments on this section. It was widely thought that dose and time-dependent PK (non-linear) influencing single versus multiple dose BE study design confuses formulated product performance with drug disposition characteristics. There are only two rare possibilities where non-linear kinetics could result in a degeneration when going from single and multiple dose (MD) BE studies (most MD studies improve the ratio of test to reference). 1) The drug has supraproportional decrease in clearance with concentration AND accumulation with multiple dosing. For	The following text is recommended: 'In general, single dose studies are most sensitive to demonstrate differences between formulations.' … Multiple Dose BE studies are only necessary in rare scenarios: If differences in formulation has the potential to be significantly impacted by a time dependent factor such as in the following situations:	The paragraph has been removed, see comment above.

	example, saturable Michaelis-Menten kinetics, with half-lives considerable longer than the dosing interval and concentrations exceeding maximal reaction rate Vmax. There are theoretical examples of this effect (phenytoin, Ther Drug Monit. 1991 Mar;13(2):120-5), but no published actual studies. 2) There is an influence of formulation over time on systemic disposition characteristics. This is an extremely rare (mostly theoretical) occurrence. A single publication may support this idea. [Clinical Drug Investigation 2002, (22)9:585-592] However, this is misleading example of the failure of single dose BE to predict bioinequivalence as the single dose in the same study also demonstrated bioinequivalence and the *In Vitro* dissolution in the same study also predicted the result. "*In general, single dose studies will suffice*". It is not only sufficient, it is mostly the best choice.	• Does longer term PD influence a formulation difference (i.e. enteric coating difference and acid suppression)? • Does the drug have supraproportional decrease in clearance with concentration AND accumulation with multiple dosing? Theoretically, a formulation which is absorbed in a different portion of the GI tract than the reference could influence an anatomically specific inhibition/induction of metabolizing enzymes/transporters. It is recommended to quantify concentration and time-dependent pharmacokinetics (nonlinearity) and probability of an impact of formulation on the same. This potential for a formulation difference will form the basis a requirement to provide multiple dose BE data.' Remove requirement on multiple-dose BE studies, or some further discussion is needed on the 90-111% confidence interval criterion as a threshold to obtain a waiver for a multiple dose study.	
Lines 153-159	The need to study BE at steady-state in case of dose- or time-dependent pharmacokinetics is considered useful only in exceptional cases.	In the context of global regulatory acceptance and harmonisation, it is recommended to allow BE studies at steady-state in case of 1) a difference in rate, but not in extent of absorption, 2) excessive within-subject variability of Cmax and AUC, 3) concentrations after single dose are too low to be measured.	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above. A steady state study would be less sensitive than a single dose study to detect differences in rate of absorption (in case of

			accumulation) and option 1) is therefore not accepted. In case of high within-subject variability in Cmax widening of the acceptance range using scaling and a replicate design may be acceptable as defined in section 4.1.10. Multiple dose studies may be allowed in rare cases if concentrations after single dose are too low to be measured. See revised text in section 4.1.1.
Lines 153-159	This paragraph is not clear. Dose and time-dependent PK can result in lower as well as higher SS concentrations than predicted. At what level of departure from linearity would a multiple dose BE be requested? Would it be requested only for "higher" concentrations (safety?) and not for lower (efficacy?)? What examples are available to justify this approach? It seems to be an extremely rare case.	Please give example or delete this paragraph.	The paragraph has been removed, see comment above.
153-159	"In general, single dose studies will suffice. However, in case of dose or time-dependent pharmacokinetics, resulting in markedly higher concentrations at steady state than expected from single dose data, a potential difference in AUC between formulations may be larger at steady state than after single dose. Hence, a multiple dose study may be required in addition to the single dose study to ensure that the products are bioequivalent regarding AUC also at steady state. However, if the single dose study indicates very similar PK profile for test and reference (the 90% confidence interval for AUC is within 90-111), the requirement for steady-state data may be waived. "	The wording "markedly higher" is not well defined and appears too general. Clear-cut criteria (number or range) for the increase in AUC at steady-state compared with single-dose administration that will require an additional multiple-dose study (e.g. 2-fold increase in AUC) would be desirable.	The paragraph has been removed, see comment above.
153-156 4.1.1 Alternative Designs	The EGA does not favour broadening the scope of the applicability of multiple dose studies through tightening the requirements to waive the need for these studies. EGA member companies concur with the current international approach and remain of the opinion that single dose studies are more discriminative than multiple dose studies when it comes to detecting differences in *in-vivo* performance between formulations	CLARIFICATION: Please re-word the paragraph in order to state precisely that alternative designs are only applicable in exceptional cases.	The paragraph has been removed, see comment above.

	(not safety studies). Single dose studies are adequate for the purpose of determining the bioequivalence of two formulations and therefore should be the design of choice. Multiple dose studies should be limited to those exceptional cases where suitable information cannot be adequately derived from single dose studies.		
153-156 4.1.1 Alternative Designs	Dose and time dependent pharmacokinetics should be defined to limit the unnecessary use of steady-state studies. The ambiguity of this paragraph might lead to an unnecessary increase in steady-state studies due to sponsors opting for a conservative approach in order to avoid the risk of delay.	CLARIFICATION: Please refine the cases where steady state studies would be required.	The paragraph has been removed, see comment above.
152	On the subject of alternative design (single dose/multiple dose), this is an interesting approach from a scientific stand point but it may add more challenges to a generic company since, in case there is lack of sensitivity of the assay, single dose and multiple dose studies may be necessary. Single dose may still be possible by increasing the dose as long as there are no safety issues. One can also think about performing either a single or a multiple dose study instead of both.	A focus on the SINGLE-DOSE approach is preferred since it is most discriminative.	The request for an additional multiple dose study has been removed. The possibility of using a higher single dose has been added to section 4.1.6
153-156 4.1.1 Alternative Designs	If there are problems of sensitivity of the analytical method, a single dose study using a double daily dose is sometimes performed. We consider this an appropriate design provided the safety of the test subjects is acceptable.	CHANGE: Please include this study design in the guideline.	The possibility of using a higher single dose has been added to section 4.1.6
4.1.1 Lines 153-156	It is not clear the cases where a steady state study is required.	Please clarify the cases where steady state studies would be required. It would be helpful to clarify here the meaning of “markedly higher”.	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above. Multiple dose studies may be allowed in rare cases where concentrations after single dose are too low to be measured. Multiple dose studies are also allowed when the study must be conducted in

			patients.
154, 4.1.1	"Markedly higher concentrations at steady state" should be expressed more accurately.	Suggestion: …resulting in significantly higher concentrations at steady state …	The paragraph has been removed, see comment above.
4.1.1 :153-159	All pharmacokinetics are time-dependent	No need for multiple dose studies or narrower interval	Time-dependent pharmacokinetics is a change of clearance or F over time. When clearance decreases over time (or F increases), higher concentrations than expected after single dose is obtained after multiple dose and the sensitivity to detect differences between formulations will be higher at steady state than after single dose. However, the paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above.
153-159, 4.1.1	Apart from the fact that the term "dose or time-dependent pharmacokinetics" is not clearly defined, there is not sufficient scientific evidence of situations where a multiple dose study is more sensitive to detect formulation differences than a single dose study. If the EMEA is of the opinion that based on the theoretical consideration of a higher discriminatory power the request for a multiple dose study is needed, it should be sufficient to demonstrate bioequivalence for C(max) only after single dose administration and AUC only in steady state in a combined study design (as suggested in line 167 in case of bioanalytical sensitivity problems) in order to avoid duplication of bioequivalence testing under both single dose and multiple dose conditions.	Either delete this paragraph or modify wording in such a way that in clearly defined situations, AUC has to be determined in steady state, while C(max) is still assessed after single dose administration (i.e. after the first dose of the multiple dose study).	It is agreed that demonstration of bioequivalence for Cmax only after single dose administration and AUC only in steady state would be preferred in case a multiple dose study is requested for drugs with dose or time dependent pharmacokinetics leading to markedly higher exposure at steady state than expected. However, the paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above
153-159	There is no reference in the new draft guideline to a wash-out	CHANGE:	Agreed. A modified version of the

4.1.1 Alternative Designs	period in steady-state studies, however, the current guideline CPMP/EWP/QWP/1401/98 states the following: *"In steady-state studies, washout of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life)."*	We recommend adding this sentence: ***"In steady-state studies, washout of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life)."*** to be included in the new guideline as well (Section 4.1.1.)	proposed text has been added.
157, 4.1.1	It should be further clarified, if for drugs with dose or time-dependent pharmacokinetics, the proposed multiple dose study should prove bioequivalence for AUCt only.	If this is the case, please clarify: "In this case, it is sufficient to demonstrate bioequivalence on AUC only under steady state conditions."	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above
157-159 4.1.1 Alternative Designs	The "very similar" criterion with 90% confidence interval for AUC to be within 90-111 seems unjustified as such a requirement would increase the necessary sample size significantly. We therefore propose widening the "very similar" criterion. However, if required to use stricter acceptance criteria, we would recommend considering point estimates for AUC that would also be valid wherever a narrow confidence interval is considered applicable. In addition, if the non-linearity is due to post-absorption mechanism and independent of the absorption or pre-systemic metabolism, and hence formulation effect, it should be excluded from the above requirements.	CHANGE: Please change the "very similar" criterion to 85-118% or use the point estimates for AUC for definition of the similarity criterion.	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above.
Lines 158-159	Are there data supporting the more narrow 90% CI of 90 – 111% and the fact that two formulations being BE on that range will be within 80 – 125 % after multiple dosing?	Please give example or delete this paragraph.	The request for a 90-111% confidence interval was arbitrary chosen to ascertain that a potential difference after single dose would not exceed 20% at steady state (i.e. 90% CI within 80-125%). However, the paragraph requesting multiple dose studies in case of dose-or time

			dependent pharmacokinetics has been removed, see also comment above.
159	Please clarify whether 90% confidence interval for AUC is within 90-111 parameter should be pre-specified in the study protocol.		The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above.
# 153-159 § 4.1.1	Please clarify what is implied by "markedly" higher concentrations at steady-state as this is an arbitrary statement which in some cases would require steady-state studies in lieu of single-dose studies. Please clarify whether the 90-111 interval is analogous to 90-112% on the natural ln-transformed scale.		The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above.
Line 159	The first 90% confidence interval mentioned is the narrow version for no specific reason here. Indeed; the thresholds are mentioned several times in several paragraphs : 90-111 in section 4.1.1, section 4.1.6…, 75-133 in section 4.1.10 Moreover in the introduction bridge data are mentionned but then no further information appears in the acceptance limit section	Suggest regrouping all different thresholds of interest and reasons for considering them in section "acceptance limit" (line 548).	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comment above.
163-169 4.1.1 Alternative Designs	This paragraph implies that single dose assessments are only performed for Cmax. This raises both ethical (additional blood samples) and practical issues. Among the practical issues are the following examples: inclusion of full wash-out periods, analytical method development, etc. In addition, it is not clear as to whether a capture of the whole plasma concentration profile should be attempted or whether just a few plasma samples around the expected tmax should be collected after the single dose.	CHANGE: Please reconsider the separate C(max) assessment after the first dose. CLARIFICATION: Please specify what is expected in terms of sampling schedule.	The draft guideline stated: "bioequivalence should, if possible, be determined for C_{max} after the single dose administration (i.e. after the first dose of the multiple dose study) as a measure of peak exposure". This would require additional samples around Cmax after the first dose in the multiple dosing regimen, but there would be no need for a wash-out period. However, given that the need for a multiple dose study because of low sensitivity of the analysis method is likely to be a very rare situation given that analysis methods

			nowadays are much more sensitive than before, that Cmax after the first dose likely would be very variable if at all quantifiable, and in order not to complicate the guideline, the guideline has been simplified and now requests for both Cmax and AUC at steady state.
165, 4.1.1	In case a steady state study is performed instead of a single dose study due to lack of sensitivity of the bioanalytical method, the bioequivalence decision should be solely based on AUC and Cmax after steady state. In this cases, Cmax after single dose should not be taken into account for the following reasons: - The requirement of the draft guideline to base the bioequivalence decision on Cmax after single dose "if possible", is imprecise and might be subject to a lot of discussions. - If the measurement of Cmax after single dose is possible, will largely depend on the LLOQ of the bioanalytical method. Therefore, bioequivalence studies of different applicants using different methods might be assessed based on either Cmax under single dose or Cmax under steady state. - In a lot of cases, a reliable measurement will probably not be possible. However, in order to demonstrate this, the applicant would need to perform blood sampling during the entire single dose portion of the study and measure the samples. - From an ethical point of view, blood sampling is questionable when hardly any measurable concentrations are expected. For this reason, it seems more straightforward to base the bioequivalence decision in such cases on AUC and Cmax under steady state only.	Please delete: „As Cmax at steady state … AUC at steady state."	The arguments put forward are acknowledged. The requirement for demonstration of Cmax after the first dose has been removed, see also comment above.
Line No:	"as Cmax at steady state may be less sensitive to difference in the		The requirement for demonstration

165 to 171	absorption rate than Cmax after single dose, bioequivalence should, if possible, be determined for Cmax after the single dose administration (i.e. after the first dose of the multiple dose study) as a measure of peak exposure while extent of exposure can be based on demonstration of bioequivalence of AUC at steady state." **Q.1** If Cmax in steady state is less sensitive to the difference in the absorption rate than Cmax after single dose, the subjects may unreasonably incur excess of blood loss in case if the studies are designed to calculate Cmax after first dose in multiple dose studies, making Ethics committee approval difficult.	Can the Cmax be considered as a primary efficacy parameter only for single dose studies and Cmin and AUC_{tau} for steady state studies?	of Cmax after the first dose has been removed, see also comment above.
170, 4.1.1	The requirement to perform steady state studies preferably with the highest usual dosage recommendation should be deleted, as this implies several problems: - There may be safety concerns to give this dose to healthy volunteers. - It may be difficult to perform a study in patients, as the highest usual dosage recommendations may not be frequently used in patients. - The highest usual recommended dose may differ between countries. In addition, this requirement is contradictory to line 399 - 400, which allows both the dose and the strength to be selected based on safety and analytical grounds. For this reason, we propose that one tablet per dosing interval should be dosed in steady state studies. This reduces also the variability caused by the intake of several tablets and is straightforward to the formulation approach as differences in galenic formulation can be seen with one tablet.	Please delete: "In steady state studies the administration scheme should preferably follow the highest usual dosage recommendation (see also section 4.1.6 Strength and dose)."	The comments are acknowledged. The paragraph has been deleted.
170 to 171	For immediate release formulations, steady-state studies are only required in case of dose or time-dependent pharmacokinetics, resulting in markedly higher concentrations at steady-state than expected. In case of dose dependent PK the use of the highest dose is reasonable. A rationale for requiring the administration of the highest dose/strength in case of time-dependent PK is not obvious.	Modify the sentence as follows: "In steady-state studies the administration scheme should follow the highest usual dosage recommendation in case of dose-dependent pharmacokinetics"	The paragraph requesting multiple dose studies in case of dose-or time dependent pharmacokinetics has been removed, see also comments above.

170-171	"In steady-state studies the administration scheme should preferably follow the highest usual dosage recommendation (see also section 4.1.6 Strength and dose). "	The demand to investigate the highest recommended dose (especially in multiple-dose studies) might lead to an increasing number of BE studies to be conducted in patients because of unacceptable adverse events in healthy volunteers. So far, the highest strength was considered the most appropriate dose (except in certain cases) for BE assessment, but the NfG offered the opportunity to select a lower dose based on safety reasons. Please refer also to the comment on section 4.1.6.	The comment is acknowledged. The paragraph has been removed. Evaluation of the highest strength is now recommended (see section 4.1.6), and in case of safety/tolerability problems in healthy volunteers, the highest tolerable strength may be selected.
Lines 172-175, 3rd § page 6/29		"parallel designs for substances with very long half-lives" --> please add: "of for biologicals with the potential of inducing anti-antibodies"	Biologicals are out of the scope of this guideline.
Lines 173-174	Please clarify what is a parallel design, a replicate design, a substance with a very long half-life and a substance with highly variable pharmacokinetic characteristics.	The wordings "*parallel design*", "*replicate design*", "*substances with very long half-life*", "*substances with highly variable pharmacokinetic characteristics*" should be defined and added in the proposed annex-glossary.	It is not considered necessary to define these wordings. Parallel design is well known. Replicate design and high variability is further explained in section 4.1.10.
4.1.2 Reference and test product (line 177-220)			
	All information on the reference product and the test product should be separated instead of being interspersed between the two products. It is quite confusing to the reader. Recommendations for pre-approval and post-approval activities are combined together. These should be separated under different sections. The dosage strength of the reference and test products for bioequivalence assessment is not clearly described. Generally it is acceptable to conduct bioequivalence study on the highest marketed strength, unless there is a known safety concern, in which case a		Partly agreed. The section has been partly restructured. Post-approval changes have been moved to section 4.4 variations. The dosage strength to be used is described in section 4.1.6.

	lower strength is recommended. If there are multiple strengths, the guideline should describe what tests and information are required to approve other strengths.		
Section 4.1.2 Lines 176 through 220	The order of paragraphs in this section is difficult to follow.	Delete lines 193-194, include the concept in lines 184-185: "Test products in an application for a generic product or its variations are normally compared with the corresponding dosage form of a reference medicinal product, which will be referred to as the comparative medicinal product". Use consistent wording on throughout section on test and reference product	See previous response
Line 152-220 + 4.1.1-4.1.2	If similar product from the same originator is available both in EU and USA, BE comparison with either reference should be enough for both regions to reduce number of BE studies.	We would like to se more harmonisation between FDA and EMEA on guidances for bioequivalence studies.	Not agreed. Bioequivalence has to be shown with EU reference product for legal reasons for generic and hybrid applications. For other applications, the Applicant has always the option to justify that the Reference product in other country outside EU is identical (e.g. manufactured with the same process, composition, specifications, etc.) to the European reference product. There is no reason to limit this to products from USA.
4.1.2 Reference and test product	As the bioequivalence for a test and a reference product is evaluated based on administration of the same molar dose (as mentioned in Section 4.1.8), we recommend to add, in this paragraph, a statement on the molar equivalence dose to be reached between the test and comparator products. This statement is particularly important for fixed dose combinations where active substances interactions may occur. Could you also indicate when the molar equivalence dose is recommended (in case of API interactions, non-linear PK….)		As stated in the paragraph on selection of reference, content between test and reference should not differ more than 5%. Section 4.1.8 has been revised to allow content correction in case a reference differing in content less than 5% from test cannot be found.

177-183 4.1.2 Reference and test product	This paragraph should be revised so as to transpose the exact provisions of Directive 2001/83/EC in which the chosen reference medicinal product must be a medicinal product which is or has been authorised in the Community. "*the medicinal product is a generic of a reference medicinal product which* ***is or has been authorised*** *under Article 6"*	CHANGE: Please amend as follows: *"For Article 10(1) and 10(3) applications the chosen reference medicinal product must be a medicinal product* ***which is or has been authorised*** *in the Community"*	Agreed.
177-183 4.1.2 Reference and test product	A statement is needed relating to reference products that are approved under the hybrid provision but which are not part of the global MA as these are also valid reference products. The current wording does not allow for a generic or generic hybrid application to be made against such a product.	CHANGE: Please include a statement related to reference products approved under hybrid provision.	As stated on the CMD(h) website, it is acknowledged that in some specific circumstances that it is also admissible for an application for marketing authorisation to be based on an abridged dossier, which refers both to the complete dossier of a reference product and to clinical studies contained in a hybrid dossier, authorised according to Article 10(3) of Directive 2001/83/EC, as amended. However, the text has not been revised as it is in line with general NTA statements and given that it is not the purpose of the bioequivalence guideline to outline such specific regulatory scenarios. In any such case the applicants are advised to discuss the dossier requirements with the competent authority
178, 4.1.2	The requirement to use a reference product which is authorized based on a complete dossier is contradictory to lines 863-864, which states that for generic fixed dose combinations, the reference product in the bioequivalence study should be the originator fixed combination product, which may not be authorized based on a	Please add: "… on a complete dossier **(exceptions may be possible in accordance with lines 823-824 and 863-864)** …"	The first paragraph has been revised to clarify that - in accordance with NtA Chapter 1 - marketing authorisation on the basis of a complete dossier refers to Articles

	complete dossier. Furthermore, it is also contradictory to lines 823-824, because an originator ODT formulation (to be used as the reference product in a generic ODT biostudy) may not be authorized on the basis of a complete dossier.		8(3), 10a, 10b or 10c of Directive 2001/83/EC, as amended. The reference to the legal basis for fixed combinations (Article 10b) is hence included. Regarding the reference to the originator ODT it should be noted that in case of a line extension the concept of the global marketing authorisation applies.
180, 4.1.2	The phrase "should be part of a global marketing authorisation" should be further explained, as different Member States interpret this differently.		Not agreed. The term "Global Marketing Authorisation" is a legal term of the European Union that is defined in legal texts. This is out of the scope of this guideline.
Lines 180 & 185	Reference is now made to 'global' manufacturing authorisation of the reference medicinal product, however, this is not relevant for formulation changes made during development phases.	Remove reference to global MA or clarify its application to post approval manufacturing changes We recommend the use of the terminology 'pre-change' and 'post-change' to identify reference and test products as this indicates the suitability of development formulations as appropriate reference products in the development phase.	Not agreed. This is a general and introductory text that is clarified in the following paragraphs. There is no need to remove the legal term of global MA. On the contrary it is informative. Post approval changes have been moved to section 4.4 variations.
Lines 184-185	It is stated "*Test products in an application for a generic product are normally compared with the corresponding dosage form of a reference medicinal product*". This is limited compared to the current definition for generic products of the Directive 2001/83/EC, which states that various immediate-release oral pharmaceutical forms are considered to be one and the same pharmaceutical form (as mentioned in Section 1, lines 64-66). This means that the dosage form of the reference product for a generic application could be in tablets, capsules, oral solutions, oral suspensions, etc.	To take into account the current generic definition, we propose to replace by : "Test products in an application for a generic product are normally compared with the corresponding dosage form of a reference medicinal product **but could be also compared with other immediate release oral pharmaceutical forms, such as tablet, capsule, oral solution or suspensions."**	Not agreed. If several immediate release oral dosage forms are available: capsules, tablets and oral solution, the logical way to compare is with the same dosage form. Obviously, if only one is available and others are being developed by the generic company the new ones should be compared with the existing reference dosage form. That is why the sentence states normally. However, it will be

			clarified with: if available on the market.
Lines 186-189	The reference dosage form used for the initial approval must be used and is fine if still marketed. However, this formulation may no longer be available/marketed.	Add wording to indicate that the dosage form used for the initial approval should be used if still available on the market.	Agreed. It will be clarified with: if available on the market.
184-189, 4.1.2	The reference medicinal product should normally have the corresponding dosage form. However, for extension applications the dosage form used for initial application should be used. Even for extension applications of generic products the corresponding dosage form of the reference product should be used. This provision is in contrast to the model of a global marketing authorisation.	Please change: "In an application for extension of a concerned medicinal product **which has been initially registered under Art. 8 (3) of directive 2001/83** and when there are several dosage forms on the market, the dosage form used for the initial approval….should be used as comparative product…"	Agreed.
Line No: 186 to 189	"In an application for extension of a concerned medicinal product and when there are several dosage forms of this medicinal on the market, the dosage form used for the initial approval of the concerned medicinal product (and which was used in clinical efficacy and safety studies) should be used as comparative product, unless otherwise justified" **Q.1** What if the dosage form for which clinical safety and efficacy studies are done, is withdrawn from the market? Kindly clarify on strategy the generic manufacturer should follow in such scenario. Considering a scenario, when clinical safety and efficacy studies are conducted by Innovator Company on propellant based Inhaler for anti-asthmatic medicines with CFC as a propellant. Innovator has recently come up with new formulation with HFA propellant, but extensive safety and efficacy studies data with this formulation is not available and innovator has withdrawn the old formulation from the market, in such situation what strategy should be followed by generic companies. **Q.2** If the initial formulation is Tablet and a new formulation is		Not agreed. This text refers to extensions of the innovator product. Q.1 refers to extensions of the generic product or new generic product. These cases are dealt in lines 193-194 and 184-185 of the draft. The generic HFA product should be compared with the innovator HFA product, as indicated in lines 193 and 194. The proposal in Q.2 is exactly what is required in lines 184 – 185.

	Capsule or suspension, then would not it be better to compare the generic version of capsule or suspension with the innovator formulation with same dosage form? Please clarify.		
Lines 186-189:	The guideline suggests that *the dosage form used for the initial approval of the concerned medicinal product (and which was used in the clinical efficacy and safety studies) should be used for comparative product.* It is often becomes very difficult to ascertain the original formulation and dosage form that was approved based on clinical safety and efficacy data. In many cases, the reference product might have undergone several changes in the formulation in course of time after approval. This becomes a formidable task to identify the "original" formulation. As a result of this, it is prudent for a responsible regulatory authority to identify the designated reference product for the bioequivalence study, whenever possible, in stead of leaving it up to the sponsor of the generic application.		Not agreed. This text refers to line extensions of the innovator. The innovator knows perfectly about their formulations. The development of a new dosage form by the generic should be compared with the corresponding dosage form if this exists according to lines 184-185 of the draft.
Lines 189-190	We propose to add a specific paragraph on the reference product to be chosen for fixed-dose combination (FDC) as there is no recommendation for this type of application. Indeed, it is also important to distinguish the reference product to be used in the initial FDC application and in case of further variations depending on the type of FDC (originator or generic FDC).	To define exactly the wording "*generic FDC*" and "*originator FDC*" and to add in the proposed annex-glossary. Proposal to add: "In an application for a fixed-dose combination (FDC), the comparative medicinal products may be either the mono-component reference products or originator FDC provided that they have been authorized in the Community on the basis of a complete dossier (clinical efficacy and safety studies proven)." "For variations of an originator FDC, the comparative medicinal product for use in bioequivalence and dissolution studies is usually the FDC authorized under the currently registered formulation, manufacturing process, packaging, etc."	Not agreed. FDC are considered as any normal reference product.

		"For variation of a generic FDC, the comparative medicinal product for the bioequivalence study should be the reference medicinal products."	
190-194 4.1.2. Reference and test product	Whilst the first paragraph indicates that a currently registered formulation should be used as the comparative medicinal product, the lack of logical connection between the two paragraphs may lead to a divergent interpretation. Which comparative medicinal product should be used for examination of variation of the generic medicinal product from the reference article when *in vivo* studies are not required? We believe that the product manufactured according to the currently registered formulation and manufacturing process should be the comparative medicinal product used for *in vitro* testing of variations. In addition, when a variation to a generic product is proposed, the reference medicinal product may no longer be available in a comparable galenic form. The guideline should address such situations.	Please modify to wording to explicitly indicate that the currently authorized product is the specified comparative medicinal product used to propose variations to generic medicinal products when *in vivo* studies are not required (i.e. when *in vitro* studies are sufficient). PROPOSED CHANGE: "For variations of a concerned medicinal product, the comparative medicinal product for use in bioequivalence and dissolution studies is usually that authorised under the currently registered formulation, manufacturing process, packaging etc; however, for variations to a generic medicinal products which require *in vivo* bioequivalence studies, the comparative medicinal product to be used in such studies should be the reference medicinal product, whenever a comparable galenic form is available on the market."	It is out of scope of this guideline to state recommendations for variations based on in vitro dissolution tests. With regards to the second cooment "if still available on the market" will be added. However, it is not possible to give detailed guidance due to the multiple scenarios that can be found. In principle, if the reference product is still available in other dosage form, even if different to that of the generic product, this different dosage form should be selected as reference, since it is assumed that all reference dosage form were bioequivalent. However, if this is not the case, and the different dosage forms were developed based on therapeutic equivalence clinical trials due to non-bioequivalence between formulations, the Applicant should discuss the approach.
Lines 193-194	Multiple companies pointed out that it is possible that the reference original product could have been withdrawn or is no longer marketed as a result of generics on the market.	Please specify what other reference product would be acceptable in the case where the initial reference medicinal product no longer exists. Is the currently registered generic formulation acceptable? Others?	Agreed, but it is not possible to identify all possible situations, it is the responsibility of the sponsor to justify the selection. See previous comment. For example, the reference may

		Add the sentence to line 194: "When direct comparison to the original reference product is not possible, then comparison to the previous formulation could be accepted, if justified.	disappear from some countries (e.g. omeprazole capsules) but not in others. Therefore, it is still available in EU. Or it may be sold to another MAH. It is still available under a different name and MAH, but it is the preferable one. The same generic product should be the last option.
193, 4.1.2 685, 4.3	There may be cases where it is not possible to use the originator as reference product, as the originator is not on the market any longer. In such cases, other reference products should be allowed.	Please change: "… the comparative medicinal product for the bioequivalence study should be the reference medicinal product, **provided that it is still on the market."**	Agreed, the text is changed accordingly.
Line 195	"*The reference and test products should be packed in an individual way for each subject and period*." This statement is overly prescriptive and implies that individualised "blister type" specialised packaging will be required for BE studies. With the open label nature of a typical BE study, bulk packaging in bottles is appropriate provided the bottles are labelled appropriately and measures are taken to ensure compliance and correct dose administration. Individualised packaging is more expensive and requires longer lead times prior to study initiation that are not warranted in this open-label, high controlled Phase 1 setting. Further, individual packaging of test and reference drug product (per subject and period) is conflicting with requirements issued by other regulatory authorities in terms of their policy on "random sampling" of test/reference study drug by the investigator from an "overage" of bulk supplies (which are the totality of study drug + reserve samples to be retained). The differences in requirements among regulatory authorities do not allow companies to execute globally acceptable BE studies.	The objective that the identity of the product administered to each subject at each trial period should be unequivocally identifiable can be met through appropriate documentation procedures, and not necessarily by an absolute requirement on individual packaging. Requirements to ensure the identity of administered drug products (reference and test products) should be included in the guideline as a general objective without recommending detailed packaging procedures. We recommend a change be made to the sentence to read: "The reference and test products should be packaged by formulation and labelled appropriately."	Not agreed. It is of utmost importance that it is possible to identify unequivocally the identity of the product administered to each subject at each trial period. Individual packaging, whether in blisters or in other type of containers, is considered essential to obtain this. This packaging can be performed either before shipment of investigational medicinal products to the trial site, or at the site itself, which remains compatible with the requirements of other regulatory authorities.
195	"This cGMP dispensing is something known and applied for phase II and III clinical studies where patient kits are often needed. We	The requirement of individual	See previous response. The aim of the requirement for individual

	think that the proposed new rule from the draft guidance has been written in the spirit of these later phases. For standard bioavailability studies often carried out at a third-party research facility, orally administered products are rarely individually packaged. They are rather packaged in blisters or bottles prior to being transported to the research facility where they are simply dispensed individually before administration. The dispensing is generally performed on the premises of a clinic which would not have a prior need for GMP licensing. We believe that this particular requirement was presented in the mindset of later research phases (ex. Phase II or III) and for BE, we don't believe that this would be an added value. From a CRO perspective, we think that this procedure if implemented would add some logistics challenges while we use to perform mostly single dose studies using trained staff and Pharmacists as compared to Phase III studies where it is mostly used a self-medication. Anapharm is an early phase I/bioequivalence center where clinical studies are conducted according to cGCP, therefore cGMP dispensing of the medication could not be done in our facilities even though up to date all the dispensing has been done in our medication area which tends to be as much GMP as possible, or GMP-like. From a technical point of view, it is possible to dispense the medication according to cGMP after receipt from the sponsor. But this operation could only be done by a cGMP provider and as a result there would present additional cost to the study budget. If the idea behind this rule is to reinforce the prevention from any fraud or products manipulation, the current approach used by FDA where some Test and Reference product are retained at the clinic facilities, may be a good way to go. For US submission, Sponsors ship the medications to the CRO who will randomly take the samples for dosing and the retained samples are kept in the clinic or in a 3d party storage company."	packaging should not be mandatory: "*The reference and test products **should be packed prior to transport or use**. Packaging, which is a manufacturing operation, should be performed and documented in accordance with good manufacturing practice".*	packaging is not only to prevent fraud, but also to limit the risk of mistakes and to improve the traceability of the identity of the product administered to each subject at each trial period. Inspections of bioequivalence trials show that the documentation of the "dispensing" of investigational medicinal products by the trial sites is almost systematically insufficiently detailed.
195-201 4.1.2. Reference and test product	Packaging in accordance to GMP requires manufacturing authorization. The wording proposed is therefore inconsistent with Directive 2005/28/EC Art. 9.2 which exempts hospitals, health care centres or clinics from the requirement of holding such authorization for reconstitution prior to use or packaging operations under conditions of performance of such operations by a legally	Please modify the wording to reflect that packaging should be adequately documented and performed in compliance with legal requirement of the country where the study is performed and in accordance with	Partly agreed. The wording has been revised to include reference also to Directive 2005/28/EC Art. 9.2.

	authorized person and for exclusive use of these institutions. Annex 13 (point 42) exempts packaging and labelling processes performed at the investigator site from QP certification when permitted by local regulations.	principles of GMP including Annex 13.	
195-201 4.1.2 Reference and test product	This paragraph refers to reference and test product 'packing'. In conventional bioequivalence studies, the reference and test products are usually dispensed individually for each subject and period rather than actually packed individually for each subject and period. Dispensing of the medication by the CRO prior to administration is a standard procedure for most CROs outside the EU. It is not deemed a manufacturing step if the medicine is dispensed. Point 42 of GMP Annex 13 reads "*42. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Qualified Person in this regard.*" A manufacturing operation would only take place if the individual packing is carried out at the manufacturing plant level, eg, in blinded studies. In this context, Annex 13 of the EU GMP guide is only applicable in cases where a manufacturing operation is taking place (ie, not in the case of dispensing at the CRO level).	CHANGE: The paragraph should be reworded so as to include the possibility of dispensing. The first sentence should read, *"should be packed* ***(as described in Annex 13 of the GMP Guide) or dispensed****".* CHANGE: The second sentence should be deleted. ~~***"Packaging, which is a manufacturing operation, should be performed and documented in accordance with good manufacturing practice, including Annex 13 to the EU guide to GMP."***~~	See comments above. Point 42 of Annex 13 waives the requirement for a certification by the Qualified Person under certain circumstances, but not the requirement for compliance with the principles of GMP.
196-197	This paragraph does not respect Directive 2005/28 EC, Chapter 3, Article 9, paragraph 2 that says "Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions."	Packaging, which is a manufacturing operation, should be performed and documented in accordance with good manufacturing practice, including Annex 13 to the EU guide to GMP. **GMP authorization is not required where those processes are carried out in hospitals, health centres or clinics,**	See comments above

		by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.	
202-204 4.1.2. Reference and test product	We believe that in order to eliminate the impact of differences in the content of the drug substance, a dose normalization adjusted to the label claim is the logical choice. This would exclude any intended bias on BE assessment due to aimed selection of test batches with "most appropriate" content relative to reference content.	The bioequivalence assessment should be based on dose-normalized data.	Not agreed. This is a possible solution, but manipulation can be performed by repeating assays untill the desired result is obtained. In addition, small differences are expected in batches on the market and bioequivalence is expected irrespective of this small differences. For harmonisation dose normalisation is generally not recommended. See also revision of section 4.1.8, which describes an exeption to not allowing content correction
202-207 4.1.2. Reference and test product	The requirement of a demonstration that a representative batch of reference product has been selected with regards to dissolution testing in 3 (4) media and the assay content, is likely to lead to divergent interpretations. The reference product batch which appears representative under one criterion (e.g. in one media) may produce divergent results in another. In addition, dissolution methods developed for generic medicinal product cannot be fully validated for reference product. Each reference batch should be treated as representative from a quality perspective as each batch released to the market should meet the approved product specification. It should also be noted that the release specification for immediate release products	The requirement of a demonstration that a representative batch of the reference product has been selected should either be removed completely or limited in scope to assay content. Potential bias due to aimed selection based on content is excluded by dose normalisation as suggested above (202-204).	Not agreed. The reference product should be characterised and the selection of the batch to be used in the BE study should be justified.

	includes single point estimates and single media dissolution performance.		
Lines 202 - 207	Multiple companies suggested that it should be clarified that the requirement to present results for 3 batches of the reference product does not apply in the development setting since 3 batches may not be available. This is felt to be an unnecessary and impracticable requirement where BE studies are conducted in the development phases.	Please add for clarification: "This requirement does not apply to the development environment since a limited number of batches may be available."	The addition is not considered needed, since the text includes the text “unless otherwise justified”.
Line No: 202 to 207	**“**Batch control results of the test and reference products should be reported. The assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test procedure proposed for routine quality testing of the test product. In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, the applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified.” Kindly clarify after three-batch dissolution profiling, which batch of reference should be considered for BE.		The decision should be taken on case by case basis. It is not possible to give detailed instructions for all the multiple scenarios that can be found. Normally, all batches should dissolve similarly in all media and contain an acceptable amount of drug. Therefore, any of them would be acceptable as representative.
202-207 4.1.2 Reference and test product	The selection of the reference product used in a bioequivalence study is the responsibility of the generic medicine applicant. The choice is made between the available marketed originator products having a valid marketing authorisation in the EU. Presumably, every reference batch will meet the required release standards according to the validated methods of the originator and thus, can be used in a bioequivalence study. Hence, it should not be critical as to which reference batch would be selected and used in a bioequivalence study. In addition, it should be noted that the dissolution method developed by the generic medicine applicant cannot be validated for the originator product (reference).	CHANGE: The paragraph should be replaced by: ***“The selection of the reference product used in a bioequivalence study is the responsibility of the generic medicine applicant.*** ***The choice is made between the available marketed originator products having a valid marketing authorisation in the EU.”*** ***Batch control results of the test and reference products should be reported. The assayed content of the batch used as test product should not differ more than 5% from that of the batch used as***	It is agreed that it is the Applicant responsibility to select a representative batch of the reference product. But this has to be demonstrated in the Application. The text will be modified to leave open the way to perform this demonstration. The second sentence of the proposal is unnecessary. Although every reference batch is expected to meet the required release standards according to the validated methods of the originator and thus, can be used in a bioequivalence study, it is advisable to compare different

		reference product determined with the test procedure proposed for routine quality testing of the test product. ~~In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, the applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified."~~	batches to improve the study validity and probability of success.
4.1.2. Lines 202-207	The company considers that the requirement of analysing 3 reference batches is extreme taking into account that that registrations of the reference product marketed in different countries should be the same with respect to quality, manufacturing aspects, etc (concept of global marketing authorisation). In addition, it is the responsibility of the company that has the products in the market to comply with the approved specifications of assay and dissolution. In many cases it is impossible to get three different batches from the market in one country. Furthermore, the analytical method developed for the test product is unlikely to be valid for the reference product. Therefore, the assay results in these conditions are not reliable. In line with all these arguments, could the Authorities rely on the data they have in the reference product registration file instead of relying on the Applicant to demonstrate the quality of the reference product?	The company ask for a position from the Authorities.	Partially agreed. The text will be modified to leave open the way to perform this demonstration. Although every reference batch is expected to meet the required release standards according to the validated methods of the originator and thus, can be used in a bioequivalence study, it is advisable to compare different batches to improve the study validity and probability of success In cases it is impossible to obtain three batches; the applicant justification would be acceptable since the present wording states unless otherwise justified.
Lines 202-207:	The significance of analytical and dissolution data on 3 batches of the reference product is not clear. Generally several marketed batches of the reference product are tested for formulation development of a generic product. This helps in understanding the product performance, the variability associated with the reference product. Once an acceptable formulation is developed, there is little		We are glad to read that "Generally several marketed batches of the reference product are tested for formulation development of a generic product". This is our intention with this requirement. The

	utility to submit data on 3 batches in the application. After all, the reference product batches are all marketed lots which have been released based on the approved regulatory specifications for dissolution and other product quality parameters. The objective of asking for dissolution data on three batches of the reference drug is not understood.		significance of this requirement is to make Applicants follow this practice. Three is an arbitrary limit to show that this comparability exercise has been performed and it is communicated to the Regulatory Agency. Another number can be used if justified. The text will be modified to leave open the way to perform this demonstration.
Line 203	Is the assayed content not differing by more than 5% scientifically justified?	It would be useful to state the rationale to support 5% and/or cite reference	This value has been selected in order to agree with other Regulatory Regions since harmonisation is desirable.
Paragraph 4.1.2; lines 202/3	As in a BE study e.g. 2x20 mg Capsules may be compared to a 40 mg capsule; or an optimized 50 mg formulation may have the same in vivo exposure as the previous 100 mg formulation, the assay should be compared on a % label claim basis, rather than on mg/dosage form basis.	The assayed content **(as % of label claim)** of the batch used as test product should not differ more than 5 % from that….	Not agreed. This clarification is not necessary since the 5% limit has been defined in percentage. Unless otherwise justified has been added to allow deviations that cannot be avoided.
203, 4.1.2	The applicant of a generic product cannot influence the assay of the originator (e.g. stability overage in originator product; shelf life limit of originator product may be 90%). Additionally, the assay is not validated with view to the composition and manufacturing process of the original product. Therefore, over- and underestimation of the content of the original product may be possible. In these cases it is unavoidable to have a difference of more than 5% to the reference product. It should be at least possible to perform a study on own risk.	Please change: "The assayed content…should not differ more than 5% from that of the batch used as reference product determined with the test procedure used for routine quality testing of the test product**, unless justified by the applicant (e.g. in situations of atypically high or low content of the reference product)."**	This has been interpreted correctly, but we think that there is no need for an example, since multiple scenarios are possible. Unless otherwise justified has been added to allow deviations that cannot be avoided. If all the batches of the reference product tested from the market were out of the limit of a 5% difference, this could be considered as a justification.
Line 203	Meeting a specification of NMT 5% between test and reference can be difficult. We wonder whether this limit of 5% is scientifically	The rationale to support the 5% should be stated.	This value has been selected in order to agree with other Regulatory

	justified. A) This would mean that target for test may differ from 100% which is not in line with the product specification file according to Annex 13. B) Some methods of manufacturing (e.g. coating procedures) are not good enough to achieve such tight limits. C) Normal limits for assay are ± 5% to allow for variations from both manufacturing and QC. D) Common analytical methods used for assay (e.g. HPLC) usually deliver an intermediate precision of 2% (see ICH Q2(R)). E) Using a method that has not been validated for reference is not appropriate.	There should be some guidance on how to evaluate PK results in light of assay difference between test and reference of more than 5%.	Regions since harmonisation is desirable. In those exceptional cases where a 5% limit cannot be obtained potency correction could be acceptable if pre-defined in the protocol. This has been added to section 4.1.8.
Reference and test product Lines 203–206	Specific comments on reference and test product: • "Assay of reference and test must be within 5% of each other": Companies usually check that the assay is within specification of the respective product. (Line 203)		See above
204 – 207 para no. 10 page 6/29	Douglas Pharmaceuticals Ltd disagrees with the requirement to present dissolution profiles and content analysis of at least 3 batches of the reference product in order to demonstrate that a representative batch of the reference product has been selected. The rationale behind this disagreement is that the reference product batch has to be purchased by the company or person performing the bioequivalence study from the market within an EU territory. That batch can only be in the market if it complies with the formulation and specifications approved for marketing in that territory. Therefore by definition, it has to be representative of the reference product and testing two further batches of the same product will not show anything different.	Delete the sentence beginning "in order to demonstrate…" and ending with "…of the reference product, unless otherwise justified."	Partially agreed. The text will be modified to leave open the way to perform this demonstration. See also prvious responses
Lines 204-207 in 4.1.2.	The requirement for assay and dissolution results of batches other than the actual reference batch is not justified. All batches of an approved reference product are certified by a QP, fulfil the terms of the MA, and have adequate and representative release properties. In case of new drug substances in development bridging studies, the required information is not relevant nor available, as the repeatability of the manufacturing process is proven in later, in	Delete the sentence "In order to demonstrate that a representative batch …, unless otherwise justified."	See previous responses

	process validation.		
205, 4.1.2	It is requested to use a "representative batch" of the reference product for the biostudy. It should be further specified and defined how a representative batch is defined, e.g. in cases where assay data and dissolution data (e.g. behaviour in one pH is different) lead to diverging conclusions with regard to which batch could be considered representative.		See previous responses.
205,206 and 207 in paragraph 7	As per the DRAFT Guidelines, it is required to present dissolution profile and content analysis of at least 3 batches of the reference product. We are of the opinion that only 1 batch of the reference product should be used for this purpose as per the existing guidelines Rationale – (1) Samples of 3 batches of Reference Product will not be readily available.(2) Analytical Work Load will be increased tremendously , since Dissolution Profile will be carried out in min.3 Media and on 12 tablets each time. Thus total 144 Tablets of Reference Product (108 tablets) and Test Product (36 tablets) will be tested for Dissolution and that too for Min.3 Time Points. (3) In most of the Dissolution Methods HPLC is used for Analysis. Thus there will be total 432 Samples of both Reference and Test Product for HPLC to complete this study of Dissolution Profile. This will not only be expensive but will also require lot many man hours. (4) **Further in case consistency is not observed in three batches of Reference Product in the Dissolution Profile, which batch of Reference Product should be taken for BE Study? This is not clarified.** (5) Generally, it is expected that there will be consistency in the quality of Reference Product, and hence there is no need to test 3 Batches of Reference Product for Dissolution Profile for the reasons stated above.	These lines should be deleted.	See previous responses.
4.1.2 Reference and test product Lines 207	1. Requiring the presentation of dissolution profiles and content analysis of at least 3 batches of the reference product is a very restrictive requirement as it will require: - to purchase several different batches of a reference product, - to perform additional full dissolution testing, - and to get final analysis report	Please change as follows: "In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, ~~the~~	See previous responses.

	… all before conducting any bioequivalence study. 2. This requirement might reveal quality issues on existing reference products after they have proved their efficacy and safety by a complete dossier: - How different inter-batches dissolution profiles for the same reference product could be managed? -Could these reference products still be considered as acceptable comparator products? 3. It is not part of the applicant responsibility to manage discrepancies revealed by dissolution tests on the reference product as the applicant may not be the marketing holder of the reference product. 4. This requirement is not fully in line with Appendix III, lines 983-984 where it is advisable to investigate more than one single batch of the test and reference products (potentially implying two?).	~~applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified~~ **it is advisable to investigate more than one single batch of the test and reference products in order to ensure that respective results are representative."**	
4.1.2 207	Dissolution profiles and content analysis of at least 3 batches of the reference product - It has been observed in the past that different batches of the reference product may not be available at all times on the market.	Line 207: replace "unless otherwise justified" by: "if possible"	Not agreed. Unless otherwise justified is considered to include if possible.
207, 4.1.2	Dissolution profiles and assay of at least 3 batches of the reference product should be presented. It should be further specified if these 3 batches should be sourced from one country or may be sourced from different countries. E.g. if the reference product in the biostudy is from the German market, should the 3 batches be sourced from the German market or could 2 batches be sourced from Germany and 1 from another EU country?		As no indication is given, the sponsor is completely free to select them from different or the same market.
207, 4.1.2	Dissolution profiles and assay of at least 3 batches of the reference product should be presented, unless otherwise justified. It may be possible that 3 different reference batches are not available on the market in one country. It should be specified that this is a valid justification for not presenting these data.	Please add: "…, unless otherwise justified **(e.g. in case where 3 different reference batches are not available on the market in one country).**"	See above
209 4.1.2 Reference and test	In this paragraph, reference is made to 'oral solid forms' only. This is not consistent with the scope of the guideline, which covers immediate release dosage forms with systemic effect which include, for example, suspensions or solutions.	CHANGE: Paragraph should address all pharmaceutical forms covered in the scope of the guideline.	The reference to solid dosage forms is exemplary only.

product			
213 4.1.2 Reference and test product	It should be stated more specifically that the batch size indicated refers exclusively to immediate release formulation for systemic action.	CLARIFICATION: The following clarification should be added: "*In case of a production batch* ***of an oral solid immediate release formulation for systemic action*** *smaller than 100,000 units, [...]"*	Not agreed. The scope of the NfG is clearly given in the executive summary and section 2, which refers to other NfGs for modified release products, which includes both prolonged and delayed release formulations
213 to 214	The sentence "If the product … this should be validated" is superfluous in this NfG. Validation of scale-ups presents a) a standard procedure and is b) covered by GMP provisions.	Remove the sentence "If the product is subjected to further scale-up, this should be properly validated"	Agreed.
215-217 4.1.2. Reference and test product	Full production batches for immediate release products are usually not available prior to approval, and therefore the requirement is outside of the content of the guideline. In addition, the current guideline for estimate of variation requires dissolution testing for changes to the batch size less than 10 fold without other manufacturing change.	The requirement should be removed.	It is accepted that full production scale batch and validation data may not be included in the initial application, for standard production methods in line with NfG on Process Validation. Nevertheless, it is considered appropriate that satisfactory comparison of the dissolution profile of production scale batches with the biobatches is undertaken (rather than simple compliance with the dissolution limit in the Finished Product Specification). This may be addressed by an appropriate commitment where the applicant comits to not market a batch until a comparison of the dissolution profile of the production scale batch with the biobatches has been undertaken and been found acceptable. In addition, the dissolution limit in the Finished Product Specification

			should be justified by reference to the dissolution performance of the biobatches. This is on the basis that during review of dossiers, it is not uncommon for the limit to be justified by reference to the exhibition and stability batch data submitted in 3.2.P.5.4 and 3.2.P.8.3, without reference to the biobatches. This practice undermines any claims that the biobatch is representative of the product to be marketed.
Lines 215 - 217	"***Samples of the product from full production batches*** *should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions*." Multiple companies had questions about this statement. As this will require additional full dissolution testing and analysis report for the applicant dossier, would it be possible to provide a commitment for performing these dissolution testing if not available at the time of the submission. Does this refer to a commitment to dissolution and assay content data provision at a later date? Where scale does not impact drug product, quality pilot scale batches are appropriate. Perhaps it would be sufficient to compare one representative full-scale batch with the BE batch.	Please change as proposed: "Samples of **a representative full-scale batch** should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions (see Appendix I). **A commitment for performing these dissolution testing may be provided in the application dossier and results will be provided immediately if dissolution profiles are not similar between the test and full production batches**."	See above
Lines 215-217	Where very rapid dissolution release criteria are met (>85% dissolved within 15 minutes), dissolution profile equivalence should not be necessary.	"Samples of the product from batches of post-change drug product should be compared with those of the test/pre-change drug product. For very rapidly dissolving drug products confirmation of >85% dissolution at 15 minutes should be shown. For rapidly dissolving drug products (>85%	Not agreed. This is described in other sections of the guideline and it is unnecessary here.

		dissolution at 30 minutes) similarity of in vitro dissolution profiles should be shown (reference Appendix I for suitable dissolution conditions)".	
215 - 217 4.1.2 Reference and test product	Comparative dissolution is not required in variation applications for up-scaling of batch size with no manufacturing change. We do not find it justified to require comparative dissolution for up-scalings with no manufacturing change performed prior to MA approval either.	CHANGE: Paragraph should be reworded to delete this requirement.	See above
Lines 215-217	"**Samples of the product from full production batches** should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions." It should be sufficient to compare one representative full-scale batch with the BE batch.	"**Samples of a representative full-scale batch** should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions."	Not agreed. The guideline has been revised to clarify that comparative dissolution profile testing should be undertaken on the first three production batches
Lines 215-217:	The significance of manufacturing a full production batch for comparing against the test batch is not understood unless the approval of the product comes before the expiration of the batch. Asking a sponsor to manufacture a huge production batches for comparative testing before approval of the product is counter-productive. This will involve unnecessary expenditure of scarce resources. Once all specifications for formulation and manufacturing processes are approved, the sponsor would strictly adhere to those requirements before releasing any production batches to the market. This is rather unnecessary and might impose unwarranted penalty.		See above
218-220 4.1.2. Reference and test product	Requirements for duration of storage of retention/reference samples included in the guideline are inconsistent with the requirements set forth in the draft revised version of Annex 13: *"Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer."* The rationale for analytical testing beyond 1 year in excess of shelf life	Requirements for duration of storage should be harmonized with Annex 13 e.g. through reference to it. Quantity of retention/reference samples to be stored should be more precisely defined e.g. through defining the minimum number of repeated testing	This section has been removed. The requirements for retainment of samples for bioequivalence studies are the same as for other studies, and does not need to be specifically addressed in the guideline as this is detailed in other regulatory

	is unclear and is very likely included under current wording*: "The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities."* The quantity of samples to be retained is not defined.	(e.g. samples of all investigational medicinal products in sufficient amount to perform release specification analyses 3 times)	guidance.
4.1.2. Line 218	The sentence "The study sponsor will have to retain a sufficient number of all investigational product samples……" does not contain much information.	Give some useful clarification on the meaning of "sufficient"	See above
4.1.2 Reference and test product Lines 218-220	Could you please clarify what is meant exactly by "sufficient number"? A sufficient number to re-iterate the full dissolution studies, the assay content, the BE study? Also, the draft guidance note requests retention of investigational product samples for 2 years after trial completion or approval (whichever is longer). For bioequivalence studies conducted in the development phases, data to support such an extended shelf-life for the drug product may not be available.	Please add requirements for clinical investigator to retain test and reference Drug Product samples. Further, we recommend the addition of text to clarify that retention samples need not be stored under the same storage conditions as clinical supplies nor should a shelf-life valid for the duration of the retention period be required.	See above
Section 4.1.2: Lines 218-220	Insufficient to meet FDA requirements: Since 8 November 1990 clinical investigators have also been required to retain samples from the test and reference drug products actually used in Bioequivalence studies they performed at the study site for 5 years; Sample size needs to be sufficient to allow the FDA laboratory to perform all release tests five times; Clinical investigators are to contact Sponsor if not sure what constitutes five times quantity; (References: 21 CFR 320.63, Retention of Bioequivalence Samples; Compliance Program 7346.832, Pre-Approval Inspections / Investigations; Compliance Program Guidance Manual for FDA Staff, Chapter 48 Bioresearch Monitoring Human Drugs In Vivo Bioequivalence Compliance Program 7348.001; http://www.fda.gov/cder/ogd/retention_samples.htm;)	Addition of requirement for clinical investigator to retain test and reference Drug Product samples, for consistency with FDA requirements;	See above
218-220 4.1.2	The term 'sufficient number' is not specific and should be defined.	CLARIFICATION: Please introduce a reference to Annex	See above

Reference and test product	The EGA's understanding is that retained samples are intended to be used for analytical purpose. The number should be defined taking into account the intended extent of analysis to be foreseen, eg, 3 times the number needed to perform batch release analysis. The relevance of analytical testing beyond 1 year in excess of shelf-life is to be explained.	13 of the GMP Guide which addresses the storage of retention samples. Please define the amount of retention samples to be kept.	
218 to 220	It should be considered that BE studies may be conducted several years prior to submission of the application for a generic product, depending on the end of the data protection period. Thus it is not uncommon that studies are submitted 5 and more years after initiation. Considering that shelf-lives of 2-3 years are also not uncommon for originator products the batches of the reference product (and the test product) used in the study may have already expired 3 or more years before the time at which an application is submitted. Storage/testing of such batches can not be expected to provide meaningful results.	It is suggested to remove the condition to retain investigational product samples until approval. If retention of investigational products beyond the shelf-life is required - despite the foregoing arguments - a maximum storage period after expiry of the shelf-life that is reasonable should be stipulated.	See above
218-220, 4.1.2	Retention of samples is covered by Directive 2003/94, Art. 11, which requires that retention samples are kept until two years after completion or discontinuation of a trial. It is not reasonable to store a product much longer than its shelf life. Furthermore, it is not useful to store retention samples until approval, as approval of the generic product in all EU countries may take much more than 5 years because applications are triggered by marketing interests.	Please change: "The study sponsor will have to retain a sufficient number of all investigational samples in the study **for two years after completion of the trial** to allow re-testing, if it is requested by the authorities."	See above
218-220, 4.1.2	*The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities.* It is rather unclear what would be the justification for a request of re-testing of an IMP after the accepted shelf life and how results of such a re-test should be handled. Is back-extrapolation with parameters found in stability testing for the product (which most	*The study sponsor will have to retain a sufficient number of all investigational product samples in the study for the accepted shelf life after completion of the trial or until approval whichever is longer. Within the shelf life re-testing may be requested by the authorities.*	See above

	likely are derived from different batches) intended?		
Lines 218-220, 3rd §, page 7/29	"the sponsor will have to retain a sufficient number of all investigational product samples" - Specify whether bulk or same individual packaging as for study (as specified in line 195) - Clarify what "sufficient number" is: for example number of units necessary for performing at least three times the compendial tests or at least 300 units whichever is higher (?)		See above
220 (Para-4.1.2)	The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities. ***Comments :Re-testing is very broad term, re-testing should be clearly define i.e whether it mean only in-vitro testing or in-vivo testing or both.***	The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow 5 times of in-vitro testing .i.e Assay and dissolution or repeat the study which ever is higher, if it is requested by the authorities.	See above
Line 220 Section 4.1.2	What is the value of retaining samples beyond shelf life? Analysis after expiry date can only reveal that the product does not meet its specifications.	Please delete "or until approval."	See above
4.1.3 Subjects (line 222-249)			
4.1.3:223	12 subjects are generally not acceptable for other agencies	24 subjects as minimum	Not agreed. If the intra-subject variability is low, 12 subjects are sufficient. An even lower number of subjects could be sufficient if intra individual variability is very low. However, a minimum number of evaluable subjects (12) is requested as this is regulatory standard. This is also in line with what is written in

			FDA, WHO and Canadian guidelines. Further, it is now clarified in the guideline that is has to be at least 12 evaluable subjects who finishes the study.
Line 223 to 229	No rationale is given for the minimum sample size to be considered for cross over designs in the document (i.e. 12 subjects). The proposed figure is not justified. If combined to section "Subject accountability" (line 573) it seems that it should be 12 evaluable (i.e. complete) patients. If the reason for this number is to make sure that a sufficient number of complete – evaluable cases are present, then suggestion is made to clarify the section. Moreover, no miminum sample size is suggested for alternative design (parallel group)	Suggest to give more details on reason for such sample size or to delete it if found out to be not appropriate. Suggest clarifying whether it is 12 included subjects or 12 evaluable subjects for the cross over design.	Not agreed. See above. A parallel design is fairly rare and the inherent variability in such a study is high. It is very unlikely that a samples size of 12 will be sufficient to show bioequivalence. However, a minimum of 12 evaluable subjects also apply to a parallel design.
Line 224	It would be useful to state the rationale to support a sample size of of at least 12 and/or cite reference. Is there data to back up the supposition that there is no substance, or careful study design, which yields a variability small enough to justify a sample size less than 12?	Replace current text with: "A sample size smaller than 12, in a crossover study design, should be fully justified prior to study initiation."	Not agreed. See above.
224, 4.1.3	The minimum number of subjects in a cross-over study should be 12. For products with documented *low variability* (CV_{intra} <10%) it is not uncommon to obtain a significant treatment effect (confidence interval does not include unity) – which regularily leads to problems in Denmark (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6437). Such a case should justify studies in less than 12 subjects.	*The minimum number of subjects in a cross-over study should be 12, unless justified otherwise.*	Not agreed. See above. The general view in Europe is that significant treatment effects (in the ANOVA) are not a problem as long as the confidence intervals are within the normal acceptance range.
223-224, 4.1.3	The number of subjects to be included in the study should be based on an appropriate sample size calculation. The term 'appropriate' should be avoided.	*The detailed section about sample size planning (expected variance, power, etc.) should essentially be kept like in the current NfG.*	Not agreed. Sample size calculations according to standard practice are considered well known and not needed to be detailed in the guideline.

225	The section on "*Selection of subjects*" mentions the selection of healthy volunteers, but no reference is made to any target population in cases where it would be applicable (ex.: when target population consists of post-menopausal women only). In addition, it is mentioned that the weight should be "*within the normal range according to accepted normal values for the BMI index*". However, the normality range for the BMI values should be specified, since the acceptable ranges vary.	In the context of crossover bioequivalence studies, the maximal limit of the BMI could be set to 30, as commonly accepted by other agencies.	Partially agreed. Healthy volunteers are deemed representative for all populations in the context of BE. We have revised the text to include a preferable range of BMI (18.5-30 kg/m^2).
Line 225	**Age** The guidance on the age of the healthy volunteers is limiting. As the population ages and life expectancy in Europe increases the proposed narrow age range of the healthy volunteers, 18 to 55 years is unrealistic. To test medications primarily designed to treat diseases of old age in eighteen year olds lacks relevance. Much better guidance would be to carry out the bioequivalence studies in volunteers at or at least approaching the age of the target population for the drugs being tested. This would go some way towards compensating for the age related decrease in the function of most physiological processes and perhaps avoid the situation, for example, in which a drug is shown to behave one way in young healthy individuals and another in elderly patients.	If possible bioequivalence study volunteers should be at an age that is at least approaching the age of the target population for the drugs being tested.	Partially agreed. We have modified the wording to not include an upper limit on age. However, healthy volunteers are deemed representative for all populations in the context of BE.
Line 225: Selection of subjects	Selection of subject is an important consideration in bioequivalence assessment as sometimes, there may be interactions between subjects and formulation. The healthy subjects should also include elderly subjects from both genders, and ethnic origin to examine the comparative product performance across the full spectrum of the population. For specific drug products requiring special or target population, information on these population should be included.		Not agreed. We believe that the current wording is sufficient. Healthy volunteers are deemed representative for all populations in the context of BE. Further, there will not be power enough to conduct subgroup analyses in a BE-study.
Line 226		" ….. with the aim **to reduce variability and consequently** to permit …"	Partly agreed. The text has been revised taking the comment into consideration.
233-243 4.1.3 Selection of	The bioequivalence study director or the principle / medical investigators should be the ultimate judge of the definition and selection of inclusion/exclusion criteria based on the study	CHANGE: Please re-word this paragraph highlighting the responsibility of the study director and/or principle / medical	Not agreed. The current wording is sufficient. It is vague and allows the investigator to decide on most

<table>
<tr><td>subjects</td><td>concerned.

The term ‘extensive review of medical history’ should be defined.</td><td>investigators in the choice and justification of inclusion/exclusion criteria.

CLARIFICATION:
Please define ‘patient medical history’ and ‘extensive review’.</td><td>inclusion/exclusion criteria.

The sentence on “medical history and review” needs no clarification but has been slightly reworded.</td></tr>
<tr><td>Line 234 ff Section 4.1.3</td><td>The BMI is controversially regarded as being appropriate to determine “normal weight”. Age and individual figure as well as the distribution of muscle and fat are not taken into account. The BMI table published by the US National Research Council (NRC) in 1989, takes the increased Age into consideration. Since higher age is generally associated with higher intake of medicinal products this approach should be considered.
<table><tr><th>AGE</th><th>BMI</th></tr><tr><td>19–24</td><td>19–24</td></tr><tr><td>25–34</td><td>20–25</td></tr><tr><td>35–44</td><td>21–26</td></tr><tr><td>45–54</td><td>22–27</td></tr><tr><td>55–64</td><td>23–28</td></tr><tr><td>Ab 65</td><td>24–29</td></tr></table>National Research Council: Diet and Health. Implications for Reducing Chronic Disease Risk. National Academy Press, Washington D.C. (1989)</td><td>“normal” body mass index should be specified, different countries interpret this in a different way.</td><td>A preferable range of BMI, 18.5-30 kg/m^2, is now given.</td></tr>
<tr><td>235, 4.1.3</td><td>The normal values for Body Mass Index should be expressed more accurately, e.g. reference to the WHO classification for BMI (http://www.who.int/bmi/index.jsp?introPage=intro_3.html).</td><td>Add reference.</td><td>A preferable range of BMI, 18.5-30 kg/m^2, is now given.</td></tr>
<tr><td>Line 239</td><td>Selection of subjects:
‘Subjects could belong to either sex:
In our past experience, regulators required both sexes to be represented in a bioequivalence study. The present text leaves all options open. Please confirm this deviation from the past approach,</td><td>“Subjects could belong to either sex and both sexes do not need to be represented in a single study; however, the risk to women of childbearing potential</td><td>It is confirmed that it is not required to include both sexes in a study. The proposed text is clear enough and there is no need to revise it.</td></tr>
</table>

	which means that the choice is entirely left to the sponsor.		
Line 239	**Women** Rather than saying that volunteers can be of either sex, there should be some obligation for studies to be balanced for numbers of men and woman unless there is a good reason supplied why only one sex or the other should predominate. Widening the age range of subjects as suggested above make it easier to recruit women who were not of child bearing age and therefore not at risk of damaging unborn children.	Volunteers should be balanced with equal numbers of men and women unless there is a good reason supplied why only one sex or the other should predominate.	We see no need for this. BE demonstrated in healthy subjects is sufficient regardless of the sex of the participants.
	Patients Although healthy volunteers are adequate in most instances to detect formulation differences there are good examples in which the results from healthy individuals have not extrapolated to patients. Like the use of women, there should be an obligation on sponsors to demonstrate bioequivalence in patient groups if it has been previously shown that patients have pharmacokinetics that are very different from those seen in healthy individuals. For example see Pouwels MJ *et al* (DICP, 25(10), 1043, 1991) in which digoxin in Lanoxicaps was better absorbed than from Lanoxin in healthy volunteers, but in elderly patients the opposite was true.	There should be an obligation on sponsors to demonstrate bioequivalence in patient groups if it has been previously shown that patients have pharmacokinetics that are very different from those seen in healthy individuals.	We believe that healthy subjects are representative for all populations when we are dealing with IR formulations.
lines 240-241 and 245, 6th and 7th §, page 7/29	Restriction on non-smoking status seems a bit old fashioned and is not supported by an obvious rationale.		Agree. The restriction on smoking has been revised.
Lines 240-242	The requirement to identify all moderate smokers: would this be needed in all studies or only in studies with compounds in which metabolism CYP1A2 is involved? It is customary at some CRO sites that smokers refrain from smoking from the day before dosing until 1 or 2 days after dosing. However, we would recommend, to decrease the number of nicotine withdrawal AEs, to continue consistent smoking habits throughout the study.	In cross over studies, the requirement should only be to maintain current levels of consumption throughout both periods.	Agree. Restriction on smoking has been revised.
# 241-243 § 4.1.3	The statement: "If moderate smokers are included, consequences for the results should be discussed" requires further clarification as to the nature of the justification required. Please clarify the		It should be noted that the sections on genotyping and smoking are separate. Further, restrictions on

	circumstances where phenotyping and/or genotyping would be warranted with respect of inclusion of smokers, particularly when the drug product under assessment is not considered a substrate for the P450 CYP 1A2/1A6.		smoking have been revised.
# 244 § 4.1.3	Please clarify where genotyping and/or phenotyping is warranted in the evaluation of essentially similar product through bioequivalence studies (e.g. parallel) and at what point, temporally to the randomization would this characterization occur.		Genotyping/phenotyping is primarily mentioned for safety reasons. Regarding the special case of a parallel design study, it also concerns the validity of the results. In such studies, genotyping/phenotyping should be performed prior to the study in order to be able to balance the study.
Lines 244-246 Paragraph 4.1.3	It is recognized that some of the "prognostic factors" (ethnicity, smoking status, metaboliser status) mentioned may potentially affect the PK of the active substance. It is recommended to include these as examples only as they may not be relevant in all cases. Additionally, it may be useful to add other demographic covariates that could be relevant (e.g., body weight, sex).	In parallel design studies, the treatment groups should be comparable in all known prognostic variables that affect the pharmacokinetics of the active substance, such as demographic factors (e.g. body weight, sex), but also other factors like, e.g., ethnic origin, smoking status, extensive/poor metabolic status.	Agreed.
Lines 244-246:	For parallel design studies, in addition to the comparable prognostic variables specified, the subjects should also have phenotype and genotype similarities in the two parallel groups.		This is already covered by stating that similar "metabolic status" is a prerequisite.
4.1.4 Study conduct (line 251-308)			
Line 251 et seq	The requirement to abstain from xanthine containing products: would this be needed in all studies or only in studies with compounds in which metabolism CYP1A2 is involved? We would recommend, to decrease the number of xanthine withdrawal AEs, to continue consistent xanthine habits throughout the study.	In cross over studies, the requirement should only be to maintain current levels of consumption throughout both periods. In parallel studies, a suitable abstention from xanthine containing products prior to dosing would be 3	We have changed the text to a less strict version. There is no longer a requirement to abstain from xanthine containing products.

		days based on Greenblatt et. al., Clin Pharm & Therap, Aug 2003.	
4.1.4:251	better to control gastric state in Standardisation	Please see: Nasir Idkaidek et al. Gastric State-Controlled Bioequivalence studies. BioPharm International, Oct 2004	Not agreed. The revised guideline provides sufficient recommendations regarding control of gastric state.
# 257 § 4.1.4	Statement regarding fluid standardization taken after the treatment may be interpreted as implying that the volume of fluid consumed should be consistent between subjects and dosing periods. Typically there are fluid restrictions within +/- 1-2 hours of dosing, depending on the jurisdiction of dossier registration (e.g. 2 hours for Canada, 1 hour for United States) and *ad libitum* at all other times. Please clarify what is intended by "suitable period" for standardization and clarify whether specific volumes and timings for fluid administration throughout the confinement period is the intention of this statement.		The restrictions on fluid intake have been harmonised with the FDA guideline. Water is allowed as desired except for one hour before and after drug administration.
257, 4.1.4	"All meals and fluids taken after the treatment should also be standardized in regard to composition and time of administration during the sampling period" according to draft guideline. If this is required during the entire sampling period, this would mean: - No ambulatory blood samplings would be allowed, because standardized meals cannot be ensured. This would have a high impact on studies with long half-life drugs. - Water intake ad libitum would not be allowed, which is common practice in BE studies.	Please change: "All meals and fluids taken after the treatment should also be standardized in regard to composition and time of administration **during an adequate period after dosing**."	Agreed. The guideline now states "Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours)."
257-258	It is not feasible to assure the standardized meal and fluid during the sampling period unless to conduct the studies in full confinement without any out-patient samplings.	All meals and fluids taken after the treatment should also be standardised in regard to composition and time of administration during the confinement/suitable period after administration.	Agreed. The guideline now states "Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours)."
257-258 4.1.4 Standardisati	The text does not specify the period during which standardisation should apply after medicine administration.	CLARIFICATION: Please specify periods for standardisation of meal and fluid intake	Agreed. The guideline now states "It is recommended that water is allowed as desired except for one

on	Considering the usual gastrointestinal transit times, one proposal would be to standardise fluid intake during 2-4 hours after administration and to standardise meal intake during 12 hours after administration.	after medicine administration.	hour before and after drug administration and no food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours)."
257-260 4.1.4. Study conduct	Standardization of fluid and meals intake does not seem relevant during the post absorptive, elimination phase and may not be feasible after the subjects are discharged from the clinic.	Duration of requirement of standardisation of fluid and meals should be limited to 12 hours. A minimum period of no fluid and/or food intake after administration should be defined. For IR formulations, we recommend 4 h for food and 1 h for beverages.	Agreed. The guideline now states "Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours)." Further, water is allowed as desired except for one hour before and after drug administration and no food is allowed for at least 4 hours post-dose.
261-263, 4.1.4	*The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic or xanthine-containing beverages or grapefruit juice) during a suitable period before and during the study.* Food and beverages do not contain *xanthine*, only *methylxanthines*, namely 1,3,7-trimethylxanthine (caffeine: coffee, tea, cola, energy drinks), 3,7-dimethylxanthine (theobromine: cocoa, chocolate), and 1,3-dimethylxanthine (theophylline: traces in tea). The term *xanthines* for the methylated derivatives of xanthine – although sloppily used – is unknown in biochemistry.	*The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic or beverages containing <u>methyl</u>xanthines or grapefruit juice) during a suitable period before and during the study.*	Noted. We have also changed the text to a less strict version. There is no longer a requirement to abstain from xanthine containing products.
262	Avoiding all juices during a study is recommended since in addition to grapefruit juice both orange juice and apple juice have been shown to interfere with intestinal absorptive transport of some drugs.	Modify line 262 to "fruit juices) during a suitable period before and during the study"..	Partly agreed. It is now stated "certain fruit juices such as grape fruit juice".
264, 4.1.4	It should be clarified that the intake of oral contraceptives is allowed.	Please change: "Subjects should not take any other concomitant medication	Agreed

		(including herbal remedies) **with the exception of oral contraceptives** for an appropriate interval before as well as during the study."	
264-268 4.1.4. Study conduct	Oral contraceptives should be allowed unless there is a contradiction regarding the concomitant administration of oral contraceptives and the reference product in the SmPC	Use of oral contraceptives should be generally allowed in bioequivalence studies.	Agreed
264-268 4.1.4 Standardi-sation	Subjects should normally avoid concomitant medications. However, in some cases a concomitant medication is required as part of the study design (eg, naltrexone for studies of opioids, anti-emetic in some cases where subject tolerability is very low). Additionally, the use of contraceptives should be allowed.	CHANGE: Add that, in some cases, the protocol can specify the use of a concomitant medication by all subjects if the safety of the subjects necessitates it (eg, opioid antagonists, anti-emetics). This needs to be determined *a priori* with a justification regarding the lack of interaction between the study drug and the concomitant drug. CHANGE: Furthermore, it should be mentioned that the general restriction to use concomitant medication does not apply to contraceptives.	Agreed. The text has been revised taken the comment into consideration.
Lines 269-270 Paragraph 4.1.4	"In case the study is to be performed under fasting conditions, "subjects should fast during the night prior to administration of the products, unless otherwise justified.	If the study is to be performed under fasting conditions, subjects should fast for at least 8 hours, or for a specified interval such as 8-12 hours prior to administration of the products, unless otherwise justified.	Agreed. Subjects are now requested to fast for at least 8 hours prior to administration of the products, unless otherwise justified.
Line No: 269 to 270	"In case the study is to be performed under fasting conditions, subjects should fast during the night prior to administration of the products, unless otherwise justified." Kindly specify the exact fasting hours required to be maintained during pre-dose overnight fasting.		Subjects are now requested to fast for at least 8 hours prior to administration of the products, unless otherwise justified.

Lines 269-270:	The guideline doesn't specify the minimum number of hours of fasting before dosing. Generally the subjects should fast overnight and/or a minimum time appropriate to be specified by the agency.		Subjects are now requested to fast for at least 8 hours prior to administration of the products, unless otherwise justified.
271	Great news to see that AUC truncation is now acceptable. We have used this approach for long half-life drugs as it is accepted by other agencies such as FDA and Health Canada. According to Anapharm Experience, a truncated sampling at 72h or a bit longer have shown robust PK profile characterization when the sampling is adequate.		Ok
Lines 274-275	Sampling scheme should avoid Cmax being first point of concentration time curve. As this is not always possible, please change language to be less restrictive.	Please change to "Sampling scheme should avoid, if possible, Cmax being first point of concentration time curve"	There is no need to change. The proposed text is sufficiently vague as we only ask for the schedule to be planned for Cmax not being the first point.
# 275-313 § 4.1.4	Please provide examples of drug products where partial AUC requirements would apply.		Partial AUC will be removed.
Lines 277-278:	Generally AUCt should cover 80% of total exposure. However, if it becomes apparent that the absorption would be completed before achieving the 80% of the total area based on the pharmacokinetics principles, it may not be mandatory to collect additional samples. Furthermore, for most Immediate Release products the blood samples have been collected at least for a period covering 5 times of Tmax (resulting in the completion of absorption); there is no necessity to collect blood samples further simply to cover 80% of total exposure. The data from this parallel exposure would be equally reliable for assessing bioequivalence. This will avoid unnecessary additional blood draws. (WHO and Technical Report Series No. 937, 2006, pg 374, corrected reference 6.)		The sampling schedule should allow a reliable estimation of extent of exposure so that AUCt covers >80% of AUC_{∞}. If this is fulfilled AUCt will adequately reflect extent of absorption. A truncated AUC at 72h is an allowed alternative. A truncation at earlier time points is not considered needed in bioequivalence studies.
278, 4.1.4	At least three samples are enough to estimate the terminal rate constant.	Suggestion: At least three samples are needed …	Not agreed. We prefer to keep the suggested text which is in agreement with the old guideline and other agencies´ guidelines.
Line 278	Should be modified to: „.....is achieved if AUC_t is at least 80%	See cell Comments and Rationale. The	This is covered by the wording in

	of AUC_{inf} **in more than 80% of observations".**	minimal number of observation where AUC_t is at least 80% should be specified. Observation in 100% cases are practically not possible. We suggest 80% of all observations.	section 4.1.8.
line 279, 5th §, page 8/29		"at least 3 to 4 samples are needed" : suggest to change to "at least 3 samples are generally needed"	Not agreed. We prefer to keep the suggested text which is in agreement with the old guideline and other agencies´ guidelines.
281 4.1.4 Sampling times	It is written "A sampling time longer than 72 hour is not considered necessary for any immediate release formulation". Does this mean that calculating AUCinf is not needed for drugs where blood sampling above 72 hours would have been necessary so that AUCt is at least 80% of the AUCinf? The sampling time can even be further truncated for endogenous components regardless of the half life, eg, L Thyroxine.	CLARIFICATION: Extend, for example, the statement in lines 601-602 in such a way that it is clear that AUCinf will need to be calculated only if a non-truncated design has been used.	That is correct interpreted. This has been clarified in section 4.1.4 No detailed advice on truncation for endogenous compounds is given as it is a case by case situation. More details on bioequivalence for endogenous compounds are given in other sections of the guideline.
Line 281	These sentences are not justified and likely to be misleading	Please delete	The text has been slightly revised in order to make it clearer.
Paragraph 4.1.4; lines 281-283	Several companies mentioned that these 2 sentences may not be justified and are likely to be misleading. If the drug has a half-life of greater than 24 h, then it is justified to collect blood for longer than 72 hours to ensure an accurate estimate of AUC. This also implies that the requirement would be that BE is established using AUC_{0-72} (AUC_t [t is last quantifiable concentration]).	The paragraph can simply be deleted as it is well established and understood how long blood samples must be collected to get a reliable estimate of AUC. If a reference continues to be made to how AUC_{0-72} hours is considered acceptable for some immediate release formulations, we would request that you add that $AUC_{0-infinity}$ is also acceptable.	The text has been slightly revised in order to make it clearer.
4.1.4:281-283	AUC Truncation	Only recommended for low variability drugs since pharmacokinetics in high variability drugs may be affected at later times than 72 hrs.	Not agreed.
281-283	The proposed sampling period is that endpoints AUCt for short half-	Please consider harmonisation across	We do not see a problem with the

	life drugs and AUC_{0-72} for long half-life drugs would not be consistent with the requirements in other regulatory jurisdictions.	regulatory jurisdictions	differences across the regulatory jurisdictions. Several primary endpoints may be included in studies.
281-283, 4.1.4	A sampling period of longer than 72 h is not considered necessary for any immediate release formulation. It should be clarified that this is independent of the half-life of the drug. It should further be clarified that in such cases, AUCinf, t1/2 and kel need not be calculated and AUCt/AUCinf need not be > 80%, independent of the half-life of the drug.	Please change: "A sampling period longer than 72 h is not considered necessary for any immediate release formulation**, independent of the half-life of the drug. In such cases, AUCinf, t1/2 and kel need not be calculated and AUCt/AUCinf need not be > 80%.**"	The text in sections 4.1.4 and 4.1.5 have been revised taking this comment into account.
281-283, 4.1.4	*A sampling period longer than 72 h is not considered necessary for any immediate release formulation. Hence, for drugs with a long half-life, comparison of extent of exposure using truncated AUCs at 72 h is acceptable.* There's an abundance of literature (based both on simulations and real data) demonstrating that point estimates of bioavailability do not change once absorption is completed, only variability increases. *Midha KK, Hubbard JW, and MJ Rawson;* Retrospective evaluation of relative extent of absorption by the use of partial areas under plasma conentration versus time curves in bioequivalence studies on conventional release products. Eur J Pharm Sci 4, 381-384 (1996) *Endrenyi L and L Tothfalusi;* Truncated AUC evaluates effectively the bioequivalence of drugs with long half-lives. Int J Clin Pharmacol Ther 35/4, 142-150 (1997) *Midha KK, Hubbard JW, McKay G, Rawson MJ, and D Hsia;* The role of metabolites in a bioequivalence study II: amoxapine, 7-hydroxyamoxapine and 8-hydroxyamoxapine. Int J Clin Pharmacol Ther 37/9, 428-438 (1999)	*Either: the second sentence should be deleted (preferred),* *Or: a definition of 'long half-life' should be given (e.g., like 24 hours in Canada's guideline http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/notice_longhalflife_avis_longuedemivie-eng.pdf or in Japan's: $3 \times t_{½} + t_{max} \geq 72$ hours http://www.nihs.go.jp/drug/be-guide/QA061124_BE.pdf)*	The section has been revised taking the comment into consideration.
Lines 281-283	We question the value of truncation of AUC at 72 hours. If the drug has a very long t1/2, AUC0-72hr may be more sensitive of a measure of exposure compared to AUCt or AUCinf, and therefore		It is not necessary to truncate AUC at 72 h. The sponsor has the right to

	essentially raise the bar for BE. The sponsor should reserve the right to sample beyond 72 hours, if justified.		sample beyond 72 h.
# 282 § 4.1.4	Please clarify what is considered as a long half-life (in terms of hours).		The text has been revised and the rationale for truncated AUC at 72h clarified
284-302 4.1.4 Fasting or fed conditions	The specific scenario for medicinal products which should be taken immediately before meals (eg, certain anti-diabetic drugs) as per the SmPC recommendation is not depicted here. Should the study be done under fasting or fed conditions?	CHANGE: Please add the requirements applying to medicinal products which should be taken immediately before meals (eg, certain anti-diabetic drugs). The following terms should be defined in terms of their implications on a bioequivalence study design: • "With food" • "With or after food" • "Before or with food"	We believe that the guideline cannot cover all situations. Vague recommendations in originator SPCs unfortunately exists and must be handled on a case by case basis. We have clarified the requirement regarding timing of administration of the drug product in relation to food as much as possible. In situations where it cannot be determined if the study should be conducted in fasting or fed state, companies are adviced to apply for scientific advice.
Line 284:	This section is confusing and poorly written.		The section has been revised.
284-302 4.1.4 Fasting or fed conditions	Flexibility is required as the situation is not always clear-cut. For example, if absorption is higher in the fasted state but food is required for tolerability, a fasted study is more sensitive to formulation differences, but the applicant, if following the guideline, is expected to perform the study in the fed state. This is contradictory to the objective of comparing formulation performance in bioequivalence evaluation and the guideline should address this as well as other situations.	CHANGE: The guideline should address this scenario as well as other situations.	For products where the SPC recommends intake of the reference medicinal product only in fed state, the general recommendation is that the bioequivalence study should be conducted under fed conditions as bioequivalence then is established under the recommended use of the product.
Lines 285-291:	It is generally accepted that single dose bioequivalence study under fasting conditions is sensitive to formulation differences. Thus to examine equivalent product performance, generally a single dose bioequivalence study under fasting conditions is recommended. However, it is necessary to examine the comparative release of		See comment above.

	drug from the drug product under postprandial conditions as the drug release and absorption characteristics could be modified in the presence of food because of the influence of food intake on gastrointestinal (GI) physiology and on the drug product. The objective is to examine the formulation performance under maximum gastrointestinal (GI) stress conditions. Food might decrease or increase the bioavailability, causing either efficacy or safety concerns respectively. Furthermore there are situations where the ingestion of the drug product causes gastric irritation, i.e., NSAIDs. For these drugs, it becomes essential to examine the performance of the drug under fed conditions, as these drugs are usually taken with food. This point has been stated (lines 288-289), but should be clearly explained. For these drug products only fasting studies wouldn't be justified nor should be acceptable.		
Fasting or fed conditions Lines 292-294	Specific comments on fasting or fed conditions : The guideline asks BE studies to be conducted under both fasted and fed conditions for formulations with enhanced release characteristics differing from conventional IR formulations (e.g. microemulsion or solid dispersion). This proposal is different from the current FDA guidance which is limited to the fasted state unless products are taken with food. This might have significant impact on future product development with respect to risk, cost, and timeline. Products with enhanced-release characteristics: The guidance only gives examples as microemulsions or solid dispersions. Expansion of this definition and an understanding of what is defined as "enhanced-release characteristics" should be included. For example would the definition be based on dissolution-type testing? (Line 292) In addition, the guidance needs to clarify why the products with enhanced release characteristics are subject to BE testing under fasted and fed conditions?	Formulations with enhanced release characteristics be tested under fasting conditions. For products with enhanced release characteristics differing from conventional immediate release formulations (e.g. microemulsions or solid dispersions), bioequivalence studies performed under fasted conditions are required.	For products to be taken only on an empty stomach, bioequivalence should be demonstrated in fasting state. For products to be taken only in fed state, bioequivalence should be demonstrated in fed state. For products which can be taken with or without food, there is either no food effect on rate and extent of absorption or the food effect is considered clinically irrelevant. For such products, one BE study in fasting condition is usually considered sufficient as, in general, fasting conditions is considered to be the most sensitive condition to detect a potential difference between formulations. Several comments ask for clarification of the wording "enhanced release characteristics". However, it is very difficult to specify this better. The guideline

			now states: "for products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state." The reason for this request is that some formulations may have been developed to decrease a food effect. If, for such formulations, it cannot be excluded that there may be a difference between formulations in fed state although bioequivalence has been demonstrated in fasted state, due to differences between test and reference formulations in reducing the food effect, bioequivalence would need to be demonstrated also in fed state. Companies are advised to seek scientific advice in case of difficulty in determining if an additional study in fed state is required.
292, 4.1.4	The term *'enhanced release characteristics'* is unclear.	This term should be clearly defined.	See comment above
292, 4.1.4	The term "products with enhanced release characteristics" should be further defined.		See comment above
Line 292	"Products with enhanced release characteristics" are out of the scope of the guidance which focuses on immediate release formulation.	Please delete	See comment above
292-294 4.1.3. Study conduct	Requirement of bioequivalence studies performed under both fasted and fed conditions for products with enhanced release characteristics differing from conventional immediate release formulations (e.g. micro-emulsions or solid dispersions) is	More precise definition of products having "enhanced release characteristics" should be provided.	See comment above

	introduced. The term "Enhanced release characteristics" can be interpreted in a number of ways. For example, ODT products or products where drug micronisation has been performed may be considered by some to be enhanced release products. This may lead to performance of unnecessary studies.		
4.1.4 Study conduct Lines 292-294	As this paragraph concerns "products with enhanced release characteristics", it does not apply for immediate release formulations for which this guidance was intended (see lines 84-85).	Please delete the entire paragraph: "~~For products with enhanced release characteristics differing from conventional immediate release formulations (e.g. microemulsions or solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required.~~"	See comment above
292-294 4.1.4 Fasting or fed conditions	There is no clear definition of the term "enhanced release characteristics". The examples do not add to the understanding of this term. The use of a different disintegrant compared to the reference product might also meet this definition. On the other hand, some excipients are used to improve dispersion rather than dissolution. For products with truly enhanced release characteristics, bioequivalence studies under both fasted and fed conditions should only be needed if a significant difference in bioavailability is reported in the SmPC between the fasted and fed conditions. There is a need for the elaboration of standard terms relating to the administration conditions (eg, food effect and the need for fasted and fed conditions) in the SmPC. The current terminology, when present, does not always allow appropriate assessment.	CLARIFICATION: Please provide a precise definition of "enhanced release characteristics" (examples as available). CLARIFICATION: Please specify that for products with enhanced release characteristics, bioequivalence studies under both fasted and fed conditions should only be needed if a significant difference in bioavailability is reported in the SmPC between the fasted and fed conditions. CHANGE: The development of a separate document should be considered in order to summarise the standard terms to be used in SmPCs (QRD) to identify the administration conditions (by analogy with the standard terms for stability conditions and expiry date) (see general comments)	See comment above Regarding standard terms, this issue will be addressed in the revised interaction guideline.
Lines 292-	The definition of "microemulsion" and "solid dispersion"		See comment above

294:	formulation should be clearly defined. The release characteristics should be stated as per the product labeling (SPC).		
295	The guidance states that "*In cases where information is required in both the fed and fasted states, it is preferable to conduct a four-period single dose crossover design study (both products fed and fasted) rather than conducting two separate bioequivalence studies in fed and fasted state*". However, in certain cases this raises certain challenges such as • Long study duration due long washout period • High blood volume – safety • Variability • Study meets the BE criteria in one state but not the other In addition, it would be important to know if in this type of combined studies, PK/Stats analysis could be performed separately.	We are in favour of keeping fed/fast studies separate.	Agreed. The 4 way crossover study will only be mentioned as an alternative.
295, 4.1.4	The draft guideline recommends that a fasten and a food study should be performed as a 4-way study. However, there are situations where a 4-way study is not feasible, e.g. due to a long wash-out period or large sample volume. Therefore, two 2-way studies should also be allowed.	Please change: "In cases where information is required in both the fed and fasted states, **either two 2-way or a 4-way single dose crossover design study (both products fed and fasted) can be performed.**"	The 4 way crossover study will only be mentioned as an alternative.
295-302 4.1.3. Study conduct	Preference for conducting a four-period single dose crossover study rather than two separate fasted and fed studies is introduced for immediate release products that require both fasted and fed studies. Four-period studies may not be feasible due to excessive blood samples required and a higher drop-out rate, or may lead to unnecessary exposure (e.g. repetition of four-way study when only fasted or fed arms were inconclusive or when different variability in fasted and fed state requires significantly different number of subjects). Separate two-period studies should remain the standard approach for bioequivalence assessment for fasted and fed state. In the case where the food effect is to be compared between formulations then a four-way design should be adopted. It should remain the choice of the sponsor whether two- or four-period studies are performed.	The paragraph should be modified to clearly indicate that separate two-period or single four-period studies are equally acceptable. For four-period studies, sequences and evaluation strategy should be more precisely defined.	The 4 way crossover study will only be mentioned as an alternative.

Lines 295-302	A four-period single-dose crossover design instead of 2 two-way crossover studies (one under fed conditions and one under fasting conditions) offers certainly the advantage that the magnitude of the food-effect (if existing) can be estimated. However, the similarity between the generic product and the originator product in the extent of the food-interaction is not relevant with regard to the bioequivalence assessment. Of course, the generic product is required to demonstrate bioequivalence with the originator product under fasting conditions as well as under fed conditions. This can however be done in two separate studies, i.e. 2 two-way crossover studies. This approach is also mirrored in the Nfg on modified-release oral and transdermal dosage forms (CPMP/EWP/280/96) which explicitly recommends performing two studies for generic products. Furthermore, there are som disadvanteges inherent to the proposed four-period design: It is known that for many drugs, variability (CVres) differs depending on whether the drug is given in the fasted or the fed state. Therefore, the estimated sample size for BE studies is frequently not identical under both situations. From a scientific and ethical point of view, it appears problematic to include an unnecessary high number of subjects in such a study. For instance, it might be necessary to enroll 48 subjects to show bioequivalence between test and reference formulation under fed conditions while on the other hand only 24 subjects would be required to demonstrate BE under fasting conditions. In addition, the high number of blood samples that has to be taken during a four-period study (which might be considerably higher than usual because the drug's concentration-time profile may differ between the fed and the fasted state requiring different blood sampling schedules) migh raise safety concerns. This holds especially true in cases where the blood volume to be collected per time point needs to be higher, e.g. for a fixed combination product where two active substances have to be measured or if beside the parent compound an active metabolite has to be analysed.		The 4 way crossover study will only be mentioned as an alternative.
Lines 295-302	Multiple companies pointed out that in many cases it is preferable to perform 2 parallel cross-over studies instead of the 4-way cross-over study, since the intention of a BE study is not to investigate	It is recommended that a fed 2-way crossover trial and a fasted 2-way crossover trial be routinely allowed in	The 4 way crossover study will only be mentioned as an alternative. Bioequivalence should be

	the food effect on the reference product. For example, variability may change with dietary conditions and one may therefore not have the required confidence in all comparisons if dietary conditions alter variability. Some regulatory agencies outside the EMEA recommend that when fed and fasted BE must be demonstrated, two separate BE studies (one fed and one fasted) be conducted (for example see US FDA - Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, Section IV.A http://www.fda.gov/cder/guidance/5194fnl.htm#_Toc516914749). It is desirable to have regulatory uniformity such that studies do not have to be repeated unnecessarily. Finally, it is suggested that if the test product is shown to be bioequivalent under both fed and fasted conditions, the test product can be safely substituted for the reference product under either conditions and that the effect of food can be inferred from the reference products label. It is assumed that the test product would be given an identical label to the reference product rather than to introduce this fed/fasted comparison into the label as differences in meal composition could lead to differences in the food effect.	those instances where demonstration of fed and fasted bioequivalence is necessary. The 4-way combined study may also be stated as an acceptable option. It would be better to say "it is acceptable to conduct either a four-way cross-over study…..", or two parallel 2-way cross-over studies. Please clarify, for a compound specifically recommended to be given with food or without food (depending what conditions provides the higher bioavailability) that drives the MAA to develop formulation that would reduce the food effect, is it acceptable to be only bioequivalent in the condition of the higher exposure?	demonstrated in the recommended state. If bioequivalence should be demonstrated both in fed and fasting state and bioequivalence can be shown in one state and not the other due to a lower food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application.
295-302 4.1.4 Fasting or fed conditions	A four-period single dose crossover design study would not be of greater benefit than 2 separate bioequivalence studies in terms of detecting formulation differences under fasting and fed conditions. If the test and reference products have been demonstrated to be bioequivalent in separate fasted and fed studies, this implies that they would have a similar food effect. This 4-period study could even prove problematic to conduct for drugs with long half-life or simply because of higher risk of dropouts and high volume of blood. If intra-subject variability differs in the fed and fasted state using a 4-period design the study will be overpowered in either the fed or fasted state. If it is concluded that the food effect is critical for bioequivalence assessment, specific criteria for evaluating the food effect should be added.	CLARIFICATION: The four-period single dose crossover design should be an option equal to two separate bioequivalence studies in fed and fasted states. The applicant should be allowed to choose. CLARIFICATION: Specific criteria for evaluating the food effect should be added. It should be mentioned that the four-period crossover design can be used to demonstrate the lower food effect of a test product compared to the reference.	The 4 way crossover study will only be mentioned as an alternative.

295 to 302	The results obtained conducting a four period single dose crossover study enable the most precise evaluation of the effect of food. However, considering that it is a generic applicant's obligation to prove bioequivalence in the fasted state and in the fed state, but not to generate data allowing for an assessment of the extent of the food effect of the innovator product. Acceptance of a staggered approach, i.e. conducting two separate studies is considered to be of major economic relevance, as this allows the company to control major development costs if a test product should fail to confirm bioequivalence in the first study.	It should be clearly stated that the proof of bioequivalence in the fasted and in the fed state by two separate studies is sufficient to grant a marketing authorisation for a generic.	The 4 way crossover study will only be mentioned as an alternative.
295-302, 4.1.4	In cases where information is required in both the fed and fasted states, it is preferable to conduct a four-period single dose crossover design study (both products fed and fasted) rather than conducting two separate bioequivalence studies in fed and fasted state, respectively. In a four-period crossover design study, the food effect on test and reference product can be evaluated which is not the case when conducting two separate two-period, two-sequence single dose crossover design studies under fasting and fed conditions, respectively. In addition to the bioequivalence evaluation of test/reference in fasting and in fed state, the food effect can be presented for test and reference, i.e. the ratio food/fasting and 90% confidence interval for test and reference, respectively. It should be noted that in a four-period single dose crossover design study (both products fed and fasted) treatment effects and food effects are massively confounded and no unbiased estimates can be obtained. In a BE study the main effect of interest is '**treatment'** (≥2 different formulations, but **either** in fasting **or** in fed state). In a food effect study it's '**food'** (using the **same** treatment). One of the main assumptions in the usual (nonreplicate) cross-over model is an Independent Identically Distribution (IDD) of effects. This assumption simply may not hold. If **e.g.**, the variability of the reference is higher than the one of the test, one will obtain a high common variance and the test will be penalized for the reference performing badly. For most MR formulations one yet would expect	*Suggestions should be considered.*	The 4 way crossover study will only be mentioned as an alternative.

	different variabilities in fasting and fed state. Even for IR formulations food will change liver blood flow → hepatic clearance → not only the absorption, but also the elimination may be altered (note: constant clearance is the main assumption in BE). Since the suggested design study is of a nonreplicate design with 2 effects (2 levels: fasting|fed, 2 levels: T|R) the assumption of a common variance is downright absurd. An alternative to two different studies ($T_{fasted}|R_{fasted}$ & $T_{fed}|R_{fed}$), where an inter-study comparison as parallel groups (T_{fed} *vs.* T_{fasted} and R_{fed} *vs*. R_{fasted}) is lacking power, a 2-sequence, 4-period design of following type would avoid confounding issues: T_{fasted} R_{fasted} T_{fed} R_{fed} R_{fasted} T_{fasted} R_{fed} T_{fed} In such a design treatments in periods 1&2 can be compared in fasted state and in periods 3&4 in fed state as a conventional cross-over. Additionally T_{fed} *vs.* T_{fasted} and R_{fed} *vs*. R_{fasted} can be evaluated as a *paired* design (with high power, but avoiding confounding issues).		
Lines 295-302	It is not unusual that the intra-individual variability after fed administration is considerably higher than under fasting conditions. As such, the sample size necessary to demonstrate bioequivalence under these both conditions can differ considerably. In a 4-period crossover, the fasting treatments would be statistically over-powered by the requirement to recruit more subjects than necessary and the exposure of these extra-subjects would not be justified from an ethical point of view. It would be preferable to perform 2 parallel cross-over studies instead of a 4-way cross-over study since the intention of a bioequivalence study is not to investigate the food effect on the reference product.	Change into "It is acceptable to conduct either a four-way cross-over stud or two parallel 2-way cross-over study"	The 4 way crossover study will only be mentioned as an alternative.
Lines 295-300:	Combining both fasting and fed studies in a single 4-way crossover design is not acceptable for various reasons. First, the treatment conditions are different. Second, large volumes of blood need to be drawn from each subject during the four periods of the study. Third, the study would take a long time to be completed, thus there will be a high probability of subject dropouts, causing problem in		The 4 way crossover study will only be mentioned as an alternative.

	the power of the study. Fourth, most importantly, because the treatment conditions are different, i.e., fasting and fed within the same study, the variability arising from the fasting and the fed conditions will be combined (pooled). This is not appropriate as the variability from the fasting treatment could be different from that under the fed conditions. It could either widen or narrow the 90% confidence interval under both treatment conditions and thus may influence the outcome of the study. Fifth, if bioequivalence is established between the test and reference drugs both under fasting and fed conditions, it is expected that the food effect for the test drug would be similar to that of the reference drug. There is no need to examine the magnitude of food effect from a combined fed/fasting.		
Lines 298-300	The food effects can be evaluated by two separate two-period, two-sequence crossover designs, except that the precisions of the evaluation which are based on between-subject comparisons, will be lower than those by the 4-period crossover design in the guidance, which are based on within-subject comparisons.	Please revise the wording accordingly.	The 4 way crossover study will only be mentioned as an alternative.
Line 302	Add, please, the sentence: **„In four period study design model of ANOVA should not include the term sequence“**	See cell Comments and Rationale. As there are 12 different sequence group (contrary to two groups in two periods design model). We suggest not to include the term sequence into the ANOVA	The 4 way crossover study will only be mentioned as an alternative.
Line 302 Section 4.1.3	We suggest that there is a typo: ‘food/fasting’ should be replaced with ‘fed/fasting’.	“… i.e. the ratio in fed/fasting…”?	The 4 way crossover study will only be mentioned as an alternative.
303-308 4.1.4 Fasting or fed conditions	A problem with using a 4-period design is that if intra-subject variability differs in the fed and fasted state, the study will not be properly powered for one of the arms (fasted or fed) (eg, overpowered).		The 4 way crossover study will only be mentioned as an alternative.
300-306, paragraph 4.1.5	Administration of standardised meals is essential in order to evaluate the impact of food intake on the in vivo performance of solid oral dosage forms. However, the "physiological stress" of a given meal can be individually very different and is often	Considering such differences between subjects the amount of standardised food given should be adjusted to body weight. The 650 kcal meal suggested by	Not agreed. In order to keep the recommendation clear, adjusted amounts of meal is not included in the guideline. It is up to the sponsor

	dependent on the individual conditions of the volunteers, especially their body weight. It is well established that digestion of a meal takes different periods of time in subjects with "high" compared to "low" body weight.	the guideline should be the standard meal for a 70 kg subject. Volunteers with deviating body weight should receive adjusted amounts of this meal (proposal: stepwise adjustment in 5 kg steps)	include a population which can adhere to the protocol.
Lines 303 - 308	*"the meal should be a "standardized non high-fat meal."* Multiple companies mentioned that a high-fat meal is expected to have the greatest effect on the GI tract and have the maximal effect on oral absorption. For this reason, it is unclear why a "non high-fat meal" is recommended by EMEA. In addition, other regions globally prefer a high-fat meal for similar rationale making it difficult to conduct one bioequivalence study that will satisfy most regions when different types of meals are required. (for example see US FDA -Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, Section IV.D http://www.fda.gov/cder/guidance/5194fnl.htm#_Toc516914753)	The recommendation in this guidance is to perform the assessment under meal conditions which would have the greatest effects on GI physiology so that systemic drug availability is maximally affected. Please consider changing the wording to reflect using a high fat meal. It could say "It is preferable to perform the assessment under meal conditions which would have the greatest effects on GI physiology so that systemic drug availability is maximally affected. This condition typically occurs during a high fat meal."	Changed. The meal should be a high-fat meal unless the originator SPC specifies a certain type of food which then should be used.
Lines 303-308	The guideline recommends a standardized non high-fat meal (unless the meal composition is given by the reference product). This is different from the current FDA general guideline (although the sponsor can justify the use of low fat meals if appropriate to product labels which is a positive change as less food effect is likely seen with a standard non high-fat meal.) We recommend including clarification as to what the difference between non high-fat meal and low fat meal are.		Changed. The meal should be a high-fat meal unless the originator SPC specifies a certain type of food which then should be used.
Lines 303-308:	The significance and rationale of a non-high calorie meal is not understood. The objective of the fed study is to examine the food effect under high GI stress conditions. The GI transit time and the GI physiology are under high stress when a high fat meal is ingested. It is generally recognized that maximum food effect is achieved under this condition. Thus, observations from the non-high fat meal may be misleading, if fat content of the meal is increased.		Changed. The meal should be a high-fat meal unless the originator SPC specifies a certain type of food which then should be used.

305	This section directs the sponsor to conduct food interaction studies with a low-fat meal. This would become an EU-specific requirement.	Please consider harmonising requirements across regulatory jurisdictions in order to help minimize the exposure of healthy volunteers to investigational medicinal products.	Changed. The meal should be a high-fat meal unless the originator SPC specifies a certain type of food which then should be used.
306	Products with enhanced release characteristics are frequently used to formulate drugs with poor aqueous solubility. In this case use of a high fat meal in comparison to administration in the fasted state may well be most relevant to differentiate between test and reference product. But even if a non-high-fat meal is still to be recommended, a range of caloric content (e.g. 500 to 1000 kcal) would be preferred over a single value.	Modify 306 to "(500 to 1000 kcal with about 30% of calories derived from fat".	Changed. The meal should be a high-fat meal unless the originator SPC specifies a certain type of food which then should be used.
306 (Para-4.1.4)	the meal is given in the reference product SPC, the meal should be a "standardized non high-fat meal" (about 650 kcal with about 30% of calories derived from fat). The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%). ***Comments : Range should be defined in guideline for food consumption in fed study*** ***Since some volunteers fail to consume full meal it is advisable guideline should discuss this***	the meal is given in the reference product SPC, the meal should be a "standardized non high-fat meal" (about 650 kcal with about 30% of calories derived from fat). The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%). Subject should be excluded from study in case consume less than 90% specified calorie during fed study unless scientifically justified.	Changed. The meal should be a high-fat meal. Regarding the issue of not finishing the meal, it is up to the sponsor to include a population which can adhere to the protocol. The protocol may also be written to include decision rules regarding this matter e.g. "subjects not finishing the meal should be excluded from the study"
03-308, 4.1.4	According to the modified release guideline for a delayed release formulation, a fasten and a fed study has to be conducted. It should be clarified what meal is to be used for these studies, if the SmPC states that the product should be taken with a meal. Should in such cases a study with the standardized non high-fat meal and a high-fat meal according to FDA guideline be performed or rather a fasten study and a study with the standardized non high-fat meal?		Modified release formulations are not covered by this guideline. The section on fasting/fed studies has been clarified.
303-308, 4.1.4	The timing of the food and the application of the study medication should be specified. For a food study according to FDA, the medication has to be administered 30 minutes after starting the		The text on timing of food has been clarified. Vague recommendations in

	breakfast. It should be specified how to proceed if the SmPC of the reference product defines that the medication should be taken before a meal. In addition, it should also be clarified how to proceed in cases where there are differences in the SmPCs of different Member States with regard to the intake recommendation (with/without food, before/after meal).		originator SPCs unfortunately exists and companies are adviced to apply for scientific advices in these rare situations as this issue cannot be addressed in the guideline. Potential differences in the SmPCs of different Member States with regard to the intake recommendation (with/without food, before/after meal) cannot be covered in the guideline. Companies may apply for scientific advice in the very rare situation where one member state recommends intake with food and another without. It is more plausible that one country has no restriction with regards to food intake and another one has it. In such cases, the applicant can probably choose the condition which is approved in both countries.
4.1.5 Characteristics to be investigated (line 310-381)			
Lines 309-322 Section 4.1.5 Lines 548-562 Section 4.1.8 Lines 707-725	<u>Comment:</u> Lines 376-381 of the guideline under discussion allow for the use of urinary excretion data as a surrogate for a plasma concentration. Consequently, pharmacokinetic parameters and acceptance limits should be stipulated for determination of bioequivalence based on urinary excretion in: - Section 4.1.5 Characteristics to be investigated / Pharmacokinetic parameters - Section 4.1.8 Evaluation / Acceptance limits - Section 5. Definitions		Agreed. Text has been amended.

Section 5.			
# 310 § 4.1.5	Please clarify whether non-parametric analysis on Tmax should be required.		Non-parametric analysis of tmax is not required. This has been clarified in section 4.1.8
311-312, paragraph 4.1.5	In accordance with lines 601-602, it should be mentioned here that AUC(inf) is not to be determined if a measurement using a truncated AUC is employed.	Change the sentence to: “In studies to determine bioequivalence after a single dose, AUC(t), AUC(inf) (if the sampling period is shorter than 72 hours), C(max) and t(max) should be determined.”	Agreed, this issue has been clarified.
line 312, 2nd §, page 9/29	"Additional parameters that may be reported include lambda$_z$ and t1/2" --> This statement might be deleted as it adds nothing and suggests that other parameters must not be reported	Remove :"Additional parameters that may be reported include lambda$_z$ and t1/2"	Not agreed. These parameters are not mandatory, but can be reported.
313-317, 4.1.5 555, 4.1.8	It is suggested not to introduce the parameter partial AUC for the following reasons: - The definition of drugs where a rapid absorption is of importance (e.g. in terms of expected Tmax) is unclear. Therefore, diverging interpretations may be possible. - As a high variability of this parameter may be expected, the introduction of this parameter as a bioequivalence parameter might lead to clear increases in sample sizes. - In case the applicant has not planned to include this parameter in the bioequivalence decision, because he did not consider a rapid absorption of the drug to be of importance, a post hoc calculation may not possible due to lack of power. For these reasons, this parameter should not be introduced, but the provisions of the current guideline should be kept.	Please delete partial AUC and add evaluation of Tmax in case of clinical relevance.	Agreed. Partial AUC has been removed from the guideline. Tmax has been introduced in section 4.1.8 for products with a clinically relevant claim for rapid release or onset.
313-317, 4.1.5	For products where rapid absorption is of importance, partial AUCs can be used as a measure of early exposure. The partial area can in most cases be truncated at the population median of t_{max} values for the reference formulation. However, an alternative time point for	Preferred: The nonparametric assessment of t_{max} should be kept as in the current NfG (the entire concept of early exposure based on truncated AUC	Agreed. Partial AUC has been removed from the guideline.

504-505, 4.1.8 555-557, 4.1.8	truncating the partial AUC can be used when clinically relevant. The time point for truncating the partial AUC should be pre-specified and justified in the study protocol. A non-parametric analysis is not acceptable. For products where rapid absorption is of importance, equivalence between test and reference should be supported by demonstration of bioequivalence for partial AUC as a measure of early exposure. The same acceptance interval as for C_{max} applies to partial AUC. There is almost no literature justifying a truncation time point based on clinical grounds (one rare exception: AUC_{0-3h} for glibenclamide). Both FDA and Health Canada do not call for a *justification* of the truncation time point for early exposure. It is quite unclear why the nonparametric assessment of t_{max} was removed – at least there is no published evidence that this metric has lead to any problems in bioequivalence in the past. Retrospective evaluation of studies from our database with a claim of rapid onset of action with low variability in C_{max} (CV_{intra} <15%) showed very high variability (40% – 60%) for early exposure. The proposed method of assessment of early exposure by means of partial AUC (especially for a conventional acceptance range of 0.8 – 1.25) would lead to high sample sizes for essentially uncomplicated formulations. Even for a widened acceptance range (AR 0.75 – 1/0.75) the proposed metric should be reconsidered based both on ethical grounds and financial burdens. *Midha KK, Hubbard JW, Yeung PKF, Ormsby E, McKay G, Hawes EM, Korchinski ED, Gurnsey T, Rawson M, and R Schwedes;* Application of Replicate Design. In: *KK Midha and HH Blume;* Bio-International: Bioavailability, Bioequivalence and Pharmacokinetics. medpharm Scientific Publishers, Stuttgart, pp 53-68 (1993) *Midha KK, Hubbard JW, and MJ Rawson;* Retrospective evaluation of relative extent of absorption by the use of partial areas under plasma conentration versus time curves in bioequivalence studies on conventional release products. Eur J Pharm Sci 4, 381-384 (1996)	should be removed). Or: Only the point estimate should lie with 0.8 – 1.25 (no assessment of the confidence interval).	

311-322 4.1.5 Pharmacokinetic parameters	There is no clear definition of the term "rapid absorption of importance". Definition of this term is necessary to establish for which medicinal products partial AUCs should be considered.	CLARIFICATION: Please provide a precise definition of "rapid absorption of importance" (examples as available).	Partial AUC has been removed, see above. A clarification on when an evaluation of tmax is needed is given in section 4.1.8.
Lines 313 + 555	*"For products where rapid absorption is of importance, partial AUCs* ***can*** *be used as a measure of early exposure."* In line 555 it reads that for products where rapid absorption is of importance partial AUC **should** be determined. In this context, the definition of the phrasing "where rapid absorption is of importance' becomes important and should be given. Is this when rapid absorption is part of the SPC/label/product characteristics as a specific claim or do other criteria play a role?	There is a discrepancy between the wording used in line 313 (**can**; i.e. not mandatory) and line 555 (**should** i.e. mandatory). We propose that **can** should be maintained in both places to allow the greatest justifiable flexability.	Partial AUC has been removed, see above.
4.1.5:313-317	Paragraph info is not clear (recommended or mandatory)		Partial AUC has been removed, see above.
4.1.5 Line 313 and 4.1.8 Line 555	The sentence "For products where rapid absorption is of importance….." is not clearly enough.	The wording might be improved by defining when the rapid absorption is of importance and when partial AUCs should be used.	Partial AUC has been removed, see above.
Line 318 Paragraph 4.1.5	*"In studies to determine bioequivalence at steady state,* AUC_τ*,* $C_{max,ss}$*,* $C_{min,ss}$*,* $t_{max,ss}$ *and fluctuation should be determined"* $C_{min,ss}$ is defined as a parameter, but from the definition as defined in section 6 it is not clear whether C_{min} = minimum observed concentration at steady-state during the dosing interval, or the concentration at steady-state at the end of the dosing interval (trough). Also, the parameters swing $((C_{max}-C_{min})/C_{min})$ and C_{av} should also be requested as optional parameters.	Clarify definition of C_{min} in section 6 as the minimum concentration over dosing interval, or at end of dosing interval. Include swing and C_{av} as optional parameters	By Cmin,ss we mean the concentration at the end of the dosage interval, i.e. Ctrough. However, in bioequivalence studies for immediate release formulations there is no need to report C_{trough} and fluctuation. The guideline has been revised. We see no need to include swing and Cav.
Line 318	Fluctuation as defined in line 723 is a composite parameter consisting of both $C_{max,ss}$ and $C_{min,ss}$ and would not be critical in assessment for bioequivalence, but would be of secondary interest.	In studies to determine bioequivalence at steady state, AUCτ, $C_{max,ss}$, $C_{min,ss}$, and $t_{max,ss}$ ~~and fluctuation~~	This section has been revised, see also comment above.

318 – 319, 4.1.5	Following multiple dosing, the parameters swing ((C_{max}-C_{min})/C_{min}) and C_{av} should also be requested as optional parameters.	Include swing and C_{av} as optional parameters.	We see no need to include swing, see also comment above. Although C_{av} may be a parameter of interest in other pharmacokinetic studies, we see no need to report C_{av} in bioequivalence studies.
Line 319	Provision of additional parameters for steady-state.	Additional parameters that may be reported include the terminal rate constant, λz, $t_{1/2}$, and fluctuation.	Not agreed to add terminal rate constant, λz, $t_{1/2}$, for steady state studies, where sampling may not be optimised for evaluation of these parameters (i.e. sampling only during the dosing interval).
318-319, 4.1.5	Should there be a reference to Note for guidance on modified release oral and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation) (http://www.emea.europa.eu/pdfs/human/ewp/028096en.pdf).	Add reference.	A reference to Note for guidance on modified release oral and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation) is given in section 3. We see no need to add a reference in section 4.1.5.
Line 320	There is a typographical error referring to a Section 6 where the definitions of PK parameters are listed. This section is actually titled "DEFINITIONS" section starting on line 707	Please change the reference here to "Definitions of the pharmacokinetic parameters are given in DEFINITIONS.	The sentence has been deleted
320, 4.1.5	A reference to definitions is incorrect (there is no section 6 in this document).	Suggestion: Definitions of the pharmacokinetic parameters are given at the end of section 4.4.	The sentence has been deleted
Line 321	There is no instruction whether actual or nominal sampling times are to be used.	Add sentence "Actual sampling times are to be used in the estimation of the pharmacokinetic parameters."	Agreed. The proposed sentence has been added.
4.1.5 Characteris-tics to be investigated	Multiple companies commented on the draft guideline indication that the use of compartmental methods for the estimation of parameters is not acceptable. They all felt that if a validated compartmental model exists, such as with a limited sampling strategy (with 4-5 points in the dosing interval) using a POPPK	Add that "The **exclusive** use of compartmental methods …." Or that "*the use of compartmental methods for the estimate of parameters*	Not agreed. Compartmental methods and especially population PK analysis involve a number of assumptions. These analyses are acceptable for other types of

Line 321	approach, this would seem appropriate to assess PK parameters. Can this specific case be mentioned opening the door for compartmental analysis? In many cases predicted results should be consistent with actual findings. For other specific drugs, compartmental methods would be required to analyze the pharmacokinetic parameters	*is not generally accepted, unless otherwise justified"*	pharmacokinetic evaluations but not in bioequivalence studies. Non-compartmental analysis should be used in bioequivalence evaluation.
Line 322	For some specific drugs, compartmental methods would be required to analyse the pharmacokinetic parameters.	Change to "the use of compartmental methods for the estimate of parameters is not generally accepted, unless otherwise justified"	Not agreed, see comment above.
321 – 322, 4.1.5	The draft guideline indicates that the use of compartmental methods for the estimation of parameters is not acceptable. But: If a validated compartmental model exists, predicted results should be consistent with actual findings.	The use of validated compartmental models should be considered.	Not agreed, see comment above.
Lines 323-362	Comment: For the sake of clarity subheadings should be added to ease comprehension of this section about "parent compound or metabolite".	Proposed subheadings for the section 4.1.5 Characteristics to be investigated / Parent compound or metabolite: lines 324-328: General principles lines 329-341: Inactive parent compound (prodrug) / active metabolite lines 342-351: Active parent compound / metabolite of no or minor contribution to clinical efficacy lines 352-357: Active parent compound / metabolite of major contribution to clinical efficacy lines 358-362: Evaluation of the	Subheading have been added

		contribution of a metabolite to clinical efficacy	
323, 4.1.4 Appendix IV	We acknowledge that the reasoning and the decision tree on the issue of parent compound or metabolite were prepared with great attention to detail trying to include any possible case. However, a clear decision on this issue is hampered by the fact that the necessary information is not available in the literature or ambiguous in the majority of cases, so that it could be interpreted differently by the clinical assessors of different EU Member States and the applicant, e.g. - It may be difficult to determine if a prodrug is inactive (line 329). - Information on linear PK of parent and metabolite may be ambiguous or not available (line 330, 355-356). - A definition for low prodrug exposure and very much higher metabolite exposure is missing (line 339) and available data on this issue may be missing or ambiguous. - In case the metabolite data can be used because the parent cannot be reliably measured, the Cmax of the parent should be determined, if possible (line 346). This is imprecise and might lead to a lot of discussions, including different assessments depending on the used bioanalytical method and LLOQ. - Metabolite ”major” contribution to clinical efficacy is not defined (line 353). - It is difficult to predict cases in which metabolite concentrations may reflect differences in formulation which may not be detected in parent compound (line 355). - Definition of “active” parent compound is missing. - The dotted line on the right side of the flowchart is not understandable. E.g. in a case where it is possible to reliably measure the parent, one would need to demonstrate BE for parent only following the arrow “yes”. On the other	In accordance with the FDA guideline, it is suggested that the parent compound should always be used for the bioequivalence decision. Metabolite data should not be required. The only exception to this rule should be rare cases where the parent compound cannot be reliably measured. In such cases, the bioequivalence decision should be based on the major metabolite.	It is agreed that there are a number of potential difficulties with the text proposed in the draft guideline. The comment clearly points out the most important issues. Although there are situations where parent compound may not fully reflect a difference in active metabolite, these cases are rare. Ideally, bioequivalence should also be demonstrated for active metabolite in these cases. However, it is agreed that these cases are difficult to predict. Hence, any writing to define these rare cases could be interpreted differently between different companies and different regulatory authorities. As the risk that there would be a clinically relevant difference in metabolite exposure when bioequivalence has been demonstrated for parent is low, it is agreed that bioequivalence can be based on parent drug alone.

	hand, if the exposure of the active metabolite is very much higher than for the parent compound, one would need to demonstrate BE for the main metabolite only, following the dotted line and the arrow "yes". This is contradictory. For these reasons, it is recommended to change the requirements with regard to parent compound and metabolite data.		
Line 323:	This section has a lot of complexity regarding the selection of the analyte or analytes to be assayed and used for bioequivalence determination. How does a sponsor know which analyte to select and who is going to provide that information? The chances are: a sponsor would analyze all analytes including the metabolite(s) if these are active to support the study. The contribution to therapeutic activity of metabolite(s) is most often in humans not known. On the other hand different sponsors may select different analyte(s) based on pharmacological and/or some receptor binding studies. Thus, for each drug, there should be clear understanding of the selected analyte(s) by all sponsors of that drug. This topic requires a lot more considerations. The decision tree in Appendix IV is very complex. A separate detailed section to this guideline on this topic may be considered.		It is agreed that this is a complex section. The section has been changed. See also comment above.
323-362	There is no clear definition of the terms "low concentrations" or of "reasonably sized bioequivalence study".	CLARIFICATION: Please define the terms "low concentrations" or of "reasonably sized BE study".	It is acknowledged that this is unclear. The guideline has been revised.
323-362 4.1.5 Parent Compound and Metabolites	On line 346, if the parent drug cannot be reliably measured due to rapid absorption and elimination, the Cmax of the parent drug will usually be variable. ***The requirement for the applicant to measure the metabolite and thereafter to determine Cmax of the parent compound seems to create a requirement for two barriers/ranges to pass.*** ***If a drug is both quickly absorbed and metabolised then there will be little utility in measuring the parent and it will be inherently extremely variable.*** ***This will result in little increase in the likelihood of claiming equivalence erroneously and a larger chance of producer risk***	CHANGE: The requirement to use Cmax of the parent drug for bioequivalence assessment of peak exposure should be excluded.	C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite. For that reason, evaluation of C_{max} for parent is preferable also when metabolite data are used to establish bioequivalence for extent of absorption (AUC) and the draft guideline recommends evaluation of parent C_{max}, <u>if possible</u>. However,

	causing study failure. The bioequivalence of Cmax (as it is done for AUC) can be based on the data available for the metabolite as opposed to the parent compound.		given the advancement of the bio-analytical methodology, it nowadays is unusual that parent drug cannot be measured accurately and precisely. Hence, the use of metabolite as surrogate for active parent compound is expected to be very rare. Therefore, as parent Cmax likely would be very variable if at all quantifiable and in order not to complicate the conduct of bioequivalence studies in this rare situation, the guideline has been revised as proposed.
4.1.5 Lines 324-325 Appendix IV	**Parent compound or metabolites** The choice of parent compound versus metabolite evaluation for the conclusion of bioequivalence, including a decision tree is clarified in this paragraph and corresponding Appendix IV. However, products that do not fall into the tree also exist, for example when the active metabolite depends on the state of the disease and not on the dose.	It would be helpful to state here the recommendation on what should be measured in this case, the active metabolite or the parent compound.	The section has been revised. See also other comments
4.1.5:329-341	In case of non-linear kinetics and parent compound is inactive but can be assayed.	Parent compound should also be measured and bioequivalent as it is the one most affected by formulation differences. Metabolite measurement should only be done if metabolism reflects formulation differences.	Partly agreed. The section has been revised.
Lines 331-334	If there is a non-linear relationship or it is difficult to conclude linear PK from data available, and then a BE determination based on the more active metabolite is suggested. What are the quantitative measures of PK linearity? How much data need to be shown to demonstrate non-linearity?	Propose that additional guidance be provided on what data are needed to demonstrate non-linearity in PK	This paragraph has been revised and does no longer refer to linear or non-linear PK. See also response to comments on definition of non-linearity in section 4.1.6. Published or in-house data can be used to support the decision on linearity in PK. When no in house

			data are available the applicant is recommended to search the literature for all published data on PK of the substance, summarise this in module 2.7.2 discuss the linearity and draw conclusions regarding appropriate strength(s) to evaluate. This is briefly addressed in the revised section 4.1.6.
331-333, paragraph 4.1.5	There is no clear definition of linearity/non-linearity. This ambiguity might lead to the non-acceptance of a study if the authority comes to a different conclusion to the applicant. Furthermore, depending on the mechanism that leads to non-linear pharmacokinetics (e.g. related to post absorption processes or related to processes which have nothing to do with metabolite formation), a less specific measure arising from dosing with the formulation may be selected for BE assessment.	Differentiation between parent or metabolite on the basis of the linearity of pharmacokinetics should either be more precisely defined or removed. It is good practice that only one compound, i.e. either the parent compound or the metabolite, should be judged relevant for the assessment of BE. The decision which analyte is determined in case of inactive pro-drugs should be taken by the CHMP (irrespective of linearity of the pharmacokinetics) based on general principles: - parent compound: might better reflect differences in formulation, however may not reliably be measured and is clinically irrelevant. - metabolite: higher clinical relevance. As clinical relevance seems to have priority in this section of the guideline (metabolite data preferred in case of non-linear pharmacokinetics and if metabolite concentrations are	The guideline has been revised. This paragraph does no longer refer to linear or non-linear PK. The revised text recommends use of parent compound also for pro-drugs, but allows the use of active metabolite if parent cannot reliably be measured.

		very much higher compared to the parent compound), an option would be to request bioequivalence for the active metabolite specifically for inactive pro-drugs.	
Line 333 Paragraph 4.1.5	***"in case the pro-drug or active metabolites display non-linear pharmacokinetics (or it is difficult to conclude linear pharmacokinetics from available data), it is recommended to demonstrate bioequivalence for the main active metabolite."*** This does not take into account whether the active metabolite is detectable in significant concentrations, nor the fact that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. It is unclear how the non-linearity of a metabolite may be affected by the formulation? This is similar to the multiple dose BE question that was discussed in slides above. Is it likely that inactive ingredients may influence enzyme activities of enzymes only relevant for the metabolites? Are there any examples of this in the literature?	Determine BE for parent, unless parent cannot be measured, irrespective of nonlinearity PK of parent or metabolite.	The guideline has been revised taking this and other comments into account. Regarding the last part of the comment, see response to a similar comment on line 352-357 below.
334-335, paragraph 4.1.5	Specific data on the "inactivity" of a pro-drug from safety perspectives may not be available. This might lead to the request to assess bioequivalence both for the parent compound and the metabolite.	Evidence on "inactivity" of a parent compound from efficacy perspective might be sufficient.	The guideline has been revised taking this and other comments into account.
334-335 4.1.5 Parent Compound and Metabolites	The data relating to the "inactivity" of a parent compound from safety perspectives may not be publicly available. As it does not make sense to request bioequivalence for both parent and active metabolite, it should be sufficient to request bioequivalence for the metabolite only in those cases where determination of the metabolite is recommended in inactive pro-drugs (which usually means inactive from efficacy point of view).	CHANGE: Please correct the sentence accordingly. ***"****In such case, the parent compound does not need to be measured provided that it is inactive from an efficacy* ~~***and safety***~~ *perspectives*~~***.***~~*"*	The guideline has been revised taking this and other comments into account.
334-335	Some drugs have some *in vitro* activity, but because of low	CLARIFICATIONS:	The guideline has been revised to

4.1.5 Parent Compound and Metabolites	concentrations or relatively low affinity to the target receptor their *in vivo* activity is negligible. Hence, there is also a need to provide a definition of "inactive" to include such situations.	An indication of what is meant by inactivity should be provided.	include "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 the clinical efficacy." Morover in the revised guideline it is recommend use of parent compound also for pro-drugs, but allows the use of active metabolite if parent cannot reliably be measured. With this wording, we see no need to further define "inactive".
335-337, 342-34 4 .1.5 Parent Compound and Metabolites (Appendix IV)	Both for active and inactive pro-drugs there is the option to use metabolite data if the parent compound cannot be reliably measured. In cases where reliable measurement under multiple dose conditions is possible (but not under single dose conditions) it should be made clear whether preference is always given to bioequivalence based on the parent in a steady-state study rather than bioequivalence on the metabolite in a single dose study (one criterion should be sufficient).	Define procedure for cases where it is possible to reliably measure a parent compound only in a multiple dose but not in a single dose study.	The guideline has been revised. In case <u>active</u> parent cannot be reliably measured in a single dose study using the highest strength, it is recommended to use a higher single dose (provided it is well tolerated and there is not absorption or solubility limitation at this dose). If this is not possible, a steady state study to evaluate parent is generally preferred over a single dose study to evaluate metabolite. In case <u>inactive</u> parent (prod-drug) cannot be reliably measured in a single dose study, a single dose study to evaluate active metabolite is preferred.
338	In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of the parent compound.	In this situation it is acceptable to demonstrate bioequivalence for the main ~~active~~ metabolite without measurement of the parent compound.	Not agreed. This implies that measurement of an inactive metabolite to an inactive parent would be equally acceptable as active metabolite. Measurement of the active metabolite of a prodrug is

			preferred over measurement of inactive metabolite.
Lines 339-340	*"Exposure to active metabolite is very much higher than exposure to parent";*	Please define what is 'very much higher'	It is acknowledged that this was unclear. The paragraph has been revised.
339-341, paragraph 4.1.5, and Appendix IV	In the case of pro-drugs, it is acceptable to determine the metabolite only if its concentration is very much higher compared to the parent compound. However, no definition for "very much higher" concentrations is given. Furthermore, it is not clear whether it is an option (as suggested by the guideline text) or a requirement (as mentioned in appendix IV) for the applicant to select the metabolite in such cases.	Definition of a minimum ratio of metabolite / parent compound should be given, e.g. 5:1 or 10:1.	It is acknowledged that this was unclear. The paragraph has been revised.
339-341 4.1.5 Parent Compound and Metabolites	There is no clear definition of the term "very much higher". It is not clear in situations where exposure of an inactive pro-drug is low and exposure to an active metabolite is very much higher whether it is the choice of the applicant to use the pro-drug or the active metabolite for the assessment of bioequivalence.	CLARIFICATION: Please define the term "very much higher". CLARIFICATION: Please specify the possibility of using either the inactive pro-drug only or the active metabolite for assessing bioequivalence.	It is acknowledged that this was unclear. The paragraph has been revised.
Appendix IV & # 339-341 § 4.1.5	Please clarify what is considered "major contribution" with respect to active metabolite with major contribution. Please clarify what is considered "very much higher" with respect to active metabolite exposure versus pro-drug exposure.		It is acknowledged that this was unclear. The paragraph has been revised.
# 342-351 § 4.1.5	It is unclear whether or not it is acceptable to administer multiple units of the highest strength as a single-dose to achieve sufficient plasma concentrations for characterization of the pharmacokinetics of the parent provided the single-dose is within the labelled claim and can safely be administered to healthy volunteers.		It is acceptable to administer multiple units of the highest strength as a single-dose to achieve sufficient plasma concentrations for characterization of the pharmacokinetics of the parent provided that there are no absorption or solubility limitations

			at this dose level. The dose may exceed the highest labelled dose provided that it can safely be administered to healthy volunteers. This has been clarified in section 4.1.6
352	The guidance states "*In exceptional cases, bioequivalence of active metabolite(s) may need to be demonstrated in addition to parent drug"* Although a summary explanation is given for the cases when this would be required, additional clarification would be required and perhaps a more precise description of when this type of requirement would be necessary. In addition, from a biopharmaceutical standpoint, it might be difficult to demonstrate how metabolite concentrations may reflect differences in formulation.	An example or clarification would be helpful for circumstances where BE should be demonstrated using BOTH Parent and Metabolite.	The requirement for measurement of active metabolite has been removed, see explanation above.
Line 352-354	It is stated that bioequivalence of active metabolite(s) may need to be demonstrated if the metabolite(s) has a major contribution to clinical efficacy.	Please clarify how major contribution is defined.	The requirement for measurement of active metabolite has been removed, see explanation above.
352-357, paragraph 4.1.5, and Appendix IV	The wording "…and metabolite concentrations may reflect differences in formulation which may not be detected in parent compound" is very vague. Although the intention is to require BE studies both for the parent compound and the metabolite only in "exceptional cases", the current wording can lead to divergent interpretations and effectively lead to possibility of requiring studies on both parent and metabolite in the majority of studies.	The exceptional situations when both parent and main active metabolite have to be measured should be more clearly defined. If this is not feasible, we suggest a change in the wording to "…and there is evidence that metabolite concentrations reflect differences in formulation which cannot be detected in the parent compound".	The requirement for measurement of active metabolite has been removed, see explanation above.
352-357 4 .1.5 Parent Compound and Metabolites (Appendix IV)	It is not clearly defined to which situations the "exceptional cases" refer; the current definition, using the word "may" twice, is too vague ("…*metabolite concentrations may reflect differences in formulation which may not be detected in parent compound*…"). *"In exceptional cases BE of active metabolite(s) may need to be demonstrated in addition to parent drug."* Does this imply that for parent drug and for the active metabolite(s)	CLARIFICATION: Redefine situations when both parent compound and metabolite data have to be taken into account in BE assessment. CHANGE: In Appendix IV, amend the text in the	The requirement for measurement of active metabolite has been removed, see explanation above.

	the 90% confidence interval will have to be within the acceptance range? This may be difficult as it increases the probability of a Type II error (increased producer risk). Clarification would be welcome.	box as follows: *"Is there* ~~***a risk***~~ ***evidence*** *that metabolite concentrations may reflect differences in formations that are not detected by parent compound"*	
Lines 352-357	It is unclear how the non-linearity of a metabolite may be affected by the formulation. What are examples? Does the paragraph relate to the possibility that inactive ingredients may influence enzyme activities of enzymes only relevant for the metabolites? Please specify.	Please delete the following part of the paragraph: "…in parent compound, ~~such as drugs with linear pharmacokinetics for parent compound and where…..and/or elimination~~.	In case of saturation of the elimination, the level of saturation, ie the rate of metabolite formation, depends on the concentration in the liver. The saturation of the enzyme becomes more pronounced during first-pass. Metabolite formation will decrease with increasing rate of absorption. The hepatic extraction of drug, and the amount of metabolite formed during first-pass will be formulation dependent Hence, if there is a small difference between formulations in rate of absorption of parent compound (but bioequivalence could be demonstrated for parent), the difference in metabolite exposure could be larger (resulting in 90% confidence intervals partly outside the acceptance limits) if the metabolite has non-linear formation or elimination. However, for the reasons specified above it is agreed to focus on parent compound.
352-357	"In exceptional cases, bioequivalence of active metabolite(s) may need to be demonstrated in addition to parent drug. This is applicable if the metabolite has a major contribution to clinical efficacy of an active substance and metabolite concentrations may reflect differences in formulation which may not be detected in parent compound, such as drugs with linear pharmacokinetics for	The wording "major contribution to efficacy" is rather broad. A precise definition of "major contribution" and "clinical efficacy" /e.g. primary, relevant pharmacodynamic effect? Or relevant adverse effect?) would be	The requirement for measurement of active metabolite has been removed, see explanation above.

	parent compound and where the active metabolite shows non-linear pharmacokinetics caused by significant saturation of formation and/or elimination. “	helpful.	
353, paragraph 4.1.5	Definition of “major contribution” is missing	Limits should be defined, e.g. at least 50% of the total activity or at least a comparable activity compared to the parent compound.	The requirement for measurement of active metabolite has been removed, see explanation above.
Line 353	Multiple companies asked for additional detail for the definition of a major contribution. Quantification of pharmacological activity is sometimes easier, but e.g. 10% of contribution to pharmacological activity is considered not major and 50% is? If the active metabolite leads to more adverse events than the parent compound (safety issue), it might be also important to demonstrate the bioequivalence also on the active metabolite.	To define the wording “a major contribution to clinical efficacy” and to add in the proposed annex-glossary	The requirement for measurement of active metabolite has been removed, see explanation above.
358	Definition of “significant contribution” is missing.	CLARIFICATION: Please add a definition of “significant contribution”.	The requirement for measurement of active metabolite has been removed, see explanation above.
Line 358-362	It is stated that when evaluating the significance of the contribution of an active metabolite to the clinical efficacy, available information on differences in AUC and pharmaco-dynamic activity and protein binding between parent compound and metabolite need to be taken into account. It is questioned how often this type of information is publicly available.	Please clarify how it should be determined in practise if bioequivalence of an active metabolite will be required and by whom and based on what.	It is agreed that publicly available information on activity and protein binding may be scarce. The requirement for measurement of active metabolite has been removed, see explanation above
358-362	“When evaluating the significance of the contribution of an active metabolite to the clinical efficacy, available information on differences in AUC and pharmacodynamic activity between parent compound and metabolite should be taken into account. Depending on how pharmacodynamic activity has been determined, differences in protein binding between parent compound and metabolite may also need to be taken into account.”	The assessment of differences in the relationship between the pharmacokinetic parameter (AUC) and (unspecified) pharmacodynamic activity between the parent compound and the metabolite is often not feasible or the data are of doubtful value (due to lack of adequate/ valid published data and the known drawbacks/limitations of inter-study comparisons), appears unjustified from a scientific point of	The paragraph has been deleted. It is agreed that publicly available information on pharmacodynamic activity may be limited and of poor quality and that other parts of the paragraph may be difficult to understand. For this and other reasons requirement for measurement of active metabolite has been removed, see explanation above.

		view and seems to be of questionable relevance in the context of bioequivalence evaluation. The meaning of the sentence "Depending on how pharmacodynamic activity has been determined, differences in protein binding between parent compound and metabolite may also need to be taken into account" remains unclear. It is not understood why the method of PD assessment should be influences by the unbound, free fraction of the parent compound and/or metabolite or vice versa. Overall the whole paragraph is confusing and does not help to solve the problem how to assess the magnitude to which a metabolite contributes to clinical efficacy. We suggest deleting this paragraph or revising it.	
359 4 .1.5 Parent Compound and Metabolites	Cmax may also play a role in the definition of "significant contribution".	CHANGE: Please modify the sentence as follows: *"available information on differences in AUC**, C(max)** and pharmacodynamic activity"*	It is true that Cmax also may be of importance. However, AUC is expected to be more important, and in order not to complicate this evaluation it focused on AUC. However, the requirement for measurement of active metabolite has been removed, see explanation above.
323-362, Appendix IV	Comment: When I read the section of "Parent compound or metabolite", my understanding was that the parent compound should be the primary surrogate for BE. However, appendix IV led me to a different conclusion. I find lines 323-362 easier to read than appendix IV. Rationale: For clarification and interpretation.	Remove appendix IV. Remove lines 324-325. After line 328, add a sentence to emphasize that this guideline applies to inactive pro-drugs. There is a lot of information in 329-362.	Appendix IV has been removed

		Perhaps it would be easier to describe each case as exceptions (separately in bullet form), that metabolite could be considered.	
Line 363.	This section is very poorly written. The guidelines states that the achiral bioanalytical method may be applied, as one of the requirements, if enantiomers have same pharmacokinetics and same pharmacodynamics. Please note pharmacokinetics and/or pharmacodynamics cannot be the same. However they can be similar. It is advised not to use the word "same". It should be emphasized that the pharmacokinetics and/or pharmacodynamics of enantiomers are never the same. Achiral assay should be acceptable if the proportions of the isomers are equal in the active drug. Chiral assay should be carried out if the active drug is a specific enantiomer. Inter-conversion of enantiomers is also an in vivo post absorption process. Often reliable information on these aspects may not be available in the literature. In order to acquire all stated information on enantiomers, one needs to study the clinical pharmacology under all conditions. This could be difficult and resource intensive.		The text has been revised based on this and other comments
363-370, 4.1.5	If a racemat is used in both the test and the reference product, the only scientifically sound reason for using a chiral assay is given in cases where the concentration ratio of enantiomers is modified by a change in the rate of absorption. If this is not the case, differences in PK and/or PD are not relevant, because they will apply to the test and the reference product in the same way. The requirement of the draft guideline is problematic for the following reasons: - Definitions for same PK and PD are missing (lines 366-367). - Data on the PK and/or PD of the enantiomers may not be available in literature (lines 366-367) - In most cases, no information is available if the concentration ratio of enantiomers is modified by a change in the rate of absorption. This is in particular true for well-known substances (line 368).	Please change: "The use of achiral bioanalytical methods is possible when **both products contain the racemat, unless there is documented evidence that the concentration ratio of enantiomers is modified by a change in the rate of absorption.**"	Not agreed. Lack of documented evidence is insufficient proof that there is no difference. Moreover, with the proposal enantioselective analysis would be required also if there is no difference in PD between enantiomers. The text has been revised based on this and other comments.

	Therefore, by the definitions of the draft guideline, very uncomplicated and well-known substances would require a chiral assay. Therefore, we would suggest that for racemats, chiral assays are only required if there is documented evidence that the concentration ratio of enantiomers is modified by a change in the rate of absorption.		
370-371, 4.1.5	"Low contribution to activity" should be further defined.		Not agreed. A definition is not considered needed.
363-375	Comment: The information requested in the guideline for supporting the use of achiral bio-analytical methods is very difficult to access. This information is often not available. Rationale: Information unavailability.	Word the guideline in a reversed way. i.e. chiral method will be required if there are demonstrated differences in PK, PD, concentration ratio modified by a change in the rate of absorption changes, or in-vivo inter conversion…	Partly agreed. The text has been revised based on this and other comments
366-367, paragraph 4.1.5	It is hardly possible to demonstrate the "same" pharmacokinetics or pharmacodynamics of two enantiomers.	"Same" should be changed to "similar".	Partly agreed. The text has been revised based on this and other comments
368, paragraph 4.1.5	The wording "the concentration ratio of enantiomers is not modified by a change in the rate of absorption" is open to different interpretations.	If the intended meaning of the wording is "the concentration ratio of enantiomers is not modified by a difference in the rate of absorption" it should be changed accordingly.	Agreed
Line 368	The use of achiral bioanalytical methods is possible if….. a) The criteria for the use of achiral methods have been made considerably more stringent. This means that in most cases enantiomeric bioanalytical methods will have to be used, because most enantiomers do not have exactly the same pharmacokinetics or pharmacodynamics (it is virtually always possible to find a parameter that deviates). b) It is not clear how it can be demonstrated that the concentration ratio of the enantiomers is not modified by a change in the rate of absorption other than by doing a clinical study in-vivo with different formulations (or food maybe).		Partly agreed. The text has been revised based on this and other comments and is now more similar to the FDA guidance. If it is known that there is a difference between enantiomers in both PK and PD and information regarding the third bullet point is unavailable, measurement of individual enantiomers is recommended.

374-375 Enantiomers	Clarification is required on what evidence is sufficient to confirm a lack of chiral interconversion. There is no guidance on how an Applicant may demonstrate a lack of chiral inversion. In the case of a single enantiomer, will *in-vitro* evidence of no interconversion justify the use of an achiral method?	CLARIFICATION: More guidance is needed as to the evidence required to confirm a lack of chiral interconversion.	This paragraph has been removed.
Line 376: The use of urinary data	The combined application of urinary and plasma data (peak exposure) to document bioequivalence is not scientifically appealing. Bioequivalence should be based on a single set of data from a single biological matrix. Even with advancements in bioanalytical field, in a specific case plasma drug concentration cannot be reliably measured, bioequivalence should be established on the basis of urinary data.		Not agreed. The combination of urinary and plasma data should be used, if possible.
377 4 .1.5	In case it is possible to reliably measure plasma concentrations in multiple dose studies, but not in single dose studies, it should be clarified whether such multiple dose studies are preferred over the use of urinary data.	CLARIFICATION: Should be specified.	In case active parent cannot be reliably measured in a single dose study using the highest strength, it is recommended to use a higher single dose (provided it is well tolerated and there is not absorption or solubility limitation at this dose). If this is not possible, the approach to take (a steady state study to evaluate parent, urinary data to evaluate parent or a single dose study to evaluate metabolite) needs to be decided case by case.
4.1.6 Strength and dose to be investigated (line 383-442)			
4.1.6 Strength and dose to be investigated	This entire paragraph is quite complex (see above "general comments"). To avoid any confusion on the choice of strength and dose to be investigated, it is important to define exactly the wording "strength" and "dose". What does "highest dose" mean exactly? : - the "highest unit dose" (the highest dose contained in a unit of test product)? The "highest dose recommended in therapeutic use"?	To use the appropriate wording for "strength" and "dose" and to define them in the proposed annex-glossary. To illustrate by a medicinal product example (cf. proposal In Appendix V)	Partially agreed. The section has been structured in subheadings in order to clarify. The difference between strength and dose is evident. However, for simplicity the dose is no longer considered.

	This section again is poorly worded. There is a lot of important information that needs to be separated and deleted from this section and put under different section This section should primarily describe what strength to use and at what dose to conduct bioequivalence study. Information on formulation proportionality of different strengths, solubility and dissolution characterization of different strengths, BCS approach, linearity and nonlinearity of the drug can be moved to a different section dealing with 'Wavier of bioequivalence Study". Generally, the highest strength and maximum daily recommended dose (if bioassay is a problem with the single dosage strength) as recommended in the product labeling should be applied.		The section has been restructured to be more clear. Defining the dose and strength to use is closely connected to that deciding what doses and strengths can be waived. Both aspects therefore need to be addressed together. The general recommendation is now to conduct the study with the highest strength. This applies both to drugs with linear pharmacokinetics and for drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range.
Lines 388-389	Please consider the perspective that drug product of several strengths might also be demonstrated and documented to be comparable if the drug product is manufactured at two different sites by the same manufacturing process and could adequately represent all strengths.	Please change as follows: "a) the pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process, **OR if appropriate comparability documentation is provided, the drug products may be manufactured at different sites by the same manufacturing process**"	It is accepted that the criteria should be consistent with the Variation Regulations and that reference to the manufacturing site be deleted. In line with current requirements, manufacture at two sites would need to be supported by appropriate batch and validation data, which would include compliance with the Finished Product Specification. This information would comprise any comparability documentation. Reference to the same manufacturing site has been deleted
Lines 388-389	Guideline: a) the pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process,	Guideline: a) the pharmaceutical products are manufactured by the same	Agreed

	Comment: According to the *Guideline on dossier requirements for Type IA and IB notifications* (July 2006) variation no. 7c: 7) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product c) All other manufacturing operations except batch release no additional bioequivalence studies are required for replacement or addition of a manufacturing site as long as the manufacturing process remains unchanged. Consequently, lines 388-389 of the draft guideline under discussion are contradictory to the existing guideline on notifications Type IA and IB and should be made consistent.	manufacturing process,	
388, 4.1.6	A change of the manufacturing site is normally possible without a biostudy if the manufacturing process is the same (see regulation 1085/2003). Why is it so strictly necessary to have the same site for all proportional strengths, if after approval a change of the site is easily possible without the need for a biostudy even for single strengths?	Please change: "a) the pharmaceutical products are manufactured **by the same manufacturing process.**"	Agreed
388 to 389	Considering that a change in the manufacturing site after granting of the marketing authorisation does not require the conduct of a bioequivalence study as long as the manufacturing process remains unchanged (cf. provisions for variation no. 7 "Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product" c) in the Guideline on Dossier Requirements for Type IA and IB notifications, June 2006), it is inconsistent to require manufacture of all strengths by the same company and at the same site prior to approval as a precondition for acceptance of a waiver.	Revise point a) as follows: "a) the pharmaceutical products are manufactured by the same manufacturing process,"	Agreed
382 -442 4.1.6 Strength and dose to be investigated	Throughout section 4.1.6 the highest dose is referred to as the dose of choice. Examination of the decision tree provided in appendix V shows that due to a certain lack of clarity at various decision points, (eg, the linearity of the PK is unknown), in many cases the highest dose, and not the highest strength, will be required.	CHANGE: The guidelines should be amended to remove the direction to use the highest dose and specifically allow the continued use of the highest strength.	Agreed. The requirement of the highest dose is deleted for feasibility reasons.

	This will lead to large doses in healthy volunteers and to the possibility of ethical issues. Doses may be required that are a combination of a number of tablet strengths. High doses may exclude volunteers and involve patient studies. These in turn will be steady-state studies which are commonly understood to be less sensitive. The EGA cannot rationalise this use of multi-unit dosing where unnecessary, and cannot see how this will improve the delineation of non-equivalent formulations. Inequivalency will be apparent at normal highest strength doses. There are often cases where the "highest dose" is different from country to country, and dosing at these high doses may represent only a minute proportion of the therapeutic "normal practice".		
382-442, 4.1.6 Appendix V	We acknowledge that the reasoning and the decision tree on the issue of strength and dose to be investigated were prepared with great attention to detail trying to include any possible case. However, as a lot of factors should be considered for this decision, the conclusions may be ambiguous and divergent. E.g. - Data on BCS class may be missing or be ambiguous. - It may be difficult to assess whether a filler may affect absorption or solubility. - Data may be missing or be ambiguous, if there is a greater or smaller than proportional increase with increased dose. - Data may be missing or be ambiguous with regard to the reason for non-linearity. For this reason, we propose to include a straightforward requirement similar to the current guideline, irrespective of solubility, BCS class, effects of filler and reasons for non-linearity.	In case all conditions a) to e) are fulfilled (or, if d) is not fulfilled, the 5% rule is fulfilled), one study at any dose can be performed. In case all conditions with the exception of linearity are fulfilled, one study should be performed - at the highest dose in case of greater than proportional increase - at the lowest dose in case of smaller then proportional increase - at the highest and the lowest dose in case it is unknown whether there is a greater or smaller than proportional increase.	The section has been restructured to be more clear. The general recommendation is now to conduct the study with the highest strength. This applies both to drugs with linear pharmacokinetics and for drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range. If the highest strength is not tolerable a lower strength may be justified.
382-442, 4.1.6 Appendix V	In case of a product with several strengths which are not fully proportional over the entire dose range, it should not be required to perform a study for each strength. In such cases bracketing should be allowed.		Agreed. A section on bracketing has been included

386-417 4.1.6 Strength and dose to be investigated (see also 858-864)	The guideline states without doubt that any individual active substance has to fulfil all the conditions a) to e) if a biowaiver is claimed for additional strengths. Some deviations to this rule are accepted in the case of both high and low solubility substances having less than 5% in active substances. However, the situation is not clear for fixed combinations of active substances which do not keep the proportionality between them, as is widely known to happen with the combination of most of the anti-hypertensive drugs and diuretics, in which case it is completely impossible to fulfil condition d). When bibliographic evidence exists to establish that between the concerned active substances combined in a given strength there is no interaction that could affect any of the critical PK parameters or bioequivalence, a biowaiver should be possible based on fulfilment of conditions a), b), c), e) and accepting deviations from condition d). It is unclear whether active substances should be considered separately for fixed-combination products. Lines 860-862 might be interpreted accordingly. However, the "(s)" in "substance(s)" in line 409 for example, implies that the sum of all actives, not the individual ones, has to be <5% in order to have deviations from criterion d) accepted. For fixed combination products a deviation in condition d) — provided that the "<5% criterion" is met — should be applicable for one active in a combination product if another active is present in larger quantities but meets criterion d). Example: It should be possible to extrapolate from the 80/12,5 mg strength, total tablet weight 612,5 mg, to the 40/12,5 mg strength, total tablet weight 312,5 mg, if the amount of excipients is exactly half in the 40/12,5 compared to the 80/12,5 mg strength.	CHANGE: The paragraph should include a reference to this scenario CHANGE: In line 393-4, please amend as follows: "*ie, the ratio between the amount of each excipient to the amount of* ***each*** *active substance is the same for all strengths [...]"*	Partially agreed. A section on FDC will provide some information.
390, 4.1.6	For proof of linear pharmacokinetics, it should be sufficient to refer to AUC. Registrations have been granted e.g. for ramipril only on the basis of a biostudy with the highest strength with ramipril being	Please change: "b) linear pharmacokinetics, i.e. proportional increase **in AUC** with increased dose	Agreed. Linearity will be defined based only in AUC.

	only linear for AUC and not for Cmax.	..."	
390-391, paragraph 4.1.6	Since the variability of C(max) is usually much higher than that of AUC and there is some fog in the definition of linearity of pharmacokinetics, many interpretations of the degree of linearity/non-linearity in defining C(max) as a robust measure may occur. It might be sufficient to consider just one of the terms - AUC or C(max) –provided that no strong deviations from linearity are observed. Additionally, as only the therapeutic dose range is relevant, a linear instead of a proportional increase in this range should be sufficient.	Wording should be changed to "b) linear pharmacokinetics, i.e. linear increase in AUC with increased dose, over the therapeutic dose range". Alternatively, a requirement that C(max) demonstrates no strong deviations from linearity may be added.	It is agreed that Cmax may be more variable than AUC, that estimates of Cmax are more dependent on sampling than AUC and that a larger deviation from linearity would be acceptable for Cmax than for AUC. Therefore, linearity will be defined based only in AUC.
390-391	Comment: What is defined as linear PK? The guideline uses AUC and C_{max} as measure. I think only dose-normalized AUC should be used. Additionally, the differences in percentage should be defined. Rationale: Dose normalized AUC is a better surrogate to determine the PK linearity. The criteria for assessment should be clear.	Linear PK, i.e. proportional increase in AUC with increased dose. A drug with a difference <25% in dose-normalized AUC is considered as linear pharmacokinetics.	A definition of nonlinearity similar to that proposed has been added.
390	One of the conditions to be fulfilled in order to use only one dose for bioequivalence testing is "*b) linear pharmacokinetics, i.e. proportional increase in AUC and Cmax with increased dose, over the therapeutic dose range"* However, sometime the information on linearity is not available. In those cases, would it be reasonable to assume that there are no deviations from linearity and test only one dose?		With the general recommendation in the revised wording of this section, consideration only needs to be given to a non-linear absorption resulting in less tha proportional increase in AUC with increased dose. If data on linearity is lacking, and it cannot be excluded that there may be non-linear absorption, bioequivalence should be established at the lowest and the highest strengths.
390 4.1.6 Strength and	In sub-paragraph b), it is unclear whether the condition relates to the "linearity" of pharmacokinetics or "dose proportionality". Clarification would be necessary.	CLARIFICATION: In order to gain clarity, the wording of the current guideline should be used, ie,	By definition linear PK is when the primary pharmacokinetic parameters (CL, V, F, ka) are

dose to be investigated	Active substances can have linear pharmacokinetic profiles on the dose range concerned, ie, there is a linear rise in AUC and Cmax (without passing through the origin, ie, without proportionality). Clarification is also needed as to whether "linearity" would apply to both AUC and Cmax. Cmax is usually too variable to make such a conclusion and hence, should be removed, particularly if there is evidence that AUC is linear.	*"the drug input (as measured by AUC) has been shown to be linear over the therapeutic dose range"* CHANGE: Please remove Cmax.	unchanged with dose, resulting in proportional increase in exposure with dose. A "linear" increase in AUC and Cmax without proportionality is not consistent with unchanged primary PK parameters, and may warrant selection of the most sensitive strength to detect potential differences between formulations. See comments above regarding removal of Cmax.
Line 390: (b).	How to know whether formulation factors are influencing the pharmacokinetics of the drug without conducting several studies? This information may not be available to decide on the strength and dose. Difference between "dose" and dose-strength" should be clearly separated while examining pharmacokinetic linearity. One can conduct a dose escalation study with multiples of the same strength to examine dose linearity using single strength of the drug product. On the other hand, a dose escalation study can be conducted using single unit of different strengths. The results from this study would provide information on the linearity as a function of formulation. It is necessary to differentiate between "linearity" and "dose proportionality". This section requires major revision.		Studies determining dose proportionality are conducted by the originator company during the development of the NCE. It is out of scope of this guideline to state how these studies should be conducted. See also comment above regarding "linearity" and "dose proportionality".
4.1.6 Line 393	The draft guideline states "d) […] i.e the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths …" However, the current note for guidance CPMP/EWP/QWP/1401/98, reads as follows "the ratio between amounts of active substance and excipients is the same" With the current guidance the percentage of each excipient was calculated based on total tablet weight and subsequently compared between strengths. According to the draft guideline the percentage of each excipient should be calculated based on active substance	For clarity to interpretation of this sentence the authorities are asked to state a more precise example of	Not agreed. The meaning is the same.

	amount and subsequently compared between strengths. This can result in large differences.	calculation.	
393-394, 4.1.6	The criterion should be changed, so that a combination product with a dose of 300 mg/10 mg can be considered proportional to a product with a dose of 150 mg/10 mg.	Please change: "c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount **of active substance (in case of combination products, where the active substances do not influence each other´s PK: to the amount of one of the active substances)** is the same for all strengths …"	Not agreed. In case of combination products the other active substance should be considered as an excipient for proportionality calculations. This is clarified in a separate paragraph in the revised guideline.
393-396, 4.1.6	The definition of proportionality should also include special modified-release dosage forms.	Please add: "For diffusion controlled modified-release products, the proportionality may only be restricted to the surface area of the diffusion controlling layer."	Not agreed. This is out of the scope of this guideline. This guideline refers only or mainly to immediate release
394-396, 4.1.6	Although this draft guideline refers primarily to immediate-release products, the definition of proportionality should be amended to also include modified-release products, as the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96) refers to the guideline for immediate-release dosage forms with regard to the criteria for extrapolating bioequivalence. Therefore, the criterion on proportionality should be changed, so that also for modified-release products, non-functional films, colour agents and flavours are not required to be proportional.	Please change: "**(non-functional films,** colour agents and flavours are not required to follow this rule)."	Not agreed. This is out of the scope of this guideline. This guideline refers only or mainly to immediate release.
395 4.1.6 Strength and dose to be investigated	The list of exemptions should include the composition of capsules (immediate release oral dosage forms).	CHANGE: Please amend as follows: "*for immediate release products, coating components**, capsule shell**, colour agents and flavours are not required to follow this rule*"	Agreed
Lines 395-396	Consider placing "immediate release products" at the end of the sentence so that it is not confused with one of the conditions.	"…i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths	Not agreed. the scope is only immediate release

		(coating components, colour agents and flavours are not required to follow this rule for immediate release products."	
Line 397	What does "appropriate" mean in terms of dissolution data?	Add specific requirement, e.g. f2 NLT 50	Not agreed. Details are given in section 4.2
Lines 397-398	Appropriate in vitro dissolution data may be used to waive additional bioequivalence testing in vivo. Please clarify text to indicate that IVIVC modelling may be used in lieu of any clinical testing in vivo.	"An IVIVC may be used to support the waiver of additional in vivo or in vitro testing"	Partially agreed. It has to be a level A IVIVC and it only waives in vivo studies in case of this composition changes had been considered for the IVIVC. This possibility is described in section 4.4.
399, 4.1.6 406-407, 4.1.6 425, 4.1.6 430-431, 4.1.6 435-442, 4.1.6 Appendix V	The requirement to perform studies with the highest commonly recommended dose using the highest strength should be deleted, as this implies several problems: - There may be safety concerns to give this dose to healthy volunteers, e.g. for narcotic drugs. - It may be difficult to perform a study in patients, as the highest dose may not frequently be used in patients. - It may be necessary to perform studies in patients under steady state conditions, which are generally considered to be less sensitive than single dose studies. - It is unclear which dose is to be chosen, if the highest dose is different between EU countries. - It is unclear which dose is to be used, if the dose is to be individualized according to the SmPC. - There may be cases where the applicant plans to develop additional higher strengths after he has received marketing authorization for a product. In such cases, the study was not performed on the highest strength, because this was not yet available at the time of study conduct. - The application of more than one tablet may lead to multiple peaks and thus render the estimation of Cmax imprecise.	One single tablet of the highest strength should usually be administered in these cases. Conduct of a study at a lower dose should be possible, if justified by sound reasons (e.g. safety concerns). The requirement to meet an acceptance range of 90-111%, if another than the highest dose is used, should be removed.	There is a scientific rationale for recommending the highest dose when this is most sensitive to detect differences between formulations. However, it is acknowledged that there are a number of difficulties with the text proposed in the draft guideline. In order to harmonise with other guidelines (e.g. FDA), the guideline has been revised to focus on strength instead of dose. When the highest strength is not tolerated in healthy volunteers, a bioequivalence study at the highest tolerated strength may be justified.

	- The requirement to meet a 90-111% acceptance range in cases where a lower dose was chosen leads to considerable increases in sample size. Also, this would mean that the acceptance range depends largely on the labelled dosing regimen. E.g. in one case the SmPC states that the maximum dose is one tablet, in another case the SmPC states that the maximum dose is two tablets. A study performed with one tablet would be assessed based on different acceptance ranges in these two cases.		
402 Strength and dose to be investigated	The current wording is ambiguous. A definition of "a low solubility drug substance" is missing, so it is open to interpretation.	CLARIFICATION: The guideline implementation would benefit from a definition of a low solubility drug substance.	The section has been revised and no longer refers to low solubility compounds.
Lines 402 to 404	Flexibility as needed as it is not always feasible to conduct a BE study at the highest dose in some therapeutic areas, e.g. oncology,.	However, in case of low solubility drug substances, **unless otherwise justified**, the bioequivalence study should be conducted at the highest dose, using the highest strength, as these conditions are most sensitive to detect a potential difference between products. **It is accepted that in certain therapeutic areas, e.g. oncology it may not be practical to use the highest dose.**	Partially agreed. However, the proposed addition is too specific and is covered by other wording in this section and in section 4.1.3.
402-442, paragraph 4.1.6	It is mentioned in several different parts of this chapter that studies shall not only be performed in the highest strength but in the highest dose using the highest strength. First, it is not clear which dose/strength to use if highest of these vary from country to country. Second, administration of more than one dosage form may, in some cases, result in a multiple peak profile. This can occur when dissolution is occurring prior to gastric emptying or when the disintegrating formulation is emptied as several pulses. This leads to an unreliable estimation of C(max). In addition this may lead to a requirement of steady state studies in patients. Third, the purpose of a bioequivalence study is to demonstrate	It should be clarified if the highest dose/strength approved in any EU country or in the EU countries included in the application should be used. Additionally, use of the highest strength instead of the highest dose should be sufficient. The requirement to test a higher dose, if needed in any situation, should be limited to exceptional cases (e.g. in case of a evidence of strong deviation from linearity in pharmacokinetic parameters).	The guideline has been revised to recommend use of highest strength (when relevant) and not highest dose. See also comment above.

	equivalence in biopharmaceutic quality between two products. On these grounds, it seems to be justified to select the most sensitive strength rather than the most sensitive dose, if the latter does not reflect an own product.		
405-408, paragraph 4.1.6	In case of deviations from criterion d (i.e. no strict proportionality between strengths, and under conditions of pseudoproportionality for formulations with less than 5% drug substance) no BE study at the highest dose should be requested but it should be possible for the applicant to select the dose on pharmacokinetic, safety and analytical grounds. Justification: • Safety considerations might limit administration of the highest dose in such cases. • In situations where non-linear pharmacokinetics with a less than proportional increase of PK parameters with increasing dose is observed, a study using a lower dose should be more sensitive in the detection of differences.	Same requirements should apply for formulations with deviations from criterion d) but meeting the "<5% criteria" as for those with strict proportionality.	The section has been restructured and revised to be more clear. The same requirements apply for formulations with deviations from criterion d) but meeting the "<5% criteria" and those with strict proportionality.
405-410 4.1.6 Strength and dose to be investigated	Sponsor should have the choice of selecting the strength based on sensitivity/ safety/ analytical ground also in case of deviations from a strictly proportional composition if the amount of active is <5% in order to avoid situations where more than one study is needed (eg, in case of a less than proportional increase of PK parameters with increasing dose, a study in the lowest strength would be requested) or to avoid safety issues.	CHANGE: Modify wording accordingly.	Agreed.
405-416 4.1.6 Strength and dose to be investigated	In cases where the "<5% criterion" is not met, but one of the other two options are (in lines 411-416), it is unclear whether it would be sufficient to perform a bioequivalence study on the highest and lowest strength and not at each strength within the dose range. It is not clear whether the "<5%" criterion applies only to the extrapolated strength or also to the one in the BE study. For example, is it possible to extrapolate from a study with a tablet of 260 mg total weight and 20 mg API to a strength with 250 mg tablet weight and 10 mg API (ie, identical amount of excipients in	CHANGE: The possibility to use a bracketing approach should be included. CLARIFICATION: Please clarify whether the "<5%" criterion applies only to the extrapolated strength or also to the one in the BE	Agreed. A bracketing approach is accepted and has been included in a separate paragraph. The "<5%" criterion applies also to the one in the BE study.

	both strengths)?	study.	
Lines 405-416	This paragraph defines what constitutes a "quantitatively proportional" formulation. The definition is different from the FDA's definition of "proportional similarity".	Proposal to harmonise with the FDA requirements.	Not agreed.
405-417, 4.1.6	It should be specified how many studies are required, if some of the strengths fulfill the 5% rule, but others do not, as the amount of active substance is > 5%.		Not agreed. It is not possible to define it, since it is not possible to know how many are outside of the 5% rule. A bracketing approach is accepted and has been included in a separate paragraph.
Line 409	For a bilayer FDC does the 5% refer to the whole or only one layer?	Please specify.	For a bilayer FDC the 5% refer to each layer independently. This has been clarified in the revised text
409-416, paragraph 4.1.6	In case the amount of active substance is less than 5%, two options are currently allowed: 1. strict proportionality, amount of excipients is different between strengths, ratio of active/excipients and ratio between excipients remains the same 2. amount of excipients remains the same (with the option to compensate for differences in active substance by one filler), ratio active/excipients is different between strengths, ratio between excipients obviously remains the same In order to give a little more flexibility to the applicant (e.g. to meet dissolution similarity or to develop similar formulations as the originator), it would be helpful to be able to formulate other strengths and formulations within the range defined by the two options mentioned above. For example, in a biostudy of a formulation with 2 mg of active and 100 mg of excipients, it should be possible to extrapolate to a formulation with 1 mg of active and either 50 mg of excipients or 100 mg of excipients and also to a formulation with 1 mg of active and 75 mg of excipients, provided	Add a fourth bullet point after line 416 e.g. with the wording - the ratio between different core excipients is the same and the amount of different core excipients of further strengths is within the range defined by strict proportionality between strengths on one side and same amount of core excipients between strengths on the other.	The proposed additional bullet point is not agreed. The revised guideline gives the possibility of a bracketing approach. This is, however, only possible when two BE studies have been conducted.

	that the ratio between excipients remains the same.		
409-416, 4.1.6	The principles of proportionality should not be restricted to capsules or tablets. The principle should also be applicable to other solid oral dosage forms.	Please change: "in case the amount of the active substance(s) is less than 5% of the tablet core weight, the weight of the capsule content **or an analogous reference weight of other dosage forms**…" "the amounts of the different **concerned excipients** or capsule content …" "The amounts of the other **concerned excipients** or capsule contents should be…"	It is agreed that the principle of proportionality is applicable also to other solid oral dosage forms. However, the text is considered sufficiently clear and the proposed change not needed.
4.1.6 Lines 409-416	It is not clear if less than 5% requirement is a must and one of the other two bullets should apply or if, in cases where a change in filler to account for a change in amount of active substance (3er bullet), the 5% limitation (1st bullet) is not a requirement.	Clarification is required on the wording.	Agreed. The text has been revised to clarify this
411 4.1.6 Strength and dose to be investigated	The guideline refers to the notion that "amounts of the different core excipients or capsule content are the same for all strengths". The EGA considers it sufficient if the ratio between excipients remains the same, apart from small changes in filler to compensate differences in the amount of active, as is the case in the current guideline. Particularly in case of strict proportionality, only the ratio is required to be the same, and not the actual amount of excipients. An alternative might be to keep the amount of excipients within the range defined by strict proportionality between strengths on the one side, and the same amount of excipients between strengths on the other side.	CHANGE: Should be modified.	Not agreed. The present proposal is flexible enough. Deviations from the present proposal are consider large enough as to require a BE study.
4.1.6. Line 411	In this sentence it is said that comparisons of excipients between the different strengths should be based on amount and not ratio according to line 313 of this draft guidance.	Clarification is required on this incongruence.	Not agreed. There is not need of clarification since this texts refers exactly to the case of drugs at <5% in the tablet core. In this case the amount of excipients is not changed and only the amount of the drug is

			increased or decreased to obtain the different strengths. An additional change of filler to obtain the same weight in the tablets is acceptable. If the ratio were compared it would be the rule of exact proportionality.
413, 4.1.6	Sometimes it is required that the amount of an excipient is connected with the amount of drug substance, e.g. a pH adjusting substance. I.e.: If a high amount of drug substance is included in the dosage form, even a high amount of this excipient is required, and vice versa. In this case the varying amount of the active and the varying amount of this particular excipient is compensated by the filler. These cases are not covered anymore with the new definition of proportionality.	Please change: "The amounts of the other **concerned excipients** or capsule content should be the same for all strengths**, except the amount of a particular excipients whose concentration is correlated with the amount of active substance."**	Not agreed. The situation referred to concerns a high amount of active substance. In this situation the condition c), quantitatively proportional composition applies.
4.1.6. Line 415:	For BCS class III compounds it should be reassured that the change in filler will not affect the solubility or absorption of the substance.	Could the document please indicate what considerations would apply in case of class II and class IV compounds? Does this mean that for class II and class IV compounds this will not be required?	It is agreed that the same would apply also for BCS class II and IV. However, considering that it is unlikely that such small change in the amount of a filler would affect absorption this requirement has been removed.
415-416 4.1.6 Strength and dose to be investigated	Reassurance that the change of filler does not affect solubility or absorption in case of BCS class III compounds seems unnecessary considering the small amount of additional filler (<5%) involved and the fact that the same filler is already used in the formulation in larger quantities.	CHANGE: Sentence should be deleted.	Agreed
416 4.1.6 Strength and dose to be investigated	"section IIIb Excipients" - to be corrected into section IV.2 Excipients	CHANGE: Please correct reference within the brackets.	Agreed.
417, paragraph 4.1.6	It should be made clear if a deviation of condition d) occurs (under provision that the "<5% criterion" is met) it is acceptable for one active in a combination product if the other active is contained in	Should be added.	A section of FDC has been added for clarification

	larger quantities but meets criterion d. (Example: It should be possible to extrapolate from the 80/12,5 mg strength, total tablet weight 612,5 mg, to the 40/12,5 mg strength, total tablet weight 312,5 mg, if the amount of excipients is exactly half in the 40/12,5 compared to the 80/12,5 mg strength).		
Line 417	It is suggested that application of waiver for additional strengths of fixed combination is also considering formulation principle. If the combination is a capsule product containing the active drug in two separate formulations, e.g. tablet + granulate, the dose proportionality of the compositions need only to be considered within each sub-part and not for entire formulation. For example if in vivo has BE established for the fixed combination capsule A 20 mg + B 10 mg, where A is coated pellets and B is a simple drug powder mixture, than an additional strength of A 20 mg + B 5 mg would be acceptable for bio-waiver given that the same A pellets and B powder mixture are used for both strengths.	Please add.	Agreed. This is similar to a bi-layer tablet, for which clarification is given in the revised guideline.
418-442, paragraph 4.1.6, and Appendix V	Handling of situations with deviations from criterion b (linear pharmacokinetics) and criterion d (proportionality of formulations) with an amount of active less than 5% is neither described in the text of the guideline nor in appendix V.	Should be added. The easiest option is to consider formulations with deviations from proportionality which meet the additional requirements for formulations with an amount of active less than 5% as in the case of strict proportionality (see comment to lines 405-408)	Agreed. The text will be modified to avoid this limitation.
418 4.1.6 Strength and dose to be investigated	Exemptions from condition b) should also be possible in case of deviations from condition d) as long as the additional "<5% criterion" is met.	CHANGE: Sentence should be modified as follows: "*If all conditions mentioned so far* ***(including deviations from condition d))*** *except b) above are fulfilled..."*	An additional paragraph addressing this issue has been added.
418	**Section 4.1.6 Strength and dose to be investigated**, lines 402-408 and 418-431 should be completely modified and adjusted according to my **serious issue** No. 1 as given in Appendix A (attached below). **Appendix V**, Page 29/29 should be adjusted according to above comment as presented in Appendix A. **Serious issue.**	The highest sensitivity for revealing the differences between two products in the case of the non-linear pharmacokinetics is at the lowest doses but not at the highest one as required. Therefore it is to be recommended to use the lowest strengths in both cases „greater than	It is agreed that for the example 3 given, the lowest dose would be the most sensitive. However, this scenario (most non-linear at lowest dose going towards linear at higher doses) is only one example of more than proportional increase in

		proportional increases“ as well as „less than proportional increases“ assuming that there are no analytical problems (the LLOQ of the method is sufficiently low). It is to be pointed out that lower doses should be preferred from the ethical point of view as well.	exposure with increased dose. Another scenario is when PK is fairly linear at lower doses and going into the non-linear range at higher doses due to saturation of the metabolising enzymes. In this situation, the highest dose would be most sensitive. In many cases there may be limited information on the characteristics of the non-linearity over different parts of the therapeutic dose range and it may be unclear which is the most sensitive dose to detect differences between formulations. Ideally in case of non-linearity all strengths in the non-linear range should be evaluated. This is, however, considered to be too strict as the difference in sensitivity between the different strengths is not expected to be of clinical relevance unless there is a fairly large deviation from dose proportionality. Also, the scenario with the largest non-linearity in the high dose range is considered more frequent than the one with the highest non-linearity at the lowest strength. We therefore maintain the suggestion to select the highest strength in case of more than proportional increase in exposure with increased dose.
418, 4.1.6 Appendix V	There is an inconsistency between the text and the decision tree. According to decision tree, in case of non-linear PK, proportional formulation is not required for waivers, according to line 418, this is required. Please clarify.		Section 4.1.6 has been revised and is now more simple. A decision tree is not considered needed anymore and Appendix V has therefore been

			removed.
Appendix V	The 2nd box on the bottom reads: "Conduct BE Study for each strength not fulfilling this criterion". It is unclear which criterion is meant. Please specify.		Section 4.1.6 has been revised and is now more simple. A decision tree is not considered needed anymore and Appendix V has therefore been removed.
Line No: 420 to 422	"Data on linearity in pharmacokinetics is sometimes limited or it may be difficult to conclude linear PK from the available data." If the information regarding Linearity in pharmacokinetics is not available, which strength and dose should be selected for Bioequivalence studies? Kindly clarify.		If data are too limited to conclude that there is no large deviation from dose proportionality within the therapeutic dose range the highest strength should be used unless data suggest a less than proportional increase in exposure. In this situation the evaluation of both the lowest and the highest strength is recommended if this may be related to low solubility. See also revised guideline text.
422-424, 4.1.6	If evidence of non-linearity is available or the available data suggest non-linear pharmacokinetics, the strength(s) and dose(s) to be used in the bioequivalence study(s) can be selected as follows: Since the decision of BE relies on assessment of the pharmacokinetic response (*e.g.*, AUC. C_{max}), applicants should be aware that in a massive non-linear system the requirement of ±5% differences (as stated in lines 202-203) in potencies of IMPs may be too wide (studies are likely to fail).	Add: For drugs with non-lineary pharmacokinetics the assayed content of products should differ less than ±5% (depending on the degree of non-linearity).	This is acknowledged. Applicants will need to take this into account in selecting the reference batch.
4.1.6. Line 425:	"The highest dose (using the highest strength)" It is not clear what the highest dose exactly means. Some questions raised at that point: - Is the highest *daily* dose meant, or the highest dose taken at one time? - What if the highest dose can not be achieved with the highest strength? - Would it for example be allowed to use 2 tablets of a lower	Provide more clarity on what's considered "highest dose, using the highest strength"	It is acknowledged that there are a number of difficulties, both practical and ethical, with the recommendation of the highest dose. Therefore the guideline has been revised to in general recommend use of the highest strength in healthy volunteers. The change has been introduced in order

	strength to achieve the highest dose? - Would it be allowed to take two tablets of different lower strengths, or is it preferred to have the same strength wherever possible? - If the highest dose is only a fraction higher than the highest strength (for instance, the highest dose is 1.5 times higher than the highest strength), would it then be allowed to only use the highest strength in a bioequivalence study? - What if the highest strength is not a multiple of the highest recommended dose?		not to complicate the design and conduct of bioequivalence studies and is in line with the recommendations of FDA. When the highest strength is not tolerated in healthy volunteers, a bioequivalence study at the highest tolerated strength may be justified.
Lines 425-431	Lines 425-431 define at what doses the studies should be conducted. The one around solubility saturation suggests that studies should be done in both low and high dose, necessitating two BE studies. This appears to be going beyond the FDA guideline that most of the times allows reliance on higher strength assuming proportional compositions.	We propose aligning with the FDA requirement as there is no scientific rationale for a different approach, means study to be conducted at higher strength.	We believe that in case on non-linear absorption related to solubility limitations, two studies are needed, one at the lowest and one at the highest dose. If the solubility limitation is similar (and the non-linearity thus similar) between the two formulations, the lowest strength (or a strength in the linear range) will be the most sensitive to detect differences between formulations. However, if there are any differences in non-linearity between the formulations, the difference may be most evident at the highest strength/dose.
Line No: 427 to 431	In case of non-linear pharmacokinetics, the strength(s) and dose(s) to be used in bioequivalence study can be selected as follows: "The lowest strength (or a dose in the linear range) for drugs with a demonstrated less than proportional increase in AUC or Cmax with increasing dose, e.g. if this phenomenon is due to saturable absorption. However, if this phenomenon is due to limited solubility of the active substance, **bioequivalence should be established also with the highest dose** (using the highest strength), i.e. **in this situation two bioequivalence studies are needed.**" As per above mentioned criterion, if the non-linearity in the		The guideline has been revised to recommend evaluation of the lowest and highest strength. If the highest strength is not tolerable or safe in healthy volunteers, use of a lower strength may be justified.

	pharmacokinetics is observed due to low solubility of active ingredient and if the highest dose is not safe to use, then it will be difficult to conduct a bioequivalence study with highest dose. Kindly clarify what strategy a generic manufacturer should follow in such scenario.		
Lines 427, 435-436	In this paragraph, confusion is also done between "strength" and "dose". Does it mean that the "lowest dose using lowest strength" (or within linear range) should be used? To avoid misunderstandings, please define the terms "highest dose", "highest acceptable dose" and "highest commonly recommended dose"	To use the appropriate wording for "strength" and "dose" and to define them in the proposed annex-glossary	The guideline has been revised and now recommends evaluation of highest strength and in some cases also the lowest strength.
427 – 431, 4.1.6	In many cases it is not possible to distinguish between limited absorption due to saturable absorption processes or due to limited solubility. Therefore bioequivalence should be demonstrated with the lowest and the highest dose strengths in any case of less than dose proportional pharmacokinetics.	BE should be demonstrated with the lowest and the highest dose strengths, if a less than dose proportional increase in AUC or C_{max} is observed in this range, which could be due to limited absorption or solubility.	It is agreed that if it is not possible to distinguish between limited absorption due to saturable absorption processes or due to limited solubility, the lowest and the highest strength should be evaluated. The guideline has been revised to reflect this.
4.1.6:435	When high dose can not be given to healthy, the study if done on patients, it wont reflect real formulation differences since patients PK/PD are highly variable.	Do studies on health using lower & safe doses	Agreed. The revised guideline recommends evaluation of the highest tolerable strength in healthy volunteers.
435-442 4.1.6 Strength and dose to be investigated	On line 441, the criterion of 90% CI for PK parameters to be within 90-111% is more stringent for conducting studies with lower doses in healthy subjects than that in force today. It should be taken into consideration that the alternative studies in patients for the higher strengths, which are usually multiple dose studies, have a lower discriminatory power. In addition, it is unclear which 90% confidence intervals (AUC, AUCs, C(max), C(min)) have to be within the 90-111% range in these cases. The criterion of 90–111% for 90%CI is unjustified and is influenced by sample size. This will require an unjustifiably large	CHANGE: It should be defined that for lower dose studies in healthy volunteers, AUC should be found in the 95-105% range for the ratio. No narrowed acceptance limit for C(max) should apply as C(max) in a multiple dose study (which is the alternative) would usually be even less sensitive to detect differences in formulation.	This paragraph has been removed.

	number of subjects. It might therefore prove difficult to apply this acceptance criterion in practice, thus incurring the risk of reducing access to generic medicines. It should be sufficient to define an additional criterion for AUC only (as in line 159), eg, if the point estimate ratio of AUC means is within 95-105%.		
435-442	"When the pharmacokinetics is non-linear and studies are warranted at the high dose range, they should preferably be performed at the highest commonly recommended dose. If this dose cannot be administered to volunteers, the study may need to be performed in patients. If the study is conducted at the highest acceptable dose in volunteers, the Applicant should justify this and discuss how bioequivalence determined at this dose can be extrapolated to the highest commonly recommended dose. Conduct of the bioequivalence study at a lower dose could be justified if data from this study indicate very similar PK profile for test and reference (the 90% confidence intervals are within 90-111) so that it is unlikely that there will be a risk for non-equivalence at the most sensitive dose. "	It is acknowledged that in case of non-linear pharmacokinetics with greater that proportional increase in AUC the higher the dose the higher the sensitivity to detect formulation-related differences (especially if the drug exhibits low solubility). However, requiring administration of the highest commonly recommended dose (instead of the highest strength as currently recommended) will probably lead to an increasing number of studies to be performed in patients. Since patients have no clinical benefit from studies assessing BE but might rather be exposed to several heath risks (e.g. due to frequent blood sampling, study-related procedures) this approach is critical for safety reasons. Furthermore, the approach to favour studies in patients is contradictory to the general accepted principles of BE assessment namely to investigate the in vivo performance of two formulations in a highly standardised setting in a well-controlled population of healthy volunteers (cf section 4.1.3). A high degree of standardisation is often not achieved in studies conducted in patients who show a higher inter- and intra-subject variability (the latter e.g. die to progression in disease-state or	The problems with conducting studies at the highest dose and in conducting studies in patients are understood. The paragraph has been removed. The revised guideline in general recommends evaluation of the highest tolerable strength in healthy volunteers.

		changes in concomitant disease, change in concomitant medications etc). Moreover single dose studies are frequently not feasible in patients thus BE can often only be assessed at steady state. Altogether the higher sensitivity which is gained when the highest recommended dose of a drug is used in a BE study might be lost because of the lower degree of standardisation associated with the study conducted in patients. Against this background, the requirement to study the highest recommended dose should be reconsidered.	
436 4.1.6 Strength and dose to be investigated	The term "highest commonly recommended dose" needs to be clarified. In the European market the highest recommended dose may vary from country to country. Similarly, the highest registered strength may also vary from country to country.	CLARIFICATION: Please reword this paragraph accordingly.	It is acknowledged that "highest commonly recommended dose" was difficult to interpret. The revised guideline recommends evaluation of the highest tolerable strength in healthy volunteers
436, 4.1.6	What does it mean to perform studies at the highest commonly recommended dose? Does the highest commonly recommended dose mean the dose, which is recommended to administer at a time, e.g. if the daily dose is recommended to split into two equal doses per day?	Suggestion: … at the highest commonly recommended dose <u>administered at a time</u>.	See comment above
4.1.6. Line 436:	Studies should preferably be conducted at the highest commonly recommended dose.	What happens if the recommended dose is different in different EU countries?	See comment above
437	The guidance states "*If the study is conducted at the highest acceptable dose in volunteers, the Applicant should justify this and discuss how bioequivalence determined at this dose can be extrapolated to the highest commonly recommended dose*". It should however read "if the study is <u>NOT</u> conducted at eh highest acceptable dose in volunteers, the applicant should justify this and	"*if the study is **<u>not</u>** conducted at the highest acceptable dose in volunteers, the applicant should justify this and discuss how BE determined at this dose can be extrapolated to the highest commonly recommended dose*"	See comment above

	discuss how BE determined at this dose can be extrapolated to the highest commonly recommended dose"?	Also, a clarification should be added on what the "highest commonly recommended dose" means, since it could vary from country to country.	
440	The guidance states "*Conduct of the bioequivalence study at a lower dose could be justified if data from this study indicate very similar PK profile for test and reference (the 90% confidence intervals are within 90-111) so that it is unlikely that there will be a risk for non-equivalence at the most sensitive dose*." However, it is not clear whether this would need to be demonstrated prior to study conduct and this requirement seems too restrictive.	Requirement should be limited to only AUC criteria based on ratios (ex.:T/R should be within 95-105 range).	This paragraph has been removed.
440-442, paragraph 4.1.6	The criterion to meet the 90-111% acceptance range for both AUC and C(max) seems to be too restrictive for a study using a lower strength in healthy volunteers. This will occur if the higher strength provides more sensitive measures to detect differences in formulations but cannot be administered to healthy volunteers for safety reasons. It should be considered that studies in patients, which are the alternative population, often employ a less discriminating measure such as steady state studies, especially in the estimation of C(max)	Limit narrowing to AUC (as it is suggested in the draft guideline for a waiver of steady state studies with a suspected higher discriminatory power) and/or use an intermediate acceptance range of 85-118%.	This paragraph has been removed
Lines 440 – 442, 4.1.6	Again, there is concern over the relevance of the request of narrower acceptance limits in case of non-linear pharmacokinetics. Further, this request may not be justified if the highest dose cannot be tested in healthy volunteers and a lower dose was investigated instead. For example, if the absorption is less than dose proportional with increasing doses, there is no increased risk of non-equivalence at the highest, most sensitive dose.	The request for narrower acceptance limits should be re-discussed and clearly justified.	This paragraph has been removed
4.1.7 Chemical analysis (line 444-487)			
	This is one of the most important sections in this guideline and this is an important topic in the bioequivalence study with a lot of complexities. There are no appropriate specific guidelines on this subject matter. This section is titled "chemical analysis". It is because it refers to the analysis of chemicals or it is only referring		A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. Furthermore the heading has been

	to chemical based methods of bioanalysis? This could be made clearer in the heading. If it is meant to be bioanalysis then there is need to discuss aspects of bioassays (including immunoassay). If it is meant for chemical based methods for bioanalysis the heading should read, "Chemical based methods for bioanalysis". In this section there is very limited discussion on the validation of the method using incurred samples. This should be adequately emphasized as the bioanalysis without this validation may make in certain cases data unreliable. There are number of nonspecific statements in this section. **Ideally EMEA should develop a separate Guideline for Bioanalysis/Bioanalytics**.		changed to into 'Bioanalytical methodology'.
444-487 4.1.7 Chemical analysis	This paragraph is very limited in terms of contents and requirements compared to that of current discussions on bio-analytics.	See general comments on the need for more European guidance on this topic. Further EU guidance (separate from the bioequivalence guideline) would be helpful.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
line 443 - Chemical analysis, 1st §, page 12/29	Rephrasing of the section header might be considered. Is an immunoassay method for a biological compound still considered a chemical analysis method? It is surprising that this otherwise very detailed guidance does not specify any quantitative criteria of acceptance of assays (eg, at least 6 QC samples corresponding to three concentration levels in duplicate or more, with no more than 2/6 being outside of 20% of nominal value and not 2 at the same level....). Alternatively, the published position papers of the analytical validation conferences, which are universally used, might be referenced.		A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. Furthermore the heading has been changed to into 'Bioanalytical methodology'.
443	Question: There is no mention of needs of ISR in this section. Is it required by EMEA or not?		The issue regarding ISR is under discussion. A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on the ISR issue will be proposed in the new

			NfG on validation of bioanalytical methods.
4.1.7 Chemical analysis first paragraph	The word certification of GLP laboratories is not commonly used term. In fact the GLP compliant test laboratories/ test sites are never certified.	The bio-analytical part of bioequivalence trials should be conducted according to the principles of Good Laboratory Practice (GLP). However, as such studies fall outside the formal scope of GLP, the sites conducting such studies are not required to be part of regular monitoring program of the National GLP Compliance Monitoring Authority.	In Directive 2004/9/EC on inspection and verification of GLP, the wording "certificate" is not used. The text will be adapted to "the sites are not required to be monitored as part of a national GLP compliance programme". A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
444	The reference to the principles of Good Laboratory Practices (GLP) is unclear. Although it is stated that GLP certification is not required, it is not clear what exactly is required from a non-GLP certified facility and what is necessary for a GLP-like facility.	Please clarify the reference to GLP.	This is the current legislation with regard to certification. It is obvious that sites have to perform in accordance with the principles (whether they are inspected or not), however a stricter request cannot be made here considering the legislation.
444 4.1.7 Chemical analysis	The reference to "the principles of Good Laboratory Practices (GLP)" maybe ambiguous and should be clarified. The GLP compliance certification of European laboratories carrying out the bio-analytical part of the bioequivalence study could facilitate the approval process avoiding some inspections during the dossier evaluation. To that end, GLP certification should be harmonised and recognised in all member States.	CLARIFICATION: Please clarify the reference to GLP.	This is the current legislation with regard to certification. It is obvious that sites have to perform in accordance with the principles (whether they are inspected or not), however a stricter request cannot be made here considering the legislation. Furthermore, GLP compliance certification is not possible currently. This would require to modify Directives 2004/9/E and 2004/10/EC, which are themselves derived from OECD guidelines.

444-447	In order to address the issues out lined in “general comments” and also allow clinical laboratories to exercise some judgement with respect to the parts of GLP that are appropriate to their situation I would like to suggest that lines 444-447 are amended along the following lines – (see proposed change)	"It would be appropriate to perform the bioanalyticial part of bioequivalence trials in accordance with the relevant parts of the principles of GLP to ensure that all aspects of the laboratory analysis stand up to retrospective reconstruction designed to assess the validity of the data. Additionally, laboratories must take into consideration the relevant requirements of the current GCP directives and associated national legislation".	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on this topic will be proposed in the new NfG on validation of bioanalytical methods. In Directive 2004/9/EC on inspection and verification of GLP, the wording “certificate” is not used. In the NfG the text will be adapted to “the sites are not required to be monitored as part of a national GLP compliance programme”. Furthermore, ‘clinical laboratories’ is commonly used for clinical chemistry and haematology, for which reference to GLP is clearly not relevant.
Paragraph 4.1.7; lines 444 to 447	In the paragraph 4.1.7 it is mentioned that the bioanalytical part of bioequivalence trials should be conducted according to the principles of Good Laboratory Practice (GLP). However, that the sites conducting the studies are not required to be certified. Comments Our experience in GLP inspections of bioanalytical laboratories at Swissmedic is that such laboratories are working in two different areas. 1) The laboratories perform bioanalytical analysis for preclinical and clinical studies. 2) The laboratories perform clinical biochemistry studies and in addition to the bioanalytical part of bioequivalence trials.. The laboratories mentioned under point 1 are GLP certified due to the obligation that all preclinical bioanalytical work has to be	The bioanalytical part of bioequivalence trials should be conducted according to an international accepted quality system and the sites should be certified. This may be a GLP compliance certification or another appropriate certification.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on this topic will be proposed in the new NfG on validation of bioanalytical methods. In Directive 2004/9/EC on inspection and verification of GLP, the wording “certificate” is not used. In the NfG the text will be adapted to “the sites are not required to be monitored as part of a national GLP compliance programme”. Furthermore, all laboratories doing BE trials are not involved in

	performed under GLP conditions within pivotal studies for drugs expected to be registered. If this analysis is not performed under GLP conditions, this phase has to be excluded from GLP and mentioned adequately in the GLP compliance statement sign by the study director. The laboratories mentioned under point 2 are generally subject to a certification (eg. ISO), and only a few have obtained a GLP certificate additionally In our mind, any laboratory performing bioanalytical work for preclinical studies or clinical trials should have an adequate certification. The conduct of GLP compliant bioanalytical analysis in a laboratory without GLP certification as proposed seems not appropriate. Therefore, we recommend to revise line 444 to 447 in paragraph 4.1.7.		preclinical studies.
451 – 455, section 4.1.7	The method should have sufficient sensitivity to measure precisely and accurately a concentration equivalent to a certain percentage of C_{max} and a number of points in the terminal elimination phase. If the method is too insensitive, a phase of the elimination from plasma may be captured and used for extrapolation to infinity which is not the terminal phase resulting in an erroneous AUC extrapolation. The LLOQ is the major determinant for the usefulness of the parameter AUC_t.	The term 'sensitivity' should be added to *'main characteristics of a bioanalytical method essential to ensure the acceptability…'*. It indicates more precisely the important requirement of a sufficiently sensitive assay rather than the more neutral requirement of limit of quantification. A minimum requirement should be defined for sensitivity (e.g. the LLOQ should be sufficiently low to determine a certain percentage of C_{max}).	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
451 - 455, 4.1.7	The method should have sufficient sensitivity to measure precisely and accurately a concentration equivalent to a certain percentage of C_{max} and a number of points in the terminal elimination phase. If the method is too insensitive, a phase of the elimination from plasma may be captured and used for extrapolation to infinity which is not the terminal phase resulting in an erroneous AUC extrapolation. In addition, the LLOQ is the major determinant for the usefulness of the parameter AUC_t.	The term 'sensitivity' should be added to *'main characteristic of a bioanalytical method essential to ensure the acceptability…'* It indicates more precisely the important requirement of a sufficiently sensitive assay than the more neutral requirement of limit of quantification. A minimum requirement should be defined for sensitivity (e.g.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.

		the LLOQ should be sufficiently low to determine a certain percentage of C_{max}).	
Lines 454 - 455, 4.1.7	The method should have sufficient sensitivity to measure precisely and accurately a concentration equivalent to a certain percentage of C_{max} and a number of points in the terminal elimination phase. If the method is too insensitive, a phase of the elimination from plasma may be captured and used for extrapolation to infinity which is not the terminal phase resulting in an erroneous AUC extrapolation. The LLOQ is the major determinant for the usefulness of the parameter AUC_t.	The term 'sensitivity' should be added to *'main characteristic of a bioanalytical method essential to ensure the acceptability…'*. Minimum requirements should be defined e.g. LLOQ as a certain percentage of C_{max} or coverage of defined multiples of half-life in the log-linear part of the terminal phase (e.g. at least 2 x $t_{1/2}$), etc.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
456 to 459	It is not clear if the 2 distinct phases should be included in the same study or could be performed in 2 separate studies and if the "pre-study phase" corresponds to the validation and the "study phase" to the assay of study samples.	Please clarify	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
Lines 460-468	Information provided in relation to pre-study phase method validation appears overly prescriptive regarding establishing appropriate stability and assay specificity.	We recommend removal of text form line 463 through 468: " Similarly, demonstration of stability…..should also be addressed" or that this text be clarified as illustrative rather than prescriptive.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
467-468 4.1.7 Chemical analysis	The risk of back-conversion on the metabolic pathway of the analyte is a very complex matter which is not always feasible to address (due to the lack of stability of the compounds). This implies high costs and is time consuming.	See general comments on the need for more European guidance on this topic. Further EU guidance (separate from the bioequivalence guideline) would be helpful.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
Lines 460-468	This section discusses issue related to method development. Discussion related to selectivity of the method is certainly important in those methods where selectivity is not insured by the method employed (i.e. most MS/MS methods now provide unique characteristics that support selectivity but this could be argued for isomers especially optical isomers). Other methods such as simply HPLC with UV etc may not assure selectivity. Would such discussion require the investigator to check on response functions		The EWP-PK is of the opinion that this issue should at least be addressed. However, a separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on this

	for all possible metabolites using the selective methods to ensure lack of interference? We used to do this but have moved away since the advent of LC/MS/MS due to the inherent specificity afforded by the enhanced selectivity of tandem mass spectrometry. Does this section reflect a turn backwards or simply a statement to cover all possible detection systems? The latter few sentences are really discussions at the heart of "incurred sample stability". Is the EMEA avoiding the use of incurred samples so as to make it more EMEA and less USFDA? This section also needs to have something about matrix effects mentioned. A simple statement such as, "sufficient investigation and study should be undertaken to demonstrate any potential interference or enhancement directly attributable to the biological matrix."		topic will be proposed in the new NfG on validation of bioanalytical methods.
Line 470...	After this first sentence the following should be added, "The range of the calibration curve should cover the expected range of the study samples and at least 2 levels of the quality control samples should fall within the range of the > 66% of all the study samples."		It is acknowledged that this section does not and cannot cover all issues in detail. A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
Lines 473-474	Shouldn't the necessity to validate the method of processing and handling the samples be included in the "Pre-study phase" section as it relates to "validation"?	Please move this sentence to the "Pre-study phase" section above (lines 460-468): "In addition, it is necessary to validate the method of processing and handling the biological samples."	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
473 & 474	Shouldn't the necessity to validate the method of processing and handling the samples be included in the "Pre-study phase" section as it relates to "validation"?	Move sentence to the "Pre-study phase" section above.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
Lines 475-482:	The guideline suggests discussion regarding the number of samples that have been re-analyzed, number of chromatograms that have not been automatically integrated and other necessary related information etc. This information probably is meant to be discussed in the application. However, every activity related to the conduct of the study and data generation should be dictated by the pre-established Standard Operating Procedures (SOPs). The applicant strictly should follow those SOPs and report the information in the		A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on this topic will be proposed in the new NfG on validation of bioanalytical methods.

	application. There is no reason to descriptively discuss all deviations in the application.		
475 & 476	Is this only for otherwise analytically acceptable samples or for deactivated samples as well (e.g. IS issue etc.)?		It related to all re-analysed samples, also those for IS issues. A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
477-479 4.1.7 Chemical analysis	The reasons for a different method of integration (ie, either automatic or non-automatic integration) or for a change in the integration parameters should be addressed in guidance documents.	See general comments on the need for more European guidance on this topic. Further EU guidance (separate from the bioequivalence guideline) would be helpful.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
Lines 477-481	Recommend that this is not reported but retained in source data as indicated in the Crystal City III conference proceedings (AAPS Journal 2007; 9 (1) Article 4). Discussing the number of chromatograms and percentage of total chromatograms that have not been automatically integrated does not infer improved quality of integration. Studies have shown that manual integration of chromatograms by trained staff has resulted in better quality, but this process is not used because of the speed advantages provided by automated integration and potential for misuse.	If non-automatic peak integration is required, the applicant must retain the original automatic integration, the non-automated integration and a justification for each chromatogram that has not been automatically integrated.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
477 to 481	Recommend that this is not reported but retained in source data as indicated in the Crystal City III conference proceedings (AAPS Journal 2007; 9 (1) Article 4). Discussing the number of chromatograms and percentage of total chromatograms that have not been automatically integrated does not infer improved quality of integration. Studies have shown that manual integration of chromatograms by trained staff has resulted in better quality, but this process is not used because of the speed advantages provided by automated integration and potential for misuse.	If non-automatic peak integration is required, the applicant must retain the original automatic integration, the non-automated integration and a justification for each chromatogram that has not been automatically integrated.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
477-481, 4.1.7	Similarly, the Applicant should discuss the number of chromatograms (and percentage of total number of chromatograms)	~~Similarly, the Applicant should discuss the number of chromatograms (and~~	A separate Nfg will be prepared. As such the complete section on

613-614, 4.1.8	that have not been automatically integrated, the reason for a different method of integration, the value obtained with the automatic integration and the non-automatic integration and a justification for the acceptance of each individual chromatograms that has not been automatically integrated. *Any manual integration of chromatograms should be justified and listed together with values from the automatic integration.* It seems that the guideline assumes automatic integration as some kind of *'Gold-Standard'*. The analyst always has to manually select integration parameters and save them in an integration method. This is not an automatic process (although the software may suggest some initial values), but an arbitrary selection based on several sample chromatograms. Then, all samples are integrated using these parameters and (hopefully the majority) of chromatograms will be correctly integrated, whilst several others may be not (by the way – what is correct integration? – the answer is not trivial with noisy baseline and / or tailing peaks). The text in the guideline implies that 'automatic integration' is the *'Gold-Standard'* and manual integration is suspicious, but this is simply not true. The true *'Gold-Standard'* is a properly integrated chromatogram, regardless whether this integration was obtained with pre-selected integration parameters or with manual integration. The correctness of the integration can easily be proved during an inspection. Although the last set parameters and resulting peak areas are stored in the CDS (Chromatography Data System) accompanied by an audit trail, the original areas are overwritten. The requirement will not prevent fraud: it will not give any information on whether the new integration is correct or not.	~~percentage of total number of chromatograms) that have not been automatically integrated, the reason for a different method of integration, the value obtained with the automatic integration and the non-automatic integration and a justification for the acceptance of each individual chromatograms that has not been automatically integrated.~~ ~~*Any manual integration of chromatograms should be justified and listed together with values from the automatic integration.*~~	chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
Chemical analysis Lines 477-481	Specific comments on section – "chemical analysis" : • This section goes into a lot of details. e.g. "the Applicant should discuss the number of chromatograms (and percentage of total number of chromatograms) that have not been automatically integrated, the reason for a different method of integration, the value obtained with the automatic integration and the non-automatic integration and a justification for the acceptance of each individual chromatograms that has not been automatically integrated."	Propose deleting the requirement to tabulate all of the data requested, and to replace with a requirement to report only the number/percentage of manually integrated chromatograms in a given study.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.

	• Although the percentage of manually integrated chromatograms in a given study is typically low, tabulating the data requested would, due to data system limitations, be quite challenging. Depending on companies' various computer systems and databases this process could be quite resource intensive for those runs where there are manually integrated chromatograms due to system specificities. Thus, we suggest to simply reporting a percentage of manually integrated chromatograms in a given study. Tracking an overall number of manually integrated chromatograms would be significantly easier than tracking the before and after quantitation results.		
478-482	Each chromatogram being re-integrated either by changing of the automated procedure or manually will be documented in the raw data.	Change to: "The Applicant should document in the raw data the chromatograms that have not been automatically integrated, the reason for a different method of integration, the values obtained with the automatic and the altered integration."	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
481- 482	Re-integration of chromatograms is not a deviation from the study protocol. Therefore, the words "any other" and "also" may be misleading. In general, this sentence should be moved to the reporting section.	Change to: "Deviations of the bioanalytical protocol should be discussed in the Bioanalytical Report. Additional analytical raw data (e.g. reintegration) should be available " And move the sentences to the end of section 4.1.8 Evaluation / Presentation of data.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
4.1.7 Line 482	Recommend replacing “analytical protocol” with “bioanalytical method”, for consistency with Lines 458 and 485, and also because there is no requirement in guideline to have a separate study specific “analytical protocol”	Please change as follows: “Any other deviation of the **bio**analytical ~~protocol~~ method should also be discussed in the Analytical Report.”	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened.
482	Clarification of the term ‘analytical protocol’ is required. Does this mean the Clinical Study Protocol, does in mean a local (and	Any other deviation from analytical standard operating procedures should be	A separate Nfg will be prepared. As such the complete section on

	separate) analytical protocol/study plan, or does it mean in accordance with standard operating procedures and methods?	discussed in the Analytical Report. Recommend replacing "analytical protocol" with "bio-analytical method", for consistency with Lines 458 and 485, and also because there is no requirement in guideline to have a separate study specific "analytical protocol" Replace "analytical protocol" with "bio-analytical method"	chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
# 475-481 § 4.1.7	A clarification would be required with regards to where the discussion on the following need to be reported: (1) "…the number of samples that have been re-analyzed…" and (2) "…the number of chromatograms that have not been automatically integrated…". Should it be in the raw data or the Analytical Report?		A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
4.1.8 Evaluation (line 489-614)			
Line 489-494	The guidance is explicit that the same molar dose needs to be given between test and reference. Is it possible to have a situation where different molar doses are used between test and reference, but still conclude bioequivalence? Please clarify whether different molar doses might be considered in BE studies in certain circumstances. Potency adjustment analysis may be needed if the molar doses are different for the test and the reference formulations.	Propose allowing for situations where bioequivalence may be demonstrated between test and reference with different molar doses provided the PK bioequivalence endpoints are met (for example, for a case where the test formulation has a different bioavailability compared to the reference)	This paragraph has been removed. However, the definition of bioequivalence (which is given in section 1.1) including *'after administration in the same molar dose'* is the same as in FDA, Canada and WHO guidelines.
Paragraph 4.1.8; lines 490-491	The definition of bioequivalence as same rate and extent of bioavailability is not adequate. The publication from Tozer et al gives the rationale and the following recommendation: "Defining bioequivalence in terms of rate and extent of absorption has major problems. The goal of bioequivalence trials should be to assure that the shape of the concentration-time curve of the test product is sufficiently similar to that of the reference product. To this end, the use of "exposure" rather than "rate and extent of absorption"	To adopt the wording from Tozer's publication.	The rate and extent of bioavailability is important and we want to emphasise that. If the rate and extent of absorption are the same the concentration vs time profiles will be superimposable for the two tested products. This paragraph has been removed from

	concepts is encouraged". Pharmaceutical Research, 13, 3, 1996, 453-456		section 4.1.8. See also comments on corresponding paragraph in section 1.
Line 491, 4.1.8	Certain exemptions should be allowed regarding the request for identical molar doses to be tested (see comment above regarding line 39)	The definition *'after administration in the same molar dose'* should be modified to allow certain exemptions.	See above
line 492, 1st §, page 13/29	"The pharmacokinetic parameters should not be adjusted for differences in analysed content..." It is commented that Canadian health authorities currently have the opposite requirement (must be adjusted for potency)		It is acknowledged that different authorities have taken different approaches regarding content correction. In EU pharmacokinetic parameters should not be adjusted for differences in analysed content. However, the guideline has been updated with a possibility to content correct has been added in exceptional cases where a reference batch with an assay content differing less than 5% from test product cannot be found.
Lines 492 – 494, 4.1.8	The request that pharmacokinetic parameters should not be adjusted for differences in drug content of test and reference batch is welcomed and supported in the scenario where generic substitution is made. However, in the drug development scenario, if only one tablet strength is marketed why can't a different content not be BE? Also, we suppose the analyzed content refer to assayed content obtained by the applicant for the test and reference batch with the same analytical test procedure as the one proposed for the test product. However, could you confirm and specify that a content correction is necessary to evaluate the bioequivalence if the principle of molar equivalence dose is not respected.	Please differentiate between a development scenario and generic substitution. In a development scenario, it might be beneficial, if the "to-be-marketed-formulation" has a lower drug content compared to the phase III formulation due to an improved formulation. Please add a definition of the wording "analysed content" of the test and reference product " in the proposed annex-glossary	In the development scenario use of content correction could be justified in the situation given in the comment. It is not considered necessary to be so specific in the guideline.
4.1.8 Evaluation Lines 492-	It is stated "the pharmacokinetics parameters should not be adjusted for differences in analyzed content of the test and reference batch", i.e. content correction is not accepted."	To define the wording "analysed content" of the test and reference product " and to add in the proposed	"analyzed content" has been changed to "assayed content"

493	We suppose the analyzed content refer to assayed content obtained by the applicant for the test and reference batch with the same analytical test procedure as the one proposed for the test product.	annex-glossary Could you confirm and precise that a content correction is necessary to evaluate the bioequivalence if the principle of molar equivalence dose is not respected.	See also comment above
492 – 494, 4.1.8	The request that pharmacokinetic parameters should not be adjusted for differences in drug content of test and reference batch is welcomed and supported. However, this may have the consequence that not typical batches but batches with the highest likelihood of demonstrating BE may be selected for BE testing.	This request needs to be re-discussed to prevent specific batch selection.	Specific batch selection should be avoided by the request in section 4.1.2 to select a representative batch.
Lines 492-494	If only one tablet strength is marketed, why can´t a different content not be BE?	Please differentiate between a development scenario and generic substitution. In a development scenario, it might be beneficial, if the "to-be-marketed-formulation" has a lower drug content compared to the phase III formulation due to an improved formulation.	The comment is acknowledged. However, this is out of the scope of this guideline which concerns bioequivalence as defined in section 1. Recommendations for suprabioavailability may be included in the PK EWP position paper (EMEA/618604/2008).
Lines 495-527	The suggested method of analysis is an ANOVA (or what is termed an 'equivalent parametric method'). Further, the first paragraph under Subject accountability, page 14/29 lines 574-576, gives the impression that for pair-wise treatment comparisons only subjects with completed assessments for both treatments should enter the analysis. Does this imply that a mixed linear model approach with subject, nested within sequence, and treated as a random effect will not be considered a valid choice of statistical methodology? If the answer to 1 is 'No', should subjects with incomplete data, i.e. subjects with valid PK data for only one of the two compared treatments, be excluded from the analysis?		One objective of the new guidance was to completely standardise the method of analysis. While mixed models are generally useful, for bioequivalence ANOVA is considered adequate. As such the comment is correct – a mixed linear models approach would not be acceptable, and subjects with valid data for only one of the two treatments should be excluded. No change. The phrase "or equivalent parametric method" removed to make clear that we are insisting on ANOVA
Statistical	Specific comments on statistical analysis		Non-parametric analyses are useful

analysis Lines: 495–527	In line of 504, "A non-parametric analysis is not acceptable." In some cases (such as with outlying observations), non-parametric analysis may be a better and more robust approach. Some flexibility may be needed in the guidance. Lines 508-510: please clarify whether subject (sequence) is taken as a fixed factor or a random factor in the ANOVA model. What is the suggested statistical model for crossover designs with more than 2 periods in BE studies? Lines 514-521: We agree that the statistical test for the carryover should not be performed for the pharmacokinetic parameters (AUC and Cmax). We agree the way described in the guidance to check potential carryover effects by comparing the pre-treatment plasma concentrations in period 2 or beyond if applicable with the Cmax value in that period, and the statistical analysis should be repeated with those subjects if the pre-dose concentration is greater than 5 percent of the Cmax values. One clarification is needed for the sentence in the guidance that both analyses should be presented, but the analysis with the subjects excluded should be considered as primary: should the observations from all the periods be excluded, or only the data points that may be affected by carryover effects be excluded?		in general but not considered appropriate or necessary in bioequivalence, where the lack of influence of the more extreme values is concerning. Subject (sequence) as a fixed effect is acceptable. Text added. The model is the same for designs with more than 2 periods. Text "for example if a two-period, two-sequence crossover design has been used" removed to reflect this. Text added to clarify that only the periods affected by non-zero baseline need be removed. Of course in a 2-period trial this amounts to the patient being removed.
Line 496	*"The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/reference) for the parameters under consideration"* It is unclear whether the statement is applicable to C_{max} and AUC_t only.	Refer to appropriate section to clearly define the PK parameters subject to the 90% confidence interval analysis	To clarify this, the section specifying the parameters to be analysed has been moved to before the method of analysis section, and the title changed to parameters to be analysed.
Line 496-499; 537-547	Confidence intervals (CIs) are the traditional statistical tool for BE studies, but the request for its use implies prohibition of Bayesian highest posterior density intervals (HPDIs). After an experiment, a 90% HPDI (unlike a 90% CI) has a 90% chance of containing the unknown parameter, and as such its use may be preferable to the use of a 90% CI.	Suggest expressing more openness to other statistical techniques as non-frequentist statistical techniques (in a similar way to ICH E9), e.g by adding "Alternative methods, eg Bayesian methods such as the highest posterior density interval (HPDI) may be considered." to Line 499.	One objective of the new guidance is to completely standardise the method of analysis for bioequivalence studies, where ANOVA is considered to be adequate. Bayesian analysis, although a useful approach in general, is not considered necessary here. No change made.
500	This section does not specify which PK parameters are concerned.	CLARIFICATION:	Order of sections changed to clarify

4.1.8 Statistical analysis	Tmax is a PK parameter, however, non-parametric tests do indeed apply to this parameter.	Please reword stating "The pharmacokinetic parameters under consideration ***(except Tmax)*** should be analysed using ANOVA [...]"	which parameters are of interest (see above). This should make things clearer than saying "except Tmax".
500-501, 4.1.8 574-576, 4.1.8	The pharmacokinetic parameters under consideration should be analysed using ANOVA (or equivalent parametric method). All treated subjects should be included in the statistical analysis, with the exception of subjects in a crossover trial who do not complete at least one period receiving each of the test and reference products (or who fail to complete the single period in a parallel group trial). Only subjects who completed all treatment periods in a cross-over study can be analysed by an ANOVA. However, a mixed-effects model can be used in a 2×2×2 study, even when data from just one period are available. It is unclear why a mixed-effects model should be acceptable in a higher order cross-over study, in a replicate design, or a parallel study but not in the standard 2×2×2 design. From a statistical point of view it would be desirable to include all available data in the analysis. However, the impact on the confidence interval is minor and also calls for suitable software. It should be left to the applicant which statistical method will be used in the study (ANOVA or a mixed-effects model). This would be in agreement with lines 500-501 where an *'equivalent parametric method'* [to ANOVA] is already stated.	The pharmacokinetic parameters under consideration should be analysed using ANOVA (or equivalent parametric method, e.g. mixed-effects modeling). *All treated subjects should be included in the statistical analysis (mixed-effects model), or subjects completing all treatments according to protocol (ANOVA).*	Mixed effects model is not acceptable, so no change. While mixed effects models can be useful in general, ANOVA is considered adequate for the analysis of bioequivalence data. No change. Removed "or equivalent parametric model" to avoid confusion.
Lines 503 and 504	Should be modified to: **„This confidence interval is then back-transformed to obtain confidence interval for the geometric least square means in the original scale"**	See cell Comments and Rationale. Geometric least square means should be specified in the guidelines for the evaluation of confidence intervals.	The confidence interval is for the ratio of the geometric means. This is stated in the first paragraph of this section.
Line 504 and 505	The statement that "non-parametric analysis is not acceptable" seems unnecessarily strong, as there may be situations where a non-parametric analysis may be appropriate (in particular if the analysis of T_{max} is performed, although this is not necessary in most cases).	Suggest rewording sentence to "A non-parametric analysis is not usually acceptable unless justified".	ANOVA is considered to be adequate for the assessment of bioequivalence studies. No need for non-parametric methods. In addition non-parametric methods are likely to be less sensitive to detect differences as they minimise the impact of subjects with large differences between treatments. No

			change.
504-505, 4.1.8	A non-parametric analysis is not acceptable. *Is should be remembered that application of a parametric model relies on assumptions. Parametric models are relatively robust to violations of some assumptions (*e.g.*, additivity of effects), but very sensitive to violations of the assumption of an Independent Identically Distribution (IID).* *To quote the standard textbook on cross-over studies (*B Jones and MG Kenward; *Design and Analysis of Cross-over Trials; Chapman & Hall/CRC, Boca Raton, 2nd ed. 2003):* No analysis is complete until the assumptions that have been made in the modeling have been checked. Among the assumptions are that the repeated measurements on each subject are independent, normally distributed random variables with equal variances. Perhaps the most important advantage of formally fitting a linear model is that diagnostic information on the validity of the assumed model can be obtained. These assumptions can be most easily checked by analyzing the residuals. *If violations of the assumptions needed for parametric methods are anticipated and stated in the protocol, a non-parametric method should be acceptable.*	*A non-parametric analysis is acceptable if assumptions needed for the application of a parametric model are violated and a detailed decision tree to apply such an analysis is stated in the protocol. In such a case the non-parametric analysis should be considered primary and the parametric analysis should be presented as a sensitivity analysis only.*	ANOVA is considered to be adequate for the assessment of bioequivalence studies. No need for non-parametric methods. In addition non-parametric methods are likely to be less sensitive to detect differences as they minimise the impact of subjects with large differences between treatments. No change.
506-521 4.1.8 Statistical analysis	On line 513, the rationale for calculating the respective confidence interval for Period and Sequence effects is unclear. The p-value from the ANOVA should be adequate for them.	CLARIFICATION:	Agreed. This text has been deleted
Line 509	Suggest not proposing any specific statistical model. Moreover the level of information on the proposed model for 2 by 2 cross over may not be sufficient. The role of the sequence effect (between subject information) should be clarified. The importance given to the sequence effect highlights the need for a randomised trial.	Suggestion to remove details on any specific statistical model	It is desirable to specify ANOVA to ensure consistency between applications.
Lines 510-512 Paragraph 4.1.8	*"The presentation of the findings of a bioequivalence trial should include a 2x2-table that presents for each sequence (in rows) and each period (in columns) means, standard deviations and number of observations for the observations in the respective period of a sequence."* This information is unlikely to be very helpful, as sequence effect is unlikely to be positive, and if so, is adjusted for in the model in an	Recommend to exclude this requirement. Alternative assessments for testing period and sequence effect (e.g. showing p-values) should be acceptable.	Agreed This text has been removed

	ANOVA, tests on sequence and period are included in the ANOVA table as presented by p-values. without specifying additional SD. It would add an unnecessary additional amount of study data in the report. The requirement to calculate confidence intervals for these effects, certainly in case of n-way with n>2, seems to be too much. The table with results per sequence and period as mentioned in lines 510-512 should be sufficient.		
510-514, 4.1.8	The required presentations should be further explained and the rationale should be described.		Agreed to remove these – see above
Line 512 MINOR COMMENT	Sentence should be rephrased: "… number of observations for the observations in the respective …"	Suggestion: "…number of observations ~~for the observations~~ in the respective…"	Agreed to remove these – see above
Line 512-514	The rationale for the request "In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment." is not clear as it raises the following issues: The reporting of a test for a treatment effect is not relevant for a bioequivalence study as it contradicts the hypotheses tested in a bioequivalence study. The next sentence states "a test for carry-over should not be performed", which contradicts the request for a sequence effect test. The confidence interval for a period effect is not relevant or informative.	Suggest amending the sentence "In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment." to "In addition, the test for the period effect and the confidence intervals for the treatment effect should be reported for descriptive assessment."	Agreed to remove these – see above
512-517, 4.1.8	*In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment. A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test. The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable).* Removal of the flawed method (Grizzle 1965, 1974) according to findings by Freeman (1989) and covered extensively by Senn (2000) is appreciated. However, any tests for difference are of not justified in a BE study. At least as far as standard 2×2×2 cross-over	~~*In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment.*~~ *A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test. The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in*	Agreed to remove this request – see above

	studies are considered, sequence and carry-over effects are confounded. The same is true for higher order designs with more than two treatments. Thus a required test for sequence effects and to avoid a test for carry-over is contradictory.	*period 2 (and beyond if applicable).*	
Line 513	*"In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment."* Studying sequence and period effects in addition to treatment effects is recommended. Reporting confidence intervals in addition to p-values has no added value.	Recommended to remove the requirement for confidence intervals	Agreed to remove this request – see above
514 4.1.8 Statistical analysis	The sequence effect is usually calculated using "subject nested within sequence" as an error term.	CLARIFICATION: Calculation of the sequence effect should be clarified.	Agreed to remove this request – see above
Line 514-516	This sentence contradicts the previous one. It states that a test for carryover should not be performed, but the previous sentence recommends testing for sequence effect. Sequence and carryover effects are equivalent in a simple 2x2 crossover study.	Please clarify that the test for carry-over and sequence effect are equivalent for 2x2 cross-over studies.	Agreed to remove this request – see above
516 – 521, 4.1.8	The draft guideline allows the acceptance of a BE study in which several subjects showed a carry-over effect in period 2. It even considers the evaluation primary, in which the results of these subjects are excluded. There is no definition on how many subjects may be excluded. The number of subjects remaining after exclusion of subjects will have to comply with the initial sample size estimate. Generally, the exclusion of subjects from the biometrical evaluation appears problematic from a statistical perspective.	A clear definition is missing on how many subjects may be excluded.	It is considered that any number of subjects may be removed – if it is too many the trial will fail anyway as it will lack power. Text added to clarify that it will not be acceptable to go below 12 evaluable subjects.
Lines 517-520 Paragraph 4.1.8	*"If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be repeated with those subjects excluded. Results from both analyses should be presented, but the analysis with the subjects excluded should be considered as primary."* This requirement raises multiplicity issues. If the exclusion is prespecified, additional analyses are not justified.	Recommend to present only statistical analysis after exclusion of subjects with $C_0 > 5\%$. Include requirement to report all available PK data for the excluded subjects for completeness.	No multiplicity issue as it is clearly stated that the analysis with the patients excluded is primary. However it is agreed that it may be confusing to request multiple analyses. The requirement to present both has been deleted.
Line 517-	Generally, the proposed method for dealing with carryover	Suggest adding in design section	Agreed, this has been added in

519	(exclusion of subjects with suspected carryover from the biometrical evaluation) appears problematic from a statistical perspective.	information about how to avoid carry over effect: sufficient enough wash out period should be defined in the protocol e.g 5 times t1/2 depending on the reference/ tested product.	section 4.1.1.
517-521, 4.1.8	*If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be repeated with those subjects excluded. Results from both analyses should be presented, but the analysis with the subjects excluded should be considered as primary.* Since no valid method exists to correct for a true carry-over, any analyses with subjects showing pre-dose concentrations is considered futile. Subjects showing pre-dose concentrations should be removed from the data set *before statistical analysis* (also in conformity with FDA's guideline). It does not make sense to keep these subjects in the evaluation even for a secondary analysis, since assumptions of the underlying statistical method do not hold.	*If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be performed with those subjects excluded. ~~Results from both analyses should be presented, but the analysis with the subjects excluded should be considered as primary.~~*	Agreed
Lines 517-521	When the pre-dose concentration is greater than 5% of C_{max}, it says that subject should be excluded in the repeat analysis. However, should only that period be excluded, and not other periods which do not suffer from that problem? In general, whenever data is excluded from statistical analysis (due to protocol violations, etc.), excluding one period does not require excluding all periods for that subject.		Only subjects who provide data both on test and reference should be included in the statistical analysis. Hence, exclusion of data from one period is only possible in a study with more than 2 perdiods and if data on test and reference are still available. In a 2-period trial a predose sample >5% of Cmax in one period will result in the subject being removed from the statistical analysis.
518	It is great to see a rule for pre-dose concentration not exceeding 5% as this was already implemented by other Regulatory agencies such as FDA. From a CRO perspective, this has been very helpful in case some volunteers would have minimal pre-dose values. The overall conclusion of the study would not be impacted.		Thank you.
Lines 522 – 527,	The guideline proposes to adjust for baseline differences but does not say how this should be done. This is especially important for	Clarification required on which kind of adjustment is acceptable.	The guideline has been revised to included more detailed information,

4.1.8	AUC, which is measured by the unit "Concentration*time". Indeed, the focus on a baseline correction method may not be justified, as this is not the analysis method of choice for all endogenous compounds.	*"the study should be evaluated using some form of baseline* ***adjustment****, ~~so that the calculated PK parameters refer to the additional concentration provided by the treatment~~"*	including advice on baseline correction, for endogenous compounds.
Lines 522-527:	Endogenous drugs are an important class of drug. Information on the bioequivalence assessment of endogenous drugs should be described including the appropriate method for baseline corrections in more detail similar to the NTI drugs and HVD&HVDP sections. Often subjects may be dosed in groups or at multiple sites. These issues are not discussed in this section (group effect or site effect). There may be interactions between treatment and group or site. In these cases these factors should be discussed.		The guideline has been revised to included more detailed information, including advice on baseline correction, for endogenous compounds. We see no need to specifically cover group effect or site effect as this rare situation has to be dealt with case by case.
528 4.1.8 Evaluation of data from several bioequivalence studies	Clarification as to which bioequivalence studies concerned is needed. The generic medicines industry's understanding is as follows: bioequivalence studies carried out on the same formulation, manufactured according to the same manufacturing process and supporting the European registration of a medicinal product should be presented in the dossier regardless of the outcome of the study. Two medicinal products are considered to be different if one is derived from the other following a reformulation step in the pharmaceutical development process.	See also comment on lines 142-143	This understanding seems correct. This has been clarified in section 4.1.
4.1.8 Evaluation Lines 528-547	This paragraph concerns "Evaluation of data from several bioequivalence studies". What is important is to define exactly which bioequivalence studies have to be submitted in the application dossier: - all bioequivalence studies performed even the local BE studies with local comparator products? - only bioequivalence studies performed with the reference product chosen in the application? - only bioequivalence studies performed on the current formulation of the test product ?	Please clarify.	Section 4.1 has been revised to provide more detailed advice on the studies to be submitted.
Evaluation of data from several	Specific comments on evaluation of data from several bioequivalence studies The guidance describes 3 scenarios. It's not clear what would be the		Agreed that situations 2 and 3 were difficult to distinguish. The section has been replaced by a more general

bioequivalence studies Lines 528-547	strict cut-off between scenario 2 and scenario 3. Would an increase in power for a study that failed initial BE, fall always under scenario 2? And under scenario 3, how many studies need to be conducted to outweigh the first study? Please clarify. Another source of failure could be strictly technical issues: lack of assay sensitivity; patients improperly dosed etc. We see no added value in reporting negative study results if a probable cause for study failure is clearly identified. Line 543: Please clarify what it means to clearly show that the test product is "bioinequivalent". Does this mean that the 90% CI was completely out of the pre-specified BE bounds?		paragraph in the *Presentation of results* section.
Line 528:	As discussed in this section, all studies involving the specific formulation that is included in the application should be submitted for review. The primary focus of the review should be the data from the study with the favorable results. Data from the unfavorable study may be submitted as supplementary information to assess the formulation performance in different studies and other pertinent important information. The formulation is different between the favorable and the unfavorable study there is little value to submit the unfavorable study data as the earlier formulation didn't perform properly and was modified or discarded.		It is agreed that failed studies with earlier formulations are of limited interest for the demonstration of bioequivalence. However, as stated in section 4.1, study synopses for such studies should be submitted, as they may provide information that may be useful in the assessment of the in vitro dissolution method.
537-542 4.1.8 Evaluation of data from several bioequiva-lence studies	On line 537, how wide of a confidence interval would be considered to be wide? It is proposed to introduce the notion that if the ratio of means is within 80-125%, but the 90% confidence interval is not, then a subsequent positive study can be conclusive.	CLARIFICATION: Please provide clarification	See previous responses
Line 537 – 542:	What is meant by "ambiguous" is not clear. A trial can fail due to several reasons which could be detected by meticulous review of the conduct of the study and data analysis. There could be significant deviations in the conduct of the study; the sample size could be less than optimal, and/or the conduct of biological samples of the study was suboptimal.		This is acknowledged and can be reasonable explanations for failed studies. See also previous responses.
543	The guidance states "*If the failed study(s) clearly shows that the test product is bioinequivalent with the reference, a subsequent*	A clarification to be added as to how much additional data should sponsors	See previous responses

	positive trial will then be a contradictory finding. In this situation, additional study(s) will be needed until the evidence for bioequivalence clearly outweighs the evidence against, indicating that the failed study(s) were simply unlucky chance findings. It is not acceptable to pool together positive and negative studies in a meta-analysis." Again, should the applicant submit all studies including failed ones? We need to clarify what "bioinequivalent" means (e.g.. outside the criteria range, not bioequivalent is different than bioinequivalent)	provide in the case of a non-bioequivalent study.	
543 – 547, section 4.1.8	It is unclear how to proceed in cases of contradictory studies. Is there a certain number of positive studies necessary to outweigh a negative study?	A clear guidance should be provided to indicate how to proceed in case of contradictory BE results.	See above
Lines 543-547 Paragraph 4.1.8	Multiple companies had questions over how to proceed in cases of contradictory studies. Is there a certain number of positive studies necessary to outweigh a negative study? It is not clear what is meant by "clearly shows the test product is bio-inequivalent." We feel as if it would be better to judge the bioequivalence based on the quality of the study data, such as study power, quality of drug assay, number of dropouts etc. rather than number of positive vs. negative BE outcome studies. Meta-analysis can be valuable instead of repeating a study multiple times until the studies passing outweigh the failed study(s).	A clear guidance is missing on how to proceed in case of contradictory BE results. Please incorporate study study power, quality of drug assay, number of dropouts etc. rather than number of positive vs. negative BE outcome studies.	See above
Line 543-547	These lines call on sponsors to compare various bioequivalence studies in terms of their strengths of evidence. Weighing evidence is problematic within frequentism, however. Whereas analysts often try to measure evidence using statistical tests and estimation, the theory behind those methods contains no defined concept of evidence. Without having defined evidence, one cannot determine whether some studies' evidence "outweighs" other studies' evidence.	Please clarify what is meant here as outweighing has no statistical background. Suggest removing any references to the concept of outweighing evidence in the guideline.	See above
543-547 4.1.8 Evaluation of data from several bioequivalence studies	On line 544, clarification should be provided as to how many additional studies are considered sufficient to outweigh a negative study? What will the determining factor be? We believe that the study should be repeated in case of unexpectedly low power. In addition, in the case of drugs with intra-subject CV for Cmax or AUC >30% (ie, highly variable drugs), it should be acceptable to	CLARIFICATION: Please clarify the various scenarios proposed.	See above.

	disregard an original study if this study was not properly powered. In such inadequately powered studies, the results can be unreliable and can be voided if the subsequent study is properly powered (>80%). Similarly, in a case where the original study wasn't properly designed (eg, sampling schedule was inappropriate), the subsequent positive trial alone should be adequate for proving bioequivalence.		
543 – 547, 4.1.8	It is unclear how to proceed in cases of contradictory studies. Is there a certain number of positive studies necessary to outweigh a negative study?	A clear guidance is missing on how to proceed in case of contradictory BE results.	See above
Line 546	…failed study(s) were simply unlucky chance findings… Calling the findings "unlucky" is unnecessary.	Please delete the word "unlucky"	See above
549 - 550, 4.1.8	Usage of AUC_t alone may lead to wrong BE decisions. Measurements in the terminal phase of a plasma profile are strongly dependent on the sensitivity of the assay (LLOQ). As a consequence, the true terminal phase of the plasma profile may not be determined correctly in all subjects (e.g. in case of a biphasic elimination). In such cases neither AUC_t nor AUC_∞ alone will lead to reliable estimates of the extent of absorption: Use of AUC_t will lead to an underestimation of the total extent of absorption and the extrapolation for AUC_∞ calculation may be based on biased estimates for $t_{1/2}$.	The purpose of BE testing is to identify relevant differences between a test and a reference formulation. In case of immediate-release formulations the differentiation between the formulations is complete as soon as the drug absorption has been completed. Thus, a truncated AUC (AUC(0-tx)) may be used as primary target parameter in which the time range 0-tx includes the absorption phase plus a defined safety margin, e.g. 0 to 5 x t_{max}. In addition, AUC_t and AUC_∞ may be analysed in single-dose studies together with a clear definition of the assay sensitivity (see comment to lines 451-455).	The sampling schedule should allow a reliable estimation of extent of exposure so that AUCt covers >80% of AUC_∞. If this is fulfilled AUCt will adequately reflect extent of absorption. A truncated AUC at 72h is allowed. A truncation at earlier time points is not considered needed in bioequivalence studies.
Line 549	AUCt is mentioned as main parameter for determining the extent of exposure. This might lead to artificially high differences (e.g. if a 24h value is for test only slightly over the LOQ and for reference only slightly below LOQ. This might be overcome using AUC0-inf (with reliable t1/2 determination) as primary parameter for extent of exposure.	AUC0-inf primary and AUCt as secondary parameter for determining extent of BE.	AUCt is preferred over AUC0-inf as the latter includes the uncertainty due to the extrapolated area. It seems unlikely that there will be an artificially high difference between test and reference if an appropriate sampling schedule is used so that AUCt covers >80% of AUC_∞

Lines 549/550	*"In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUCt and Cmax."* Multiple companies pointed out that using AUCt as main parameter for determining extent of exposures might lead to artificially high differences. For example, if a 24h value is for test only slightly over the LOQ and for reference only slightly below LOQ. These issues might be overcome using AUC0-infinty (with reliable t1/2 determination) as primary parameter for extent of exposure. Further, it would make this guidance congruent with other guidances (principally FDA).	In general, please make AUC0-infinty the primary endpoint and AUCt a secondary parameter for determining extent of BE. AUC_t and AUC_∞ should both be analysed in single-dose studies together with a clear definition of the assay sensitivity (see comment to lines 454-455). If AUC_∞ cannot be estimated with sufficient reliability (e.g. if more than 20% are extrapolated), a partial AUC, AUC(0-tx), should be analysed in addition to AUC_t, where 0-tx is a fixed time range (e.g. AUC(0-24) or AUC(0-48)).	See comments above
Line no: 549 to 550	"In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUC_t and Cmax." Does the demonstration of bioequivalence on the basis of $AUC_{0-\infty}$ not required as primary efficacy endpoint? Kindly clarify.		$AUC_{0-\infty}$ is not required as primary efficacy endpoint. Hence, statistical evaluation of $AUC_{0-\infty}$ is not needed.
Acceptance limits Lines 548–562	Specific comments on acceptance limits • Lines 549-559: The primary variables (where the bounds of 80% and 125% apply) in the hypotheses should be further clarified. 1. In SD studies, are AUC0-inf and Cmax the primary variables? The draft also mentioned AUC0-T. Should AUC0-T be in the primary hypothesis? 2. In MD studies, are AUC0-T and Cmax the primary variables? The draft also mentioned Cmin,ss. Should all the three be in the primary hypothesis? • Lines 555-557: "For products where rapid absorption is of importance (e.g. migraine drug candidates), equivalence between test and reference should be supported by demonstration of bioequivalence for partial AUC as a measure of early exposure. The same acceptance interval as for Cmax applies to partial AUC". Does this mean that for	MSD proposes to outline methods to determine or assess rapid absorption. MSD proposes AUC0-T and Cmax be the primary variables for MD studies.	The primary variables in single dose studies is AUCt (AUC to last measured concentration) and Cmax and in multiple dose studies AUC_τ (AUC over the dosage interval) and Cmax,ss. Cmin,ss has been removed as a primary parameter. Partial AUC has been removed from the guideline. An assessment of tmax can be made in the rare situations when there is a clinically relevant claim for rapid release or onset of action.

	this class of compounds, partial AUC BE will be a requirement? If yes, who (and how) determines that "rapid absorption is of importance?"		
Line 551	Discussion is presented through the guidance where the acceptance interval (80-125) may be tightened or widened.	Recommend addition of text 'unless determined otherwise' to this requirement.	In the revised guideline it is only for NTI and HVD that a different acceptance range may apply. These are mentioned in the last paragraph. Hence in order not to confuse the reader, no change is made to line 551.
551-552, 4.1.8	Widening of the acceptance range for Cmax should be allowed in cases, where there is clear evidence that Cmax is without any relevance for the efficacy and safety of the drug product. This decision should be independent of the variability. E.g. in cases where it has been proven that a once daily or twice daily dosing are equally effective and safe, Cmax is without any relevance. Therefore, it is not reasonable to perform a study which is powered to meet the 80-125% acceptance range. Furthermore, widening should be possible in case of highly variable drug products, as proven be valid literature data. Originators perform more and more replicate design studies in order to investigate the intra-subject CV. Valid data from the originator (e.g. SmPC or data available under the freedom of information act) should be sufficient to prove a high variability, without the need to perform own replicate design studies.	Wording of the Questions & Answers on the Bioavailability and Bioequivalence Guideline (EMEA/CHMP/EWP/40326/2006), chapter 2 should be used. However, for proof of a high variability, literature data should be acceptable. Alternatively, for highly variable drug products, the approach as described below should be possible (see comment to line 631).	This is not agreed. The only option for widening acceptance criteria in bioequivalence studies is that described in section 4.1.10 (high variability drug products). For response to second part of question, please see responses to comments on section 4.1.10
553	Confidence intervals should be presented to two decimal places.	Confidence intervals should be presented to two decimal places not be rounded off.	Proposed change not implemented as the confidence interval presented to two decimal places likely are rounded off from a higher number of decimal places.
553, 4.1.8	It is unclear whether confidence intervals may be rounded, as long as they are presented to two decimal places.	Clarification required as to whether rounding is permitted if confidence intervals are presented to two decimal places	Rounding from a higher number of decimal places to two decimal places is allowed.
Lines 553-	Multiple companies stated that the need to have sufficient precision	Providing 5 significant figures for	The situation presented is

554	reported for the CI has to be associated with the precision of the parameters. In general, 3 significant figures are already largely sufficient when using 15 to 20% in the assay precision.	125.00 is inappropriate. "80.0% and 125%" or "0.800 and 1.25" should be sufficient.	understood. However, regardless of the precision of the analysis methods many statistical programs report confidence limits with a large number of figures, and some kind of recommendations need to be included in the guideline. The wording on acceptance limits is in line with the FDA guideline and was selected for harmonisation purposes.
553-554, 4.1.8	*Confidence intervals should be presented to two decimal places. To be inside the acceptance interval the lower bound should be ≥ 80.00 and the upper bound should be ≤ 125.00.* It's unclear whether *'presented to'* means *'rounded to'*. Although commercial software (*e.g.*, SAS, WinNonlin, Kinetica) can be configured to *round* the confidence interval to two decimal places, the assessment of BE (which is given verbatim as plain text in the software's output) is always based on data in full precison. This may lead to ambigous results (*e.g.*, a rounded confidence interval of 80.00-110.00 based on 79.995-109.993, accompanied by a statement like 'Failed to show average bioequivalence for confidence=90.00 and percent=20.0'). For the conventionally allowed difference (θ) of 20% the acceptance range is given as 1-θ, 1/(1-θ).	*Confidence intervals should be presented to two decimal places. To be inside the acceptance interval based on a 20% difference the lower bound should be ≥ 80% [100%-20%] and the upper bound should be ≤ 125% (1/[100%-20]).*	Agreed that clarification is needed. Text added to state that the confidence interval should be rounded.
554, 4.1.8	The acceptance limits are given without units.	Add the precent units: 80.00 % and 125.00 %.	Agreed
555-557, 4.1.8	As demonstrated by Kamal Midha during the EUFEPS conference in January 2009, partial AUC is very variable at early time points, which are relevant for products where rapid absorption is of importance. Own data from three studies with products where rapid absorption is of importance also indicate that the intrasubject CV of partial AUC is at least three times higher than the intrasubject CV of AUC(t). Thus, the sample size of bioequivalence studies might increase tremendously just because of the high variability of this additional parameter.	For products where rapid absorption is of importance, request only the point estimate of partial AUC to lie within the 80-125% acceptance range. Alternatively, define a bioequivalence criterion for a less variable parameter like t(max) for such products.	The problems with the use of partial AUC are acknowledged. The section has been revised. Partial AUC has been removed from the guideline. The guideline now includes a recommendation for evaluation of tmax
Line 555	Using the same acceptance criteria for partial AUC as a measure of	Please state that, whenever appropriate,	Partial AUC has been removed

	early exposure is not justified.	the applicant should justify the appropriate acceptance limits for partial AUC in case of drugs with rapid absorption.	from the guideline, see also comment above.
4.1.8:555	Partial AUC for drugs with rapid exposure is not needed	Cmax and total AUC will suffice	Partial AUC has been removed from the guideline, see also comment above.
555 4.1.8 Acceptance limits	Same as 311-322 / 4.1.5 Pharmacokinetic parameters	CLARIFICATION: Please provide a precise definition for "rapid absorption of importance" (examples as available).	The section has been revised and now includes the similar wording as the former guideline
555 – 557, section 4.1.8	Experience demonstrates that partial AUC is normally highly variable even for standard immediate release products. Higher variability in measurement of this parameter may also be related to administration conditions.	An acceptance range for partial AUC should only be defined in the guideline after a comprehensive analysis of available data and of their variability. The request for identical acceptance limits as for C_{max} is too rigid. An alternative would to specify that the point estimate ratios should lie within the 80 to 125% acceptance range.	Partial AUC has been removed from the guideline, see also comments above.
Line no: 555 to 557	"For products where rapid absorption is of importance, equivalence between test and reference should be supported by demonstration of bioequivalence for partial AUC as a measure of early exposure. The same acceptance interval as for Cmax applies to partial AUC." **Q.1**What would be the %Confidence interval applicable for partial AUC? **Q.2** What would be the bounds of the partial AUC (0-1 hrs, 2 hrs, 3 hrs etc) depending upon the half life of the active ingredient?		Partial AUC has been removed from the guideline, see also comments above.
555-557 4.1.8 Acceptance limits	As partial AUC is strongly dependent on the rate of absorption, it does not seem justifiable to request that the 80-125% acceptance range must be met for both partial AUC and C(max).	CHANGE: Consider either partial AUC or C(max) as primary parameter for BE assessment.	Partial AUC has been removed from the guideline, see also comments above
555 – 557,	Preliminary experience demonstrates that partial AUC is frequently	An acceptance range for partial AUC	Partial AUC has been removed

4.1.8	highly variable. Higher variability of this parameter may also be related to administration of products without water. This administration is requested for ODT formulations.	should only be defined in the guideline after a comprehensive analysis of available corresponding data and of their variability. The request for identical acceptance limits as for C_{max} may be too rigid for special applications (e.g. ODT formulations).	from the guideline, see also comments above.
Lines 555-557	Please define the term "rapid absorption". Please clarify which parameters should be studied for products with rapid absorption; C_{max}, AUC_t and partial AUC or only AUC_t and partial AUC. ***AUC*** Please clarify if AUC_∞ should no longer be statistically evaluated according to the defined BE criteria. Section 4.1.5 states that AUC_∞ is one of the parameters to evaluate (In studies to determine bioequivalence after a single dose, AUCt, AUC_∞, Cmax and tmax should be determined.), but AUC_∞ is not mentioned in Section 4.1.8 which is the section that defines parameters to evaluate (here only C_{max} and AUC_t are included).		Partial AUC has been removed from the guideline. The section has been revised and now includes recommendations for evaluation of tmax
Lines 555-557:	For assessment of bioequivalence on the basis of partial exposure several factors need to be considered. Sample size is usually increased due to significant increase in the variability covering the early exposure region of the plasma curve. Secondly, the partial area ratio is usually very unstable on repeated occasions without much pharmacological consequences as it is the intrinsic property of the drug level appearing in the blood during the early exposure.		Partial AUC has been removed from the guideline, see also comments above.
556-557 4.1.8 Acceptance limits	It is not clear if the sentence "The same acceptance interval as for C(max) applies for partial AUC." means that extension of the acceptance range is possible for partial AUC in case of highly variable drugs. Additionally, preliminary data available from analysis of existing studies suggest that variability of partial AUC seems to be very much higher than the usual AUC variability, making it virtually impossible to meet BE criteria, even with an extended acceptance range.	CLARIFICATION: It should be clarified that extension of the acceptance range is also possible for partial AUC in the case of highly variable drugs. Furthermore, prior to implementing such a new requirement in a guideline, an extensive review of available data on partial AUC, especially when medication has been taken without water, should be carried out. If	Partial AUC has been removed from the guideline, see also comments above.

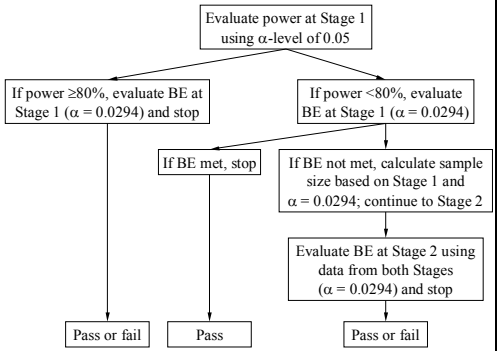
		variability in such cases turns out to be very high, it should be sufficient if only the T/R ratio of partial AUC meets the 80-125% acceptance range. Alternatively, a non-parametric test for t(max) with a predefined acceptance interval could be used for drugs where rapid absorption is important.	
# 555-558 § 4.1.8	Please clarify if bioequivalence criteria for partial AUC and C_{min} are based on 90% CI or on ratios contained within 80-125%.		Partial AUC and Cmin have been removed from the guideline.
Line 556, 4.1.8	The definition of partial AUC is not clear. Are you referring to AUC(0-t_{max})?	Clarification required as to what exactly is the recommended partial AUC.	Partial AUC has been removed from the guideline.
558 to 559	Considering that, in the case of immediate release formulations, the parameter $C_{min,ss}$ is not appropriate to characterise the release characteristics of the formulation, the APV Expert Panel proposes restriction of the proof of bioequivalence for immediate release formulations to be tested at steady state to AUC_t, and $C_{max,ss}$ only.	Revise this paragraph as follows: "For studies to determine bioequivalence at steady state AUCτ, and Cmax,ss should be analysed using the same acceptance interval as stated above."	Agreed. For immediate release formulations, Cmin,ss will not provide additional information on potential differences in rate or extent of absorption than AUC and Cmax. The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
558 – 559, section 4.1.8	It may be debatable whether $C_{min,ss}$ should be considered as a primary bioequivalence parameter and thus as equally important as AUC_τ and $C_{max,ss}$, because a higher variability of this parameter will not affect safety and often not efficacy either. Therefore, at least a potential widening of the acceptance interval may be considered as for C_{max} (75-133 %) in case of highly variable PK.	We consider that $C_{min,ss}$ is not primary parameter for the assessment of immediate release products. In the case that this parameter is considered necessary, a widening of the acceptance limits should be applied.	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
558 – 559, 4.1.8	It may be debatable whether $C_{min,ss}$ should be considered as a primary bioequivalence parameter and thus as equally important as AUC_τ and $C_{max,ss}$, because a higher variability of this parameter will not affect safety and most probably not efficacy either. Therefore, at least a potential widening of the acceptance interval may be considered as for C_{max} (75-133 %) in case of highly variable PK.	A clarification is required as to whether $C_{min,ss}$ is a primary parameter and whether a widening of the acceptance limits may also be applicable for this parameter.	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations, see also comment above.

Line 558, 4.1.8	Are you suggesting to use $C_{min,ss}$ as a primary bioequivalence parameter and as equally important as AUC_{τ} and $C_{max,ss}$? Does the potential widening of the acceptance interval for C_{max} (75-133 %) in case of highly variable PK also apply to $C_{min,ss}$?	Clarification required as to whether $C_{min,ss}$ is a primary parameter and whether a widening of the acceptance limits is also applicable for this parameter.	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
558	The guidance states "For studies to determine bioequivalence at steady state AUCτ, Cmax,ss, and Cmin,ss should be analysed using the same acceptance interval as stated above."	Could we apply widen acceptable criteria on Cmin?	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
Line 558	Exclusion of $C_{min,ss}$ as an acceptance criterion should be allowed in some circumstances, based on its known relevance to either efficacy or toxicity. For some antiretroviral NRTIs, activity is associated with the intracellular triphosphate moiety. Therefore, $C_{min,ss}$ would not be appropriate as a criterion for bioequivalence.		The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
558, 4.1.8	Cmin is required to be within 80-125% for steady state. However, for immediate-release formulations, it may be difficult to reliably determine Cmin. Furthermore, Cmin may be highly variable, thus a high sample size would be required for a reasonably powered study. This is not justified due to the low amount of knowledge gained by measuring Cmin.	Please change: "For studies to determine bioequivalence at steady state, **AUCtau and Cmax,ss** should be analyzed using the same acceptance criteria as stated above."	Agreed
Line 558-559	Cmin,ss should not always be a critical variable for showing bioequivalence in steady state studies.	Suggest to change in sentence line 558 : For studies to determine bioequivalence at steady state AUCτ, and Cmax,ss, (and Cmin when appropriate) should be analysed using the same acceptance interval as stated above.	Agreed. The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations.
558-559, 4.1.8	Cmin,ss can not be critical variable to show bioequivalence in steady state studies, because the Cmin,ss-value mainly describes the properties of the drug, not the differences between the formulations. AUCτ and Cmax,ss should be given as main variables for BE evaluation.	Suggestion: For studies to determine bioequivalence at steady state AUCτ and Cmax,ss should be analysed using the same acceptance interval as stated above.	Agreed, see also comment above.
558-559 4.1.8	Given that Cmin is usually variable and has a low value, the	CHANGE: The ratio of means for Cmin should be	The guideline has been revised. Bioequivalence does not need to be

Acceptance limits	bioequivalence criteria for Cmin are considered too strict. An appropriate way to assess equivalence would be to have the Cmin ratio within the acceptance interval of 80%-125%. This is consistent with many other jurisdictions. It might also be considered to assess only the lower end (80%) of the acceptance range as deviations on the upper end correspond to a lower fluctuation of a product, which can hardly be a disadvantage in any product.	introduced. It should be within the acceptance interval of 80%-125% or above 80%.	demonstrated for Cmin,ss for immediate release formulations.
558-559, 4.1.8 561-562, 4.1.8	*For studies to determine bioequivalence at steady state AUC_τ, $C_{max,ss}$, and $C_{min,ss}$ should be analysed using the same acceptance interval as stated above.* $C_{ss,min}$ is inherently more variable than $C_{ss,max}$, especially for drug products with low accumulation. *Moreover, for highly variable drugs the acceptance interval for C_{max} may in certain cases be widened (see section 4.1.10).* The term *'highly variable drugs'* should be replaced by *'highly variable drug products'*. Example: diclofenac formulations for rectal application are not highly variable, whereas enteric coated ones are.	Ranked according to preference: 1. *$C_{ss,}$min should be removed from BE assesment.* 2. *Only the ratio should lie within 0.8–1.25 (no CI assessment).* 3. *Moreover, for highly variable drug <u>products</u> the acceptance interval for C_{max}, $C_{ss,max}$, and $C_{ss,min}$ may in certain cases be widened (see section 4.1.10).*	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations, see also comment above.
Lines 558-559	For studies to determine bioequivalence at steady state AUC_τ, $C_{max,ss}$, <u>and $C_{min,ss}$</u> should be analysed using the same acceptance interval as stated above. <u>Comment:</u> According to section 4.1.1 (lines 153-157 and 163-169) parameters AUC and/or C_{max} are the parameters of interest in multiple dose studies conducted as alternative study program for immediate release formulations. $C_{min,ss}$ is not mentioned, which is reasonable as this parameter is not appropriate for the proof of bioequivalence of immediate release formulations. Thus, the parameter $C_{min,ss}$ should be deleted from lines 558-559.	For studies to determine bioequivalence at steady state AUC_τ and $C_{max,ss}$ should be analysed using the same acceptance interval as stated above.	Agreed, see also comments above.
558 – 559, section 4.1.8	AUC_τ may be less suitable for BE testing in multiple-dose studies in patients, because the true τ varies inter- and intra-individually (it is based on the respective **actual** dose intervals). Thus the true time range varies accordingly. This is especially true if BE studies have to be performed in patients where planned 'ideal' sampling	Instead of AUC_τ, AUC(0-tx) may be used where 0-tx is a fixed, post administration period established individually and truncated accordingly (to the shortest) 0-tx. This should be	By AUC_τ we mean AUC over the dosage interval. Samples should be taken as close as possible to time 0 (i.e. pre-dose) and the nominal dosage interval (e.g. 12 h) to ensure

	schedules might not be adhered to.	near to the planned dose interval. AUC(0-tx) is a much more robust parameter than AUC_{τ}, because its variability does not contain variable dose intervals as an additional source of variation.	an accurate determination of AUC□. This has been clarified in the guideline.
Line 558, 4.1.8	Please clarify what is meant by $C_{min,ss}$? Will it be the true $C_{min,ss}$ (i.e. the absolute minimum concentration in a dose interval independent of whether or not it is really observed at the end of a dose interval) or rather the trough concentration $C_{trough,ss}$?	$C_{min,ss}$ needs to be clearly defined (see also line 711, definitions)	By Cmin,ss we mean the concentration at the end of the dosage interval, i.e. Ctrough. However, the guideline has been revised and no longer asks for Cmin,ss.
558 – 559, section 4.1.8	The definition of $C_{min,ss}$ is not unequivocal (see also line 711). Will it be the true $C_{min,ss}$ (i.e. the absolute minimum concentration in a dose interval independent of whether or not it is really observed at the end of a dose interval) or rather the trough concentration $C_{trough,ss}$?	A clear definition of $C_{min,ss}$ should be provided.	By Cmin,ss we mean the concentration at the end of the dosage interval, i.e. Ctrough. However, the guideline has been revised and no longer asks for Cmin,ss.
558 - 559, 4.1.8	What is meant with $C_{min,ss}$ as target parameter? Will it be the true $C_{min,ss}$ (i.e. the absolute minimum concentration in a dose interval independent of whether or not it is really observed at the end of a dose interval) or rather the trough concentration $C_{trough,ss}$?	$C_{min,ss}$ needs to be clearly defined (see also line 711, definitions)	The guideline has been revised. Bioequivalence does not need to be demonstrated for Cmin,ss for immediate release formulations, see also comment above.
Lines 558-559:	One should be cognizant about the assurance of achievement of the steady state status before serial blood collection for estimating PK at steady state. The appropriate methodology to assure achievement of steady state for each subject should be recommended.		Achievement of steady state can be evaluated by collecting pre-dose samples on the day before the PK assessment day and on the PK assessment day. A specific statistical method to assure that steady state has been reached is not considered necessary in bioequivalence studies. Descriptive data is sufficient.
561 to 562	The provisions in line 561 to 562 only allow for widening of the acceptance range for C_{max}.. The current version of the NfG	Revise sentence in line 561 as follows:	Not agreed, see responses to

	considers the widening of the acceptance for AUC in "rare cases" acceptable. Attention should be drawn to the following case example: For carbidopa in levodopa/carbidopa combinations a 0.75 – 1.33 range for AUC is currently accepted in the EU. The pronounced intra-subject variability of carbidopa requires the widening of the acceptance range to facilitate a reasonable sample size. Also from a clinical perspective the widening in this case is acceptable. Thus the APV Expert Panel proposes that the acceptance of AUC in "very rare" and well justified cases be widened.	"Moreover, for highly variable drugs the acceptance interval for Cmax, and in very rare and well justified cases for AUC, may be widened (see section 4.1.10)."	comments on section 4.1.10 below.
Lines 561-562	Guideline: Moreover, for highly variable drugs the acceptance interval for C_{max} may in certain cases be widened (see section 4.1.10). Comment: According to current legislation laid down in the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* in rare cases a wider acceptance range for AUC may be acceptable if it is based on sound clinical justification. One example for a wider acceptance range for AUC accepted by EU competent authorities in the past is carbidopa in levodopa/carbidopa combinations. Therefore, AUC should be mentioned as well.	Guideline: Moreover, for highly variable drugs the acceptance interval for C_{max} may in certain cases be widened (see section 4.1.10). In rare cases a wider acceptance range for AUC may be acceptable if it is based on sound clinical justification.	Not agreed, see responses to comments on section 4.1.10 below.
563	Concnering the "Two-stage design"- it is an interesting approach but it would be nice to define the level of statistical penalty (e.g. 92%CI or 95%CI) as it is stated in the Australian guidance.		It is considered that the penalty can vary by applicant's choice. Many approaches are valid. But an example will be included.
563, 4.1.8	It should be clarified what statistical approach is expected for a two-stage design study.		An example will be included.
563, 4.1.8	We propose to add that a two-stage design with a blinded interim CV analysis and subsequent adjustment of the sample size according to Wittes et al. (Statistics in medicine, 1990; 9: 65-72) and Schwartz et al. (Pharmaceutical Statistics, 2003; 2: 263-271) is allowed without alpha correction.	Please add: "… The plan to use a two-stage approach must be prespecified in the protocol along with the adjusted significance levels to be used for each of the analyses. **Furthermore, it is possible to perform a two-stage design with a blinded interim CV analysis according to Wittes and Schwartz. In this case, no**	In practice the company could essentially do this 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

		alpha correction is required."	are truly blind in a bioequivalence trial.
563 – 572, section 4.1.8	The draft guideline mentions the possibility of a two-stage design. This should necessitate the inclusion of an extra stage parameter into the ANOVA: a second stage will be equivalent to an extra period effect in the data, which should be accounted for.	The ANOVA model should be adjusted in a two-stage design by including the stage factor as a source of variation. Statistical evaluation of the stage effect should be explicitly stated.	Agreed. A term for stage should be included in the analysis. It is not agreed that analysis of the stage effect is necessary. This is to be treated like e.g. period effect. Important to include in the model, but the size of effect not important.
Lines 563 – 572, 4.1.8	The draft guideline mentions the possibility of a two-stage design. This will necessitate the inclusion of an extra stage parameter into the ANOVA: a second stage will be equivalent to an extra period effect in the data, which should be accounted for.	Clarification required as to whether the ANOVA model should be adjusted in a two-stage design.	Agreed. Stage effect added to model
563-572 4.1.8 Two-stage design	Clarification as to statistical penalties should be provided.	CLARIFICATION: Examples of statistical penalties should be included to illustrate this paragraph.	Agreed, example included.
563 – 572, 4.1.8	The draft guideline mentions the possibility of a two-stage design. This should necessitate the inclusion of an extra stage parameter into the ANOVA: a second stage will be equivalent to an extra period effect in the data, which should be accounted for.	A clarification is required as to whether the ANOVA model should be adjusted in a two-stage design by including the stage factor as a source of variation.	Agreed. Instruction to add stage factor added
563-572, 4.1.8	An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. The possibility for a two-stage approach is highly appreciated. Although an α-adjustment is mentioned later on, these introductory two sentences may lead to naïve pooling and evaluation of 95% confidence intervals by statistical novices. It should also be recognised that sequential methods routinely used in clinical studies are based on testing for a significant difference and have been shown to be inadequate (inflated patient's risk) in an equivalence setting. The only *validated* method for 2×2×2 BE studies was recently published: *Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ and RA Smith;* Sequential design approaches for bioequivalence studies with	The entire section should be clarified. It is suggested that a decision tree is given in an Appendix, e.g., Potvin et al.'s 'Method C':  	Agreed. Example included – the example chosen was the Pocock approach – very similar to the example in the flow chart included in the comment.

	crossover designs. Pharmaceut. Statist. 2007, DOI: 10.1002/pst.294 http://www3.interscience.wiley.com/cgi-bin/abstract/115805765/ABSTRACT The method will be adopted in the Canadian guideline (presentation of Eric Ormsby, Health Canada / TGD, BioInternational 2008, London) and is currently under revision by the FDA.		
o-stage designs Lines 563–572	Specific comment on two-stage designs: It will be helpful if the guidance could provide some examples regarding the two-stage design (lines 563-573) and the evaluation of data from several BE studies.		Example added for 2-stage designs. Information has been clarified in the several BE studies section.
Line 563. Two-stage design	Two-stage design or group sequential design is probably most applicable to the highly variable drugs and drug products. It would be useful to specify the types of drugs that this approach can be applied to otherwise if this approach is applied to all drugs, the applicant may start with a very small number of subjects and then add more subjects until the study shows favorable results. Furthermore other approaches, i.e., scaled average bioequivalence approach (sABE) that can be efficiently applied for the highly variable drugs and drug products. Some consideration should be given to sABE approach in lieu of the group sequential design.		It is considered that this approach can be applied to all drugs. If the company wishes to proceed in the manner stated they could (limited to two stages) but it would not seem to be the most efficient or practical approach. Scaling for Cmax only with a cap on the amount of scaling has been added to the highly variable drugs section.
After 572, 4.1.8	After paragraph of two-stage design would be right place to discuss about the need of multiplicity adjustment also for another kind of study designs compared to two separate studies (i.e. three period study including two references (one from EU and other from USA) or four period study including two doses).	After 572, 4.1.8	Agreed, this is important. Sentence added to state that in such studies all data except that from the comparison of interest should be removed. This has been added to the subject accountability section.

Subject accountability Lines 573–590	Specific comments on subject accountability: Lines 574-576: Does this mean that in a 2-period, 2-treatment crossover design for the comparison of two formulations, the analysis must be performed on the subjects with complete data in both periods? That is, the subjects with only one period data should not be included in analysis. Please clarify and revise wording if necessary. Line 589: It is sometimes observed in PK profiles concentrations that are no physiologically possible (i.e. wide swings in plasma concentrations over a short duration); however, the sampling error in the clinic cannot be confirmed. In these cases, it may be reasonable to exclude data as well.		Yes, patients must complete both periods in a 2x2 trial to be included. Text clarified. The second reason is not agreed. Exclusions based on studying the pk profiles are not acceptable.Though some results may seem to be errors it is not clear where to draw the line.
Line 573	Adherence to protocol is like adherence to a contract. The protocol must specify the data from the minimum number of subjects that would be used for statistical analysis, irrespective of number of subjects who completed the study. If blood samples from all subjects are analyzed, irrespective of the number specified in the protocol, data from all subjects should be included in the statistical analysis. Strict criteria should be applied not to exclude data on any specific subject(s) and it should be clearly specified in the protocol *a priori*.		Agreed. Some changes made to subject accountability section to reflect this
Lines: 574-576	Multiple companies observed that this sentence is not clear. In a crossover study, is a subject included only if he/she has completed BOTH at least one "reference" period and at least one "test" period ? It is debatable to NOT use all the information, by exclusion of any subject that misses a period (or more). Recommend to include "all available valid data", that is, any subject that has completed at least one period. The standard statistical "mixed model" analysis will accommodate any "missing data", in such a manner to maximize statistical efficiency, by combining inter-subject information and intra-subject information. Also, use of all available data conforms with recommendations in the Canadian Guidance for Industry "Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A: Oral Dosage Formulations for Systemic Effects", section 7.4.1 on Statistical	Please clarify which was intended: "…with the exception of subjects in a crossover trial who do not complete at least two study periods, such that they have received both the test and the reference products" Or "…with the exception of subjects in a crossover trial who do not complete at least one period receiving either the test or the reference product" We would suggest the following: "All treated subjects should be included in the statistical analysis, with the exception in a cross-over trial who do not complete at least one period. **Thus,**	Clarification made along lines of first bullet.

	Analysis: *The analyses should include **all the data for all subjects** on measured data. Supplementary analyses may also be carried out with selected points or subjects initially excluded from the analyses. Such exclusions must be justified. It is rarely acceptable to exclude more than 5 percent of the subjects or more than 10 percent of the data for a single subject-formulation combination.*	**a subject would need to contribute at least one treatment (i.e. either reference or test) to be included in the analysis. This holds true also for a parallel design."**	
Line 574-576 Line 583-584	The exclusion of subjects who did not complete both the test and reference product period from the analysis does not make the best use of the data collected (as a mixed model analysis is able to suitably incorporate such partial data in the analysis).	Suggest rewording the sentence from lines 574-576 to "All treated subjects should be included in the statistical analysis, with the exception of subjects in a crossover trial who do not complete at least one period (or who fail to complete the single period in a parallel group trial)." Suggest rewording the sentence from line 583-584 to "Ideally all treated subjects should be included in the analysis provided that at least one treatment period has been completed."	The mixed model can include such patients, but it is not considered useful to do so. The point is to compare test and reference products in patients who have received both. No change.
574-576 4.1.8 Subject accounta-bility	This sentence should be modified as it contradicts the following paragraphs which allow exclusion of subjects from the statistical analysis prior to bio-analysis.	CHANGE: Modify to: "Ideally, all treated subjects …" (See line 583)	Agreed
574-576, 4.1.8	The statistical analysis should be performed to all treated subjects, with the exception of subjects in a crossover trial who do not complete at least one period receiving either test or reference product.	Corrected version: "All treated subjects should be included in the statistical analysis, with the exception of subjects in a crossover trial who do not complete at least one period receiving either test or reference product (or who fail to complete the single period in a parallel group trial)".	Not agreed. Subjects should complete one period with each treatment to be included.
Lines 574-576	Sentence not clearly formulated.	"All treated subjects should be included in the statistical analysis, with the exception in a cross-over trial who do not complete at least one period. **Thus,**	Not agreed. Subjects should complete one period with each treatment to be included.

		a subject would need to contribute to at least one treatment (i.e. either reference or test) to be included in the analysis. This also holds true for a parallel design."	
574-590, 4.1.8	In some cases, very unusual plasma profiles are detected after the pharmacokinetic analysis indicating e.g. that a subject might not have swallowed a tablet although no incidence was reported during the clinical part of a study. In such cases, it should be possible to perform a re-dosing study in order to prove the anomalous response in the initial part of the study and to eliminate a subject from the evaluation depending on the outcome of the re-dosing study.	Give the option to eliminate subjects on the basis of a re-dosing study as suggested by the FDA in the attached document.  FDA_Outliers.PDF	Re-dosing not currently supported. Just because a result is not reproduced upon re-dosing, doesn't mean it wasn't true. We don't expect the same results from a subject every time. Any approach which focuses on observations with large differences and targets them for exclusion is considered to be increasing the chances of falsely showing equivalence. No change.
573-590 4.1.8 Subject accountability	This section appears to set stricter elimination criteria than on line 520 (4.1.8 Statistical analysis). It should be possible to eliminate subjects with "anomalous responses" on the basis of a further "partial study", using re-dosing of the outlier subject, together with two to three other subjects from the original study to serve as "quality control". It would appear unethical to re-expose an entire subject panel to the study drug in case of such "anomalous responses". Conditions to include or remove the subject from the statistical analysis should be defined.	CHANGE: This paragraph should be in line with section 4.1.8 Statistical analysis. Option should be added.	Text changed to add non-zero period 2 values as a reason for exclusion (as also noted on line 520). Re-dosing is not supported (see comment above).
4.1.8:577	Statement is not clear (do we accept that alternates are not assayed in case of no dropouts OR all subjects entered to be assayed regardless)	Please clarify	All subjects to be assayed regardless. Sentence clarified.
Lines 580-590 / 517-521 4.1.8	In case e.g. vomiting occurred, not the complete subject with all periods should be excluded, but only that period, where vomiting occurred.	Please change	Only subjects with data on both test and reference can be included in the statistical analysis. Hence, exclusion of data from one period is only possible in a study with more than 2 periods and provided data on both test and reference are available.

580-586 4.1.8 Subject accounta-bility	Inclusion of a subject suffering from AEs in the bio-analysis might become necessary for safety reasons even if it is not planned to include the subject in the statistical PK evaluation.	CHANGE: Include the option for sponsors to discuss the inclusion or exclusion of subjects, which shall or shall not be included in the PK evaluation in bio-analysis if necessary for safety reasons. Clear documentation that such subjects were excluded from PK evaluation prior to bio-analysis should be requested/provided.	Added that samples from excluded subjects should still be reported. This is important if there is disagreement over an exclusion as it would permit a re-analysis.
580 – 583, section 4.1.8	Cases are conceivable where the decision to exclude a subject from the statistical analysis can only be made after bioanalysis if e.g. concentrations >LLOQ are observed prior to dosing, an implausible shape in the concentration-time profile, implausibly high concentrations suggesting interference, no quantifiable concentrations suggesting non-compliance, etc. Clinical events not related to study medication, such as a migraine-related gastroparesis may result in anomalous profiles. Such events might not always be detected during the clinical phase.	The guideline should take the observation of irregular results into account which have been made **after** completion of bioanalyses. Corresponding recommendations should be considered how to deal with irregular results. A possibility should be given to exclude a subject with an "anomalous response", e.g. with an anomalously low value for a key parameter in one period. The FDA suggests to exclude subjects with anomalous responses on basis of a sound justification applying a re-dosing or replicate design study.	Not agreed, see also response to other similar comments.
Lines 580-590	"…decision to exclude a subject from the statistical analysis must be made before analysis." This request is too strict. We normally perform BE trials blinded. At the "blinded report planning meeting" the decision on exclusion is being made without having the bioanalytical data in-hand. However, the bioanalysis itself has already occurred. The current request as written would result in a significant time delay.	Please change to e.g.: "…decision to exclude a subject from the analysis should be done before unblinding the trial and without consideration of plasma concentration time profiles."	Text clarified to read that the decisions should be made while the study is being conducted, i.e. recorded on the CRF in the clinic,
Line 581	*"In consequence, the decision to exclude a subject from the statistical analysis must be made before the bioanalysis".* Multiple companies pointed out that, in general, the decision to exclude a subject cannot be made prior to bioanalysis however the criteria for exclusion of subjects can be made at this time. For example,	Where outliers are observed in bioanalytical results it should be possible to exclude the results, post-study, following investigation and the identification of an assignable cause.	Not agreed. This approach of excluding outliers after the data are seen is exactly what we wish to avoid. Such an approach creates bias.

	concentrations >LLOQ are observed prior to dosing, an implausible shape of profile, implausibly high concentrations suggesting interference, no quantifiable concentrations suggesting non-compliance, etc.	Please clarify that "exclusion of subjects must be based on objective, pre-defined criteria before bioanalysis" Although data from excluded subjects are excluded from statistical analysis, stipulate that data of excluded subjects can be reported for completeness.	Agreed
582-583, 4.1.8	The provision "… the decision to exclude subjects must be made before bioanalysis" should be amended for the following reasons: From a practical point of view, this is not possible, as the full clinical data set is only available after the end of the data management process, which takes a lot of time. If bioanalysis could only start after this process, a considerable delay would be expected. If objective criteria like vomiting within 2 x Tmax are predefined in the study protocol for exclusion of subjects, no bias is to be expected even if the decision is made after the bioanalysis. Furthermore, it should be possible to exclude a subject if the reference product has failed, e.g. proven by the lack of any measurable concentrations. In cases of outliers, which cannot be explained by clinical reasons, it should be possible to perform a re-dosing study.	Please change: "Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules. **In consequence, the decision to exclude a subject from the statistical analysis is only allowed in the following rare cases:** **Based on predefined criteria, e.g. vomiting or diarrhoea within a predefined period after dosing.** **In cases where the reference product has failed, proven by lack of any measurable concentrations.** **In cases where a re-dosing study of the outlying subject and 10% of the other subjects of the study shows that the anomalous values are not reproducible, thus excluding a subject-by-formulation interaction.** **Any other exclusion is only possible in exceptional cases, which require sound justification and must be very well documented."**	Partly agreed. Lack of measurable concentrations or AUC <5% of mean AUC may indicate subject non-compliance. The guideline has been revised to allow exclusion of subjects with no or very low concentrations for reference product. However, as mouth checks should be made to prevent non-compliance, this will only be accepted in exceptional cases and may question the validity of the study. Re-dosing is not supported. Just because a result is not reproduced upon re-dosing, doesn't mean it wasn't true. We don't expect the same results from a subject every time. Any approach which focuses on observations with large differences and targets them for exclusion is considered to be increasing the chances of falsely showing equivalence. No change.
584 4.1.8 Subject accountability	Exclusion can only be made based upon reasons that have been defined or referred to in the protocol (eg, SOP).	CLARIFICATION Clarification is needed.	This seems clear – the possible reasons for exclusion must be defined in the protocol.

584 4.1.8 Subject accounta-bility	Is it possible to obtain more detailed information regarding when it is acceptable to exclude subject due to emesis or diarrhoea?	CLARIFICATION: Clarification is needed	It is always possible to exclude a subject for emesis/diarrhoea provided it has been pre-specified in the protocol and it is before bioanalysis.
584 4.1.8 Subject accounta-bility Chemical 4.1.7	The section does not provide guidance on which samples obtained during the study should be bio-analysed. It is a common practice that samples of volunteers who complete at least one period receiving each of the tests and reference products or who have been withdrawn due to adverse events are to be bio-analysed. This excludes subjects who have dropped out of the study for other reasons than adverse event reactions from being bio-analysed.	CLARIFICATION: Clarification is needed	All samples should be bio-analysed. This is useful if there is disagreement over an exclusion as it enables the statistical analysis to be repeated.
Lines: 585-586	Reasons for excluding subject data could also include violation of inclusion/exclusion criteria (noted after the conduct of the study). For example, if the subject was later found to be a poor metabolizer, which had been an exclusion criterion, his PK data could be excluded from the primary statistical analysis.	Please add additional reasons, or add flexible language on this point.	Wording already states “such as” which is flexible. Any reason is acceptable provided it is planned in the protocol and the decision is made before the data are seen.
Line No: 585 to 586	“Acceptable reasons to exclude a subject are events such as vomiting and diarrhoea which could render the plasma concentration-time profile unreliable.” **Q.1** Can subjects be withdrawn from the study if he/she experienced an episode of vomiting or diarrhoea any time during the study? **Q.2** If the answer of above question is yes, then is this applicable for immediate release as well modified release formulation?, what would be an appropriate time interval when such occurrence can be ignored for each type of formulation? Please clarify.		Exclusion can be made for vomiting/diarrhoea at any time for any formulation. Crietira should be prespecified in the protocol and the decisions should be made before results are seen.
lines 585-586, last § page 14/29 and 1st § page 15/29	"Acceptable reasons to exclude a subject are events such as vomiting or diarrhea which could render the plasma concentration time profile unreliable"	The more specific FDA guidance is preferable: “data from subjects who experience emesis during the course of a BE study for an immediate release product should be deleted from the statistical analysis if occurring at or	The current more flexible proposal seems acceptable, provided exclusions are made before seeing the plasma profiles. No change

		before 2 times the median tmax. In case of modified release products, data from subjects who experience emesis during the labeled dosing interval should be deleted."	
586 (Para-4.18)	Vomiting and diarrhoea which could render the plasma concentration-time profile unreliable. ***Comments: Vomiting criteria should be define for IR and modified release product.***	Vomiting and diarrhoea which could render the plasma concentration-time profile unreliable. In case immediate formulation if vomiting occurs 2 times median/mean Tmax of drug., subject should exclude from study In case of Modified release product and delayed product if vomiting occurs any time during sample collection schedule , subject should exclude from study	The current more flexible proposal seems acceptable, provided exclusions are made before seeing the plasma profiles. No change
588-590, 4.1.8	Exclusion of data can never 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 affecting the pharmacokinetics. This statement is considered too rigid, because many documented cases exist where high variability is often caused not by an intrinsic variability, but by poor performance of the reference formulation (*e.g.*, enteric coated proton-pump inhibitors). If foreseen and stated in the protocol two possible solutions – *in case of a suspected product failure of the reference product only* – should be considered: A non-parametric method should be applied (since the assumption of an IDD which is necessary in parametric models is violated). Alternative method as reommended by the WHO (Technical Report Series No. 937, Annex 7, Section 6.8, May 2006, http://healthtech.who.int/pq/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf) and in Japan (NIHS, Bioequivalence Studies for Generic Products, Q&A Document, November 2006, http://www.nihs.go.jp/drug/be-guide/QA061124_BE.pdf). Re-testing of subjects, which would be inline with methods applied	*Non-parametric methods or re-testing of subjects should be considered.*	Non-parametric approach and re-testing not considered acceptable. Non-parametric approach could down-weight the importance of large differences. And just because a result is not repeated on re-testing, does not mean it was not real. No change.

	in the USA (inofficially), and Japan (NIHS, BE Studies for Generic Products, Q&A Document, November 2006): Inclusion of ≥5 participants from the main study, who showed 'normal' responses (*i.e.*, size of re-tested group ≥6 or 20% of subjects, whichever is larger) in a cross-over re-test study. If the subject shows a 'normal' response, a subject-by-formulation can be excluded. The subject may be removed from evaluation of the main study (studies must not be pooled or the original value replaced by the new one). If the subject shows again discordant values, the subject may not be removed from the main study.		
589	The guidance states "*Exclusion of data can never be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone*." Is the re-dosing study approach acceptable?	We suggest allowing a "re-dosing" possibility to confirm the "*anomalous response*"	Re-dosing approach currently not considered acceptable. See above
Presentation of Data Lines 591–614	Specific comments on Presentation of Data: • Lines 596–597: Please clarify whether percentage or decimal numbers should be presented for bounds, GMR and confidence intervals. Also please provide some guidance on rounding the results. For example, if the lower limit of the CI of GMR is 0.796 (79.6%), should it be rounded down to 0.79 (79%) or up to 0.80(80%)? • Line 599: 90% CI on the GMR is not appropriate for t1/2 and Tmax. Summary stats should be provided for these parameters.	Propose to use the decimal numbers, round down the lower bound of a confidence interval, round up the upper bound of a confidence interval, and follow the rule of "rounding to the nearest hundredth" for GMR estimates. For example, a GMR estimate (90% CI) of 0.842 (0.796, 0.888) should be rounded as 0.84(0.79, 0.89) by this rule.	Rounding should be done according to the common method: - Decide which the last digit to keep is. - Increase it by 1 if the next digit is 5 or more. - Leave it the same if the next digit is 4 or less. This is standard procedure and there is no need to state it in the guideline.
592 4.1.8 Presentation of data	The term "all data" is unclear. Does it refer to all individual volunteer data? The EGA would recommend including examples of CRFs along with 20% of the raw data.	CLARIFICATION: Please define "all data".	Agreed. The section has been clarified. Concentration data and pharmacokinetic parameters are requested.
4.1.8:599	Point estimates are not reported in some programs like Kinetica	Please reconsider	No change made. A program which reports point estimates should be used.
592-594 (Para-4.1.8)	All individual subject data should be provided. These presentations should include available data from subjects who eventually dropped-out from the study. Drop-out and withdrawal of subjects	All individual subject data should be provided. These presentations should include available data from subjects	The section has been revised taking the comment into account.

	should be fully documented. ***Comments : it is not clear from above line data of dropped out or withdrawal should be represented or not*** ***Data of withdrawal subject due adverse event should also present in addition to dropped out subjects.***	who eventually dropped-out and withdrawal from the study. Drop-out and withdrawal of subjects should be fully documented. Dropped out and withdrawal data should not include in final pharmacokinetic and statistical analysis.	
Lines 601 - 602, 4.1.8	It is unclear why the *'percentage of AUC_∞ that is covered by AUC_t should be reported for each subject…'* only in those cases where *'the observation period is shorter than 72 hours"*? We are, in fact, interested in how much of the AUC has been calculated based on extrapolation. Therefore, the extrapolated part %AUC(t-∞) should always be indicated for each subject.	The extrapolated part of AUC_∞, %AUC(t-∞), should generally be indicated for each subject.	Not agreed. Extrapolated area does not need to be reported when the sampling period is 72 h or more and $AUC_{(0\text{-}72h)}$ is used instead of $AUC_{(0\text{-}t)}$. See also comments on section 4.1.4, 4.1.5 and lines 549-550. This section has revised and moved within section 4.1.8 (to *Reasons for exclusion*).
Lines 602 - 604, 4.1.8	In principle, a result for AUC_∞ is potentially less reliable if the extrapolated part is >20%. Partial AUC should be used instead. The scientific basis for suggesting that the results for AUC may be acceptable and be used as long as less than 20% of the values contain an extrapolated part of >20% is unclear. The definition appears arbitrary.	If AUC_∞ cannot be used as a reliable parameter for **all** subjects, the BE decision should not be based on this parameter but e.g. on a partial AUC, AUC(0-tx), where 0-tx is a fixed time range (e.g. AUC(0-24), AUC(0-48)).	The sampling schedule should allow a reliable estimation of extent of exposure so that AUCt covers >80% of AUC_∞. If this is fulfilled AUCt will adequately reflect extent of absorption. A truncated AUC at 72h is allowed. A truncation at earlier time points is not considered needed in bioequivalence studies.
281-283 and 601-604	Comment: - Lines 281-283 state that truncated AUCs at 72h is acceptable for immediate release drugs with a long half-life. However, lines 601-604 state that the validity of the study could be questioned if more than 20% of subjects have an AUC_t/AUC_{inf} <80%, in the case of sampling periods less than 72h,. These two sections are contradictory. - What is the cut-off half-life value in order to apply calculation of	Remove the sentence in line 603-604: "…but if the percentage is less than 80% in more than 20% of the observations then the validity of the study could be questioned."	These comments are covered by responses to other issues.

	AUC_{0-72}? Rationale: When truncated AUCs at 72h are used for long half-life drugs, the AUC_{72}/AUC_{inf} will be <80% in many cases. Should the guideline accept truncated AUCs, then it should expect AUC_{72}/AUC_{inf} to be <80%.		
601 – 602, 4.1.8	The request to report the percentage of AUC_{∞} that is covered by AUC_t only in those cases where the observation period is shorter than 72 hours is obviously derived from the recommendation to determine the plasma concentration time profiles only for 72 hours. There may be studies in which samples have been collected for any reason for a longer period of time than 72 hours. Also in these cases the percentages of AUC_{∞} covered by AUC_t should be reported.	If AUC_{∞} is reported, the percentages of AUC_{∞} covered by AUC_t should generally be indicated independent of the length of the sample collection period.	Agreed, but considered covered by wording in guideline. This section has revised and moved within section 4.1.8 (to *Reasons for exclusion*).
Lines 601-604:	Generally it is ideal to cover 80% of the total exposure. However, as stated in the comments under earlier section, if it is pharmacokinetically established that the absorption process is complete before 80% of the total exposure is reached, it may not be prudent to question the validity of the study and find it unacceptable for most immediate release products absorption is complete at 5 x Tmax. Metabolic processes are operational and formulation factors have no influence. So why should unnecessary samples be collected to cover 80% of the total exposure. It would be unethical (see Reference 6 quoted earlier).		This section has revised and moved within section 4.1.8 (to *Reasons for exclusion*). A truncated AUC at 72h is allowed. A truncation at earlier time points is not considered needed in bioequivalence studies.
602 - 604, 4.1.8	In principle, a result for AUC_{∞} is not reliable if the extrapolated part is >20%. Truncated AUC should be used instead. The scientific basis for suggesting that the results for AUC_{∞} may be acceptable and be used as long as less than 20% of the values contain an extrapolated part of >20% is unclear. The definition appears arbitrary.	If AUC_{∞} cannot be used as a reliable parameter for **all** subjects, the BE decision should not be based on this parameter but e.g. on a truncated AUC as proposed in the comment on lines 549 – 550.	This section has revised and moved within section 4.1.8 (to *Reasons for exclusion*). A truncated AUC at 72h is allowed. A truncation at earlier time points is not considered needed in bioequivalence studies.
609-611	Since the method could be confidential property, the detailed description of it may not be reported, although available if needed.	Change to: "The bioanalytical report should include a description of the bioanalytical	Agreed. The text will be adapted to the proposal.

		method used…"	
Lines 609-614	Mention of the incurred sample reproducibility (ISR) is needed in the guidance.		The issue regarding ISR is under discussion. A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. A section on the ISR issue will be proposed in the new NfG on validation of bioanalytical methods.
4.1.8 Evaluation Lines 609-611	The Crystal City III White Paper from the AAPS/FDA Workshop in May 2006 recommends a brief description of the method, not a detailed description as stated in this guideline. Validation report should not be required to include in the analytical report since it will be contained separately in the submission.	Please change as follows: The analytical report should include a ~~detailed~~ **brief** description of the bioanalytical method used, ~~a detailed pre-study validation report and a detailed description of the in study validation results including~~ **and** the results for all standard and quality control samples"	Agreed. A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
611-612, 4.1.8	A "representative number" of chromatograms or raw data should be further defined. Are the raw data of 5 subjects always sufficient or are more data required for large studies, e.g. chromatograms of 20% of subjects?		A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. A proposal is made of 20% for bioequivalence studies, in accordance with the Crystal City III White Paper from the AAPS/FDA Workshop in May 2006.
Line 612, 4.1.8	The number of presented chromatograms should be reconsidered. The total number of chromatograms for study samples, calibrators and QC samples for 5 subjects (2xcrossover, 15 sampling times) is equal to ~180-200. Please, consider the corresponding number of pages needed in reports. Even when following this request, the sponsor may select the best and not necessarily representative chromatograms.	It appears preferable and more practicable to list calibrator and QC results together with descriptive statistics in the study report and have raw data (chromatograms, MS traces, etc) available on file.	A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. A proposal is made of 20% for bioequivalence studies, in accordance with the Crystal City III

			White Paper from the AAPS/FDA Workshop in May 2006.
Line 612 para 7 page 15/29	Douglas Pharmaceuticals Ltd would suggest extension of the representative number of chromatograms to be included as it is the companies experience that some authorities consider five subjects to be insufficient. Also the subjects whose chromatograms are to be included should be randomly selected and detailed in the protocol before the study is conducted and the results analysed. This is to ensure that such data included for evaluation in the study report is not biased data.	1). Change "…raw data (e.g. for the first 5 subjects) should be…" to: "….raw data (e.g. for 5 subjects or 20% of subjects randomly selected which ever is greater) should be…" 2). Insert a new sentence after "…the specimens analysed." To read: "The subjects whose chromatograms or raw data are to be included in the study report should be prospectively defined in the protocol before initiation of the study."	A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. A proposal is made of 20% for bioequivalence studies, in accordance with the Crystal City III White Paper from the AAPS/FDA Workshop in May 2006.
609 to 611	Bionalytical assay validation report (in this paper termed pre-study validation report) is summarised in CTD Sections 2.7.1.1 (Summary of biopharmaceutical studies and associated analytical methods) and detailed in 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies) in accordance with ICH M4E CPMP/ICH/2887/99.	The Crystal City III White Paper from the AAPS/FDA Workshop in May 2006 recommends a brief description of the method, not a detailed description as stated in this guideline; Validation report should not be required to include in the analytical report since it will be contained separately in the submission. The analytical report should include a summary description of the bio-analytical method used and results for all standard and quality control samples.	A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. The Crystal City III White Paper from the AAPS/FDA Workshop in May 2006 will be taken into account.
609-614	What could be considered "representative": 20% of the chromatograms or just limit this to the first 5 subjects? Should they be included in the report?	Define what % would be acceptable	A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. A proposal is made of 20% for bioequivalence studies, in accordance with the Crystal City III White Paper from the AAPS/FDA Workshop in May 2006.

611 - 613, 4.1.8	The number of presented chromatograms should be reconsidered. The total number of chromatograms for study samples, calibrators and QC samples for 5 subjects (2xcrossover, 15 sampling times) is equal to ~180-200. Please, consider the corresponding number of pages needed in reports. Even when following this request, the sponsor may select the best and not necessarily representative chromatograms.	It appears preferable and more practicable to list calibrator and QC results together with descriptive statistics in the study report and have raw data (chromatograms, MS traces, etc) available on file.	A separate Nfg will be prepared. A more elaborate section on this topic will be proposed in the new NfG on validation of bioanalytical methods. A proposal is made of 20% for bioequivalence studies, in accordance with the Crystal City III White Paper from the AAPS/FDA Workshop in May 2006.
613-614	The automatic integration is understood to be superior to the manual one. Such an approach is not correct. Generally speaking the manual integration is more precise and correct than the manual one, assuming the subjective approach and/or tendency of „improving“ final results to achieve the best fit by repeating integration is avoided. This may be achieved in such a way that integration procedure should be fully separated and independently performed of the evaluating procedure. According to our experience the best, most correct and most objective integration procedure is as follows: 1) Integration of all chromatographic peaks of 1 analytical batch (9 standards, 6 QCs and say 46 real PK samples) is done automatically using the analytical software. 2) The analyst is visually checking all the chromatograms and whenever the automatic integration is obviously not correct, he is performing manual integration of peaks without having the chance and opportunity to see what impact such an integration on the evaluated data will bring. The integration file is then closed and signed. These data are taken as primary source data for the next evaluation process and the integration cannot be additionally repeated any more. Such an integration procedure is being performed immediately after the data acquisition of the whole analytical batch is completed. 3) The data evaluation like regression analysis, QCs and real samples concentration evaluation must be performed by another analyst using that independently obtained and	I would strongly recommend to include such a procedure into the guideline. Justifying of any manual integration in some limited number of cases (usually at the lowest concentrations) has no any impact and is therefore not necessary.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.

	signed integration file.		
613	Each chromatogram being re-integrated either by changing of the automated procedure or manually will be documented in the raw data.	Remove: "Any manual integration of chromatograms should be justified and listed together with values from automatic integration."	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
4.1.8 Evaluation Lines 613-614	The Crystal City III White Paper from the AAPS/FDA Workshop in May 2006 states that the information surrounding the manual integration of chromatograms be retained as source data, not reported	Please remove the reporting requirement.	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
613 to 614	Recommend that this is not reported but retained in source data as indicated in the Crystal City III conference proceedings (AAPS Journal 2007; 9 (1) Article 4).	Delete sentence ' Any manual integration of chromatograms should be justified and listed together with values from the automatic integration'	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
614		Add: "Deviations of the bioanalytical protocol should be discussed in the Bioanalytical Report. Additional analytical raw data (e.g. reintegration) should be available "	A separate Nfg will be prepared. As such the complete section on chemical analysis has been shortened. This topic is under discussion, and possibly a section on this topic will be proposed in the new NfG on validation of bioanalytical methods.
4.1.9 Narrow therapeutic index drugs (line 616-630)			

	This section is too general and doesn't provide enough information to the applicant regarding what are the NTI drugs (definition, etc and identifying such drugs) and whether one should tighten the 90% confidence interval range or apply some other appropriate approach acceptable to the regulatory authorities. Without some of this important information, this section provides no guidance to a potential applicant. Definition of "Narrow therapeutic index drugs" is necessary so that an applicant can identify this class of drugs. One can also use replicate designs to scale (tighten) the Test to Reference confidence intervals scaled using the Reference to Reference variability rather than accepting any hypothetical limits of 90-111%, etc.		At the moment NTIDs have not been identified at an EU level. This will be done case by case.
625	A list of the known Narrow Therapeutic Index Drugs would be very helpful since narrowing the acceptance criteria on a case by case basis would be challenging and lead to some misidentification.	Determine a short list of Narrow Therapeutic Index Drugs (see Canadian Guidance)	At the moment NTIDs have not been identified at an EU level. This will be done case by case. Therefore it is not possible to include such a list.
615 4.1.9 Narrow therapeutic index drugs	To remove ambiguity and interpretation of the guideline, a list of NTI drugs should be consolidated, either as an annex to the present guideline or preferably as a separate document (in order to allow for updates).	CHANGE: Please provide a list of NTI drugs.	See above
615, 4.1.9	A definition for narrow therapeutic index drugs should be added. If this is not possible, a positive list agreed by all Member States should be established (e.g. as the positive lists issued by the Danish or the Canadian Health Authorities).		See above
4.1.9 615 to 630	Introduction of a quantitative definition for NTID in terms of therapeutic window or other relevant parameters is encouraged. The selection of a tighter 90 – 111% confidence interval seems arbitrary. It also needs to be pointed out that a tightening of the confidence limits for drugs undergoing therapeutic drug monitoring is rather unnecessary, since, irrespective of the drug product employed, therapy needs to be dose-adjusted for each patient individually due to intra- and interindividual variability and the simultaneous need for precise control of plasma concentration.	If no general definition of NTID can be established, a positive list for NTID is encouraged.	See above. Although titration of dosing (or drug monitoring) of NTDs is often applied, this does not mean that an unnecessary fluctuation in plasma levels of such drugs when switching between originator and generic should be introduced. Therefore it is considered appropriate to tighten

			the acceptance interval.
Lines 615-630	Guideline: […] narrow therapeutic index drugs (NTIDs) may be considered to be those for which there is a risk of clinically relevant difference in efficacy or safety between two products even when the conventional criteria for bioequivalence (i.e. 90% confidence interval for test / reference ratio for AUC and C_{max} within 80-125%) are met. NTIDs often have steep concentration response relationships for efficacy, toxicity, or both. Dosing generally needs to be individualised based on plasma concentration monitoring or titrated according to clinical response and there may be a potential for serious clinical consequences in the event of too low or high concentrations. It is not possible to define a set of criteria to categorise drugs as either NTIDs or not and a judgement must be made in each individual case. Likewise, the need for narrowing the acceptance interval for both AUC and C_{max} or for AUC only should be determined on a case by case basis. Comment: Since – according to the guideline – dosing of NTDs generally needs to be individualised based on plasma concentration monitoring or titrated according to clinical response, a tightening of the acceptance interval for concluding bioequivalence is deemed redundant. In case the need for tightening of the acceptance interval remains unchanged in the final version of this guideline, a set of quantitative criteria should be included or otherwise a positive list for NTIDs is recommended.	Line 615-630 section 4.1.9	See comment above
Line 620	*"…confidence interval for test / reference ratio for AUC and Cmax within 80-125%) are met."* The criteria formats are inconsistent with line 553	Please make consistent (see above comment on line 553).	The section has been changed based on other comments
Para 4.1.9	**Narrow therapeutic index drugs** The inclusion of suggested tighter confidence intervals for narrow therapeutic index drugs (NTID) is welcomed. However, the lack of any definition of what constitutes a NTID weakens the proposed	There should be a definition in the guidance document of narrow therapeutic index drugs. Specific drugs and classes should be stipulated.	See above. The suggestion that the confidence interval should include 100% is not agreed, as the purpose of the study

	guidance. In Health Canada's Guidance for industry - Bioequivalence requirements: critical dose drugs – effective May 31st 2006 (www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/critical_dose_critique-eng.pdf accessed January 27th, 2009) the following definition is used: *"Critical dose drugs" are defined as those drugs where comparatively small differences in dose or concentration lead to dose-and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.* In addition, in the appendix to the guidance document Health Canada lists those agents which the regulatory agency considers currently to be in the NTID class. This approach gives industry very clear guidance about which existing drugs need to conform to the tighter confidence intervals as well as what new chemical entities would be classed as a NTID. The Danish Medicines Agency (DMA) has also suggested that "*the 90% confidence interval for the ratio test versus reference should include 100% irrespective of whether acceptance limits of 80-125% or narrower are employed. Deviations may be accepted if they can be adequately justified not to have impact on either the overall therapeutic effect or safety profile of the product.*" (www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6437, accessed January 27th, 2009). Effectively, the DMA is suggesting that products that are declared bioequivalent should have a relative bioavailability that is not different from 100%. Additionally, the DMA, like Health Canada, lists classes of drugs for which the tighter confidence intervals are applicable.	The confidence interval should include 100%.	is to show comparability and not to exclude a statistically significant difference. Well designed and powered studies may fail because of this.

# 616-630 § 4.1.9	Clarification is required as to drug substances which would be considered as having a narrow therapeutic index (NTI), and therefore would be subject to the narrowed (90-111%) 90% CI. An appendix of example products would be helpful for reference. Some drugs that are generally subject to therapeutic drug monitoring (TDM), such as oral anticoagulants classified as coumarin derivatives (warfarin, acenocoumarol, phenprocoumon) are challenging to manage because of a large variability in the dose-response relationship, which is in part caused by genetic polymorphisms in metabolizing enzymes and in the VKORC1 gene that encodes the target enzyme. For such drugs the narrowing of acceptance criteria makes sense. However, what about a TDM drug that has a narrow therapeutic range and wide inter-individual pharmacokinetic variability? The guidance indicates that in certain cases for highly variable drugs, "the acceptance criteria for Cmax may be widened" (§ 4.1.10, lines 631-633). Examples of drugs that are commonly considered to be NTIDs with a narrow therapeutic index include immunosuppressive agents classified as calcineurin inhibitors (cyclosporine and tacrolimus) or rapamycin inhibitors (sirolimus and everolimus), or older generation antiepileptic drugs such a phenytoin, carbamazepine and valproic acid (valproate sodium). In cases where the Cmax is not directly related to the safety or efficacy of the product, a narrowing of the 90 CI to 90-111% should not be required and the 80-125% limit should be applied to the Cmax parameter.		See above The comment regarding Cmax is acknowledged. The guideline now states: "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."
628-630 4.1.9 Narrow therapeutic index drugs	The acceptance range should be narrowed only for NTI drugs with low variability (eg, intra-subject CV < 15%). If either AUC or C(max) do not have low variability, the drug can hardly be considered as NTI for this parameter (because of the wide variation of plasma drug levels between different administrations of the same formulation), and therefore tighter criteria should not be applied for such parameters.	CHANGE: Tighter acceptance ranges should be requested only for those drugs and parameters with a low intra-subject variability according to literature data.	Not agreed.
628-630, 4.1.9	In cases where the acceptance interval needs to be tightened, the acceptance interval for concluding bioequivalence should generally	*Wording should be changed in such a way, that it's clear that the upper limit*	Agreed to change into 90.00 – 111.11%.

632-634, 4.1.10	be narrowed to 90-111%. *When this is applicable, the acceptance criteria for C_{max} can be widened to 75-133% provided that all of the following are fulfilled:* Same as comment to lines 553-554 above. For a 10% difference the acceptance range is given as 1–θ, 1/(1-θ) with 90%–111.11% (upper limit = 1/0.9 = 1.1periodic × 100%). For a 25% difference the acceptance range is given with 75%-133.33% (upper limit = 1/0.75 = 1.3periodic × 100%).	*= reciprocal of lower limit based on the accepted difference.*	
4.1.10 Highly variable drugs or drug products (line 632-641)			
	The guideline provides a set of criteria to identify HVD&DPs. Out of three criteria, the most important criterion is the drug or drug products where with within-subject variability of the reference product is >30%. The rest two are empirical and may lead to confusion. Furthermore as stated earlier, there are other approaches, i.e., scaled average bioequivalence approach that can be applied to assess bioequivalence statistically for this class of drugs and drug products. This option should be seriously considered as it gets Test product to have similar playing fields which the Reference product has had in its clinical use.		The section has been revised to the scaled average bioequivalence approach widening the acceptance range for Cmax up to 70-143%. This will however, only be acceptable when it can be adequately justified that a wider difference in C_{max} is clinically irrelevant.
Line 631	It would be helpful to have a definition of 'a highly variable drug' included in this guidance.		Agreed.
631, 4.1.10	The proposal to perform a replicate design study for highly variable drug products as a prerequisite to widen the acceptance range for Cmax should be amended for the following reasons: - The replicate design study is intended to demonstrate high variability and bioequivalence. Thus, at the time of study planning, the coefficient of variation is not yet exactly known. Therefore, it is not known if the widened acceptance range for Cmax can be used and therefore, the sample size cannot be adequately estimated. - If an applicant performs several studies for one product,	For highly variable drug products, it should be possible either to use the approach as outlined in the comment to lines 551-552 (widening of acceptance range based on high variability, documented by valid literature data) or to perform a replicate design study using scaling.	Not agreed. It must be taken into account that if it is not known if the study results will show HV or not, the sample size should be the worst case, i.e. exactly a 30% CV and no widening. It must be taken into account that variability may be large in one strength and smaller at other strength. Each study has to be

	e.g. with the lowest and the highest strength, it is not reasonable to request the proof of a high variability by replicate design in each study. - In case of a drug product with a variability around 30%, this rule might result in the situation that some applicants find a CV > 30% and can therefore use the widened acceptance range, while others find a CV < 30% and must therefore use an acceptance range of 80-125%. Therefore, we propose the option to use scaling for highly variable drug products, e.g. according to the FDA draft guidances on lovastatin/niacin or lansoprazole. It should also be noted that highly variable drug products generally have a high efficacy and safety margin. Therefore, widening of the acceptance range has no impact on efficacy or safety of the drug		assessed on its own merits. A large variability is usually accompanied by a larger shift in the study point estimate. To avoid a different criterion around the CV of 30% the SABE approach is implemented. The FDA approach is not able to solve the problem outlined in bullet point 3 because the CV_0=30% and the CV_s=25.4% are not the same and the discontinuity causes the same problem.
4.1.10 Highly variable drugs or drug products Lines 632-633	For highly variable drugs, what is the justification for the seemingly arbitrary choice of 75-133 acceptance limits? What about the idea of the "scaled average BE approach" that was formalized by SH Haidar et. al. in "Bioequivalence approaches for highly variable drugs and drug products", Pharm Research 25:237-241, 2008, and communicated in an EMEA notice in April 2006? Note that this scaled average BE approach is also recommended in the FDA Draft Guidance for Lansoprazole, October 2008.	Please add the scaled average BE approach.	See comments above
631-641 4.1.10 Highly variable drugs or drug products	The current wording indicates a need to use replicate design in <u>every</u> study which applies the widened Cmax criteria, <u>including all repeated studies</u>. This would be appropriate if scaling was considered acceptable. However, this seems inappropriate when within-subject variability for Cmax of the reference product greater than 30% has been demonstrated in one of the previous studies and this information is used only for fixed and pre-defined widening of acceptance range (75-133%). Otherwise subjects will be exposed to additional study procedures in every consequent study only to demonstrate again what has been demonstrated previously.	CHANGE: Please modify the wording to precisely define when demonstration of within-subject variability for Cmax of the reference product greater than 30% is required in the same study in support for widening of confidence interval for Cmax, and what data will be acceptable to document it in other situations.	As the Scaled approach is going to be used it is essential to estimate the intra-subject CV in the study that is going to be scaled.
Lines 631-641	- A possible, stepwise widening of the BE criterion to 75-133% is stated. This yields a <u>discontinuous criterion</u>. According to the guideline, under some conditions, if the estimated within-subject variation for Cmax of the reference product is not more than 30%	- The use of scaled average bioequivalence is strongly proposed. A secondary criterion constraining the ratio	Agreed. Scaled is implemented. The GMR constrains is also implemented.

	then the usual 80-125% should be applied. If the estimated variation exceeds 30% then BE limits of 75-133% are considered. Consequently, if a submission for a drug preparation, with a true intraindividual variation of around 30%, finds that the within-subject variation is 31% then the more relaxed criterion could be used. In contrast, if in another submission for the same drug a variation of 29% is estimated then the usual, stricter criterion must be applied. This introduces a regulatory uncertainty and raises the consumer risk. Furthermore, the approach encourages sloppiness in order to attain the more relaxed criterion. Therefore, the proposed stepwise criterion is scientifically flawed. Continuous procedures such as scaled average bioequivalence, do not share this defect. This approach, with demonstrated satisfactory properties, is recommended, possibly with an additional constraint on the estimated ratio of the geometric means of the two drugs or drug products. - The 75-133% criterion is still very restrictive for drug products for which the within-subject variation is very high. With the increasing emphasis on modified-release preparations, such preparations are seen more frequently. - The possible relaxation of the 80-125% criterion does not extend to AUC. The rationale appears to be that "in some cases, Cmax is of less importance for clinical efficacy and safety compared with AUC." This may be true in some cases but not in others. Also, the variation of Cmax is often higher than that of AUC. Nevertheless, published information from CRO's indicates that the variation of AUC's is often also sufficiently high to cause difficulties in the determination of BE. Therefore, application of the criterion also to AUC's is recommended.	of geometric means could be considered. - Consideration of extending the approach to the comparison of AUC's is recommended.	However, scaling above CV of 50% is not accepted presently to avoid an excessive widening. These are extreme and infrequent cases. AUC is presently not considered as clinically irrelevant as Cmax. Therefore, scaling for AUC has not been agreed.
4.1.10 631 to 641	In summary, the provisions of the draft guideline consider that a widening of the acceptance range for C_{max} is *per se* only acceptable for highly variable compounds. In this respect the draft fundamentally deviates from the interpretation of the current guideline indicated in the "Q&A on the Bioavailability and Bioequivalence Guideline" from July 2006. In that document it is explicitly stated in section "2. Assessment of C_{max} in bioequivalence studies. In which cases is it allowed to use a wider	Replace third bullet point in lines 638 and 639 by: • "Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for	Not agreed. The revised guideline will replace the former guideline and Q&A and does not need to be in agreement. Clinical aspects do not prevail in this guideline since the objective is to assure comparable in vivo performance in exposure to assure

638 to 639	acceptance range for the ratio of C_{max}?" that a high variability is just one scenario where widening of the acceptance range for C_{max} would be accepted. According to the Q&A document issued two years ago, widening of the acceptance range for C_{max} is also acceptable if one of the following criteria applies: "1. Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for Cmax does not affect pharmacodynamics in a clinically significant way. 2. If PK/PD data are either inconclusive or not available, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive." Of note, whenever one of the two above criteria applies a widening of the C_{max} acceptance range is currently considered acceptable. This holds true whether or not a compound exhibits a high variability. Starting from the fact that the draft guideline requires the acceptance criteria to be set "to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy" (cf. line 40 to 41) it is agreed that clinical aspects have to prevail to conclude on the widening of the acceptance range for C_{max}. Consequently it is inappropriate to require a high intra-subject variability as a condition *sine qua non* for such widening. Thus, the section 4.1.10 should be revised in line with the provisions in section 2 of the Q&A document from 2006.	Cmax does not affect pharmacodynamics in a clinically significant way, **or**, if PK/PD data are either inconclusive or not available, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive."	with a higher degree of certainty the similarity in terms of safety and efficacy. An acceptance criteria based on population mean clinical effects might not assure equivalence in all individual patients with the same certainty that mean population systemic exposure.
631-641, 4.1.10	It is disappointing that discussions of the last two decades in the scientific community have essentially been ignored. Currently Candadian and FDA's guidelines are under revison. FDA's first product specific guideline mentioning reference-scaling average bioequivalence (RSABE) was published in October 2008 (lansoprazole: http://www.fda.gov/cder/guidance/bioequivalence/recommendations/Lansoprazole_DRODT_21428_RC10-08.pdf), followed in	The reference-scaling average bioequivalence (RSABE) approach should be reconsidered. *Tothfalusi L, Endrenyi L and KK Midha;* Scaling or wider bioequivalence limits for highly variable drugs and for the special case of Cmax.	Scaling has been implemented. However, scaling should be performed at CV=30% with this proportionality constant and not another (e.g. CVs=24.5 or sigma 25%) in order to avoid discontinuity.

	December 2008 by the guideline for lovastatin/niacin (http://www.fda.gov/cder/guidance/bioequivalence/recommendations/Lovastatin;_Niacin_ERtab_21249_RC12-08.pdf). Both guidelines refer to the paper by Haidar *et al.* (2008), which suggest a three-period three-sequence replicate design (TRR|RTR|RRT), a regulatory goalpost of σ_{W0} of 0.25 and constraint on the point estimate of 0.8–1.25. Keeping this section *'as-is'* would be counterproductive in the view of global harmonisation and lead to unnecessary tretament of human subjects in clinical studies. Even restricting the widening of the AR to C_{max} is not scientifically justified – and acceptable for AUC of HVDPs in Switzerland since 2002… The demonstration of high variability in every study would lead to high samples sizes in studies of products which are already well known to be highly variable (*e.g.*, enteric coated proton-pump inhibitors). The cut-off for an HVDP given with *>30%* should be changed to the commonly accepted *≥30%* (*'at least 30%'* instead of *'higher than 30%'*). If the RSABE will not be reconsiderd and the section implemented as it is, it should be rewritten in order to give a clear 'recipe' to follow. From recent discussions (not the document itself) we would interpret the suggested procedure as follows: If the reference formulation is suspected to be an HVDP and no clinical reasons speak against widening of the acceptance range for C_{max} the pivotal BE-study may be started right away in a replicate design. The study should be powered to demonstrate BE for the conventional BE-range if $CV_{reference} \leq 30\%$. If in the study $CV_{reference} > 30\%$ the acceptance range may be widened to 75%–1/75%. Example (expected point estimate 0.95, 80% power): CV% 2-way 80%-125% 3-way replicate 80%-125% 3-way replicate 75%-133% 4-way replicate 80%-125% 4-way replicate 75%-133% 30 40 (80) 30 (90) 18 (54) 20 (80) 12 (48) 40 66 (132) 50 (150) 28 (84) 34 (136) 20 (80) 50 98 (196) 74 (222) 42 (126) 50 (200) 28 (112)	Int J Clin Pharmacol Ther 41/5, 217-225 (2003) *Haidar SH, Davit B, Chen M-L, Conner D, Lee LM, Li QH, Lionberger R, Makhlouf F, Patel D, Schuirmann DJ, and LX Yu;* Bioequivalence Approaches for Highly Variable Drugs and Drug Products. Pharmaceutical Research 25/1, 237-241 (2008, DOI: 10.1007/s11095-007-9434-x, http://www.springerlink.com/content/u503p62056413677/fulltext.pdf	>30% or ≥30% is irrelevant if scaling at CV w0=30%.

	60 134 (268) 102 (306) 56 (168) 68 (272) 38 (152) 70 174 (348) 130 (390) 72 (216) 88 (352) 48 (192) 80 214 (428) 162 (486) 90 (270) 108 (432) 60 (240) 90 258 (516) 194 (582) 108 (324) 130 (520) 72 (288) 100 300 (600) 226 (678) 124 (372) 150 (600) 84 (336) The table gives samples sizes (and number of treatments). Though more treatments are needed in 3-way design, one must expect higher drop-out rates in an 4-way design. Going deeper in the example: One suspects that the CV will be 40%. Since not sure, one should power the study for the conventional acceptance range of 80%–125% (CV<30%). The sample sizes will be 50 (150 treatments) in a 3-way replicate and 34 (136 treatments) in a 4-way replicate design. If it turns out in the actual that CV=30% one is powered with 95% to demonstrate BE within the conventional range – since one (mis-)used 50 subjects instead of the needed 30. If CV=40% as expected one may widen the acceptance range and is powered with 99.8% (or for 80% power the PE may lie within 85.4%–117.1%). One may also have performed the study as a conventional 2×2×2 cross-over in 66 subjects (with fewer treatments). In our opinion the only gain for the applicant would be the larger allowed deviation from the reference (85.4%–117.1% instead of the expected 95.0%–105.3%). We are not sure whether this is the (primary) intention of the suggested procedure.		
Lines 631-641	Comment: According to the draft guideline the acceptance criteria for C_{max} can be widened to 75-133% in case of highly variable drugs or drug products only. This is contradictory to the provisions of the document *Questions & Answers on the Bioavailability and Bioequivalence Guideline* (EMEA/CHMP/EWP/40326/2006) Question 2, which allows widening of the acceptance range for C_{max} for those products for which at least one of the following criteria applies: 1) Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for C_{max} does not affect pharmacodynamics in a clinically significant way. 2) If PK/PD data are either inconclusive or not available,	Line 631-641 section 4.1.10	See previous responses.

	clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive. 3) The reference product has a highly variable within-subject bioavailability. Please refer to the Question on highly variable drug or drug products for guidance on how to address this issue at the planning stage of the bioequivalence trial. Consequently, in line with current regulation conformance to either criterion 1) or 2) should be sufficient to justify widening of the acceptance range for C_{max}, independent of criterion 3), i.e. limitation to highly variable drugs or drug products. Section 4.1.10 should be revised in line with the Q&A document.		
Lines 631-641	As there is still some controversy around replicate design studies and the statistical analysis, it would be very helpful if more detailed recommendations could be given here. What statistical analyses to be used? How to evaluate a replicate design in an average BE approach?	Please add additional details	It is out of the scope of the guideline to give details on how to analyse the data of a replicate design, since it is standard statistical analysis.
Highly variable drugs or drug products Lines 632-640	Specific comment on highly variable drugs or drug products: • Line 632: The scientific justification for expanding the BE bounds on Cmax is based on lack of therapeutic or safety concerns, not variability in Cmax. Therefore, it does not seem necessary to complete a replicate design and demonstrate variability of >30% in Cmax to widen the Cmax bounds. • Line 640: It is not clear why a similar approach is not acceptable for AUC. If there is a lack of safety or efficacy concern, we propose that the same criteria be applied to AUC.	Propose deletion of requirements for replicate design and >30% variability in Cmax to widen bounds; propose same criteria used to widen Cmax bounds also be allowable for AUC	Not agreed. Clinical irrelevance is a prerequisite. But it is not enough to allow a widening.
Lines 632-634:	The relaxed confidence interval should be applied to both AUC and Cmax. The possible relaxation of the 80-125% criterion does not extend to AUC. The rational appears to be that "in some cases, Cmax is of less importance for clinical efficacy and safety compared with AUC". This may be true in some cases but not in others. Also, the variation of Cmax is often higher than that of AUC. Nevertheless, published information from CRO's indicates that the variation of AUC's is often also sufficiently high to cause		AUC is presently not considered as clinically irrelevant as Cmax. Therefore, scaling for AUC has not been agreed.

	difficulties in the determination of BE (as shown by Professor Laszlo Endrenyi in his presentation at the EUFEPS BABP Network Open Discussion Forum: Revised European Guidelines on Bioequivalence held in Bonn, Germany, January 14-15, 2009.)		
Line 631-641	As AUC may be highly variable (although usually to lesser extent than Cmax), widening the acceptance range based on reference variability should be considered.	Please reword to allow for more flexibility on the acceptance range especially for bridging studies	See previous response
4.1.10 Highly variable drugs or drug products Line 640	For highly variable drugs, what is the justification for using expanded acceptance limits for Cmax, but not for AUC? Recommend to allow expanded acceptance limits (or the scaled average BE approach) for both Cmax and AUC. For drugs with within-subject SD = 0.50, whether for AUC or Cmax, the required number of subjects is very large (90% power, 5% true difference ➔ N = 148).	Please delete the following sentence: ~~This approach does not apply to AUC.~~	See previous response
Line 636:	How does the applicant "prospectively" justify that relaxation of Cmax criteria does not affect clinical safety or efficacy? It is difficult to demonstrate and justify.		Based on clinical data on the dose response or concentration response relationship and/or clinical data, as it has been done with the present guideline.
636 – 637, section 4.1.10	It is unclear how to demonstrate that a widening of the acceptance limits for C_{max} has no effect on clinical efficacy and safety.	Rephrase "It has been prospectively justified that widening of the acceptance criteria for Cmax does not generate clinical efficacy or safety concerns"	See previous response
Line 636 – 637, 4.1.10	It is unclear how to demonstrate that a widening of the acceptance limits for C_{max} has no effect on clinical efficacy and safety.	Add addition language which details the determination of C_{max} effects on clinical efficacy and safety (i.e. mechanism of action, margins of safety, others?)	See previous response
636 – 637, 4.1.10	It is unclear how to demonstrate that a widening of the acceptance limits for C_{max} has no effect on clinical efficacy and safety.	This request needs re-consideration. The criteria are unclear, and any potential effect on efficacy and safety may only be detected in a larger clinical study.	See previous response
Line 638	*"the bioequivalence study is of replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30%."*	Delete the words, "the bioequivalence	Not agreed. The estimation of intra-subject or within-subject variability has to be obtained in the same study

	Multiple companies thought that it was not clear why a replicate design is required in this particular statement. In order for the study protocol to prospectively justify the widening of the acceptance criteria for C_{max}, then there must be a previous study where the within-subject variability for C_{max} was estimated and was demonstrated to be >30%. If the drug has been established as a highly variably drug with either the test or reference formulation, then the sponsor should have the choice to design the study as either a 2X2 crossover or a replicate design. In either case, if the drug is highly variable and the first 2 bullet points are met, then widening of the Cmax acceptance criteria should be acceptable.	study is of a replicate design". Statement now reads. "it has been demonstrated that the within-subject variability for Cmax of the test or reference compound in the study is >30%".	that demonstrates bioequivalence since the demonstration of bioequivalence depends on the variability obtained in the study and that is the reason to widen the acceptance range in this study. The intra-subject variability of interest is the one of the reference product that has been shown to be safe and efficacious in spite of this large variability.
Line 638	Historical data demonstrating within-subject variability of C_{max} for the reference formulation >30% should provide sufficient evidence for widening the criteria of C_{max}.	Previous evidence that within-subject variability for C_{max} of the reference compound is >30% in a similar study population to the planned study or the bioequivalence study is of a replicate design….	Not agreed. The estimation of intra-subject or within-subject variability has to be obtained in the same study that demonstrates bioequivalence since the demonstration of bioequivalence depends on the variability obtained in the study and that is the reason to widen the acceptance range in this study.
Line 638	The decision to apply a replicate design needs to be based on previous trials and cannot be based on the actual BE trial. Therefore, the residual error from the ANOVA of a previous trial should be used to approximate the within-subject CV and trigger the need for a replicate design. The actual BE trial may result in a CV slightly below 30%.	Please change accordingly.	Agreed, but there is no need to change.
Para 4.1.10	**Highly variable drugs or drug products** A similar problem exists for the guidance of highly variable drugs or drug products. Without a definition it is difficult to understand what drugs would be considered "highly variable". There is also added problem that a highly variable drug might also be considered to be a NTID. In which case which guidance should be followed?	There should be a definition in the guidance document of highly variable drugs. Guidance should also be given as to how to deal with narrow therapeutic index drugs that are also highly variable drugs.	Agreed. A definition is included. Not agreed. NTI drugs have a different section. The instructions given in that section should be followed.
632-641, 4.1.10	ratiopharm concurs with the current FDA approach to use the Scaled Average Bioequivalence Concept for highly variable drugs	Use the Scaled Average Bioequivalence Concept as suggested by the FDA for	See somments above

	considering the high discriminatory power of bioequivalence studies and the usually flat dose-response curve of highly-variable drugs. It is not our intention to repeat the different reasons in favour of this approach. However, we would like to comment one of the arguments against scaling which says that also in clinical studies, no compromises are accepted in the statistical requirements of clinical endpoints. It is true that in studies designed to detect a significant difference between two formulations, the relevant p-value is always 0.05. However, the scenario to be compared to bioequivalence studies are therapeutic equivalence studies where an equivalence margin describing a non-relevant clinical difference has to be defined. It is usually very difficult for physicians to define a difference in endpoints which is not clinically relevant. So, this margin has to be discussed with authorities and according to our experience, sample size of clinical trials is a very important argument in these discussions. Often, and this is very similar to the suggested proposal for bioequivalence studies, wider delta margins are accepted if the clinical endpoints demonstrate a high variability. So, the comparison to the situation in therapeutic studies is in fact an argument in favour of and not against scaling in bioequivalence studies.	highly variable drugs also in the EU.	
633 4.1.10 Highly variable drugs or drug products	For highly variable drugs or drug products, widened acceptance criteria are fixed as 75-133% for Cmax only. This may require a very large number of subjects to demonstrate bioequivalence for drugs where within-subject variability is 50% or higher. The concept of scaled approach (eg, for AUC) does not appear although it could prove helpful on a case-by-case basis.	CHANGE: Allow widening of equivalence limits based on the within-subject variability of the reference formulation (demonstrated in the same replicate design study).	The scaled approach is implemented, but scaling with a proportionality constant above CV of 50% is considered excessive at the present. See previous comments on AUC.
Line 632-639	"in certain cases, Cmax is of less importance for clinical efficacy and safety compared with AUC. When this is applicable, the acceptance criteria for Cmax can be widened to 75-133% provided that all of the following are fulfilled: - the widening has been prospectively defined in the study protocol	The possibility for widening of the acceptance limit should be analogous to Cmax also apply to Cmin.	This guideline refers to immediate release products and the requirement to establish bioequivalence for Cmin for immediate release products has

	. it has been prospectively justified that widening of the acceptance criteria for Cmax does not affect clinical efficacy or safety - the bioequivalence study is of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30%		been removed.
638 4.1.10 Highly variable drugs or drug products	Clarification should be provided as to whether the replicate design could be applied to any bioequivalence study whether pilot or pivotal.	CLARIFICATION: Clarify if it is acceptable to use ISCV information from replicate pilot studies. The full panel study could then be 2-way crossover instead of replicate.	Not agreed. The estimation of intra-subject or within-subject variability has to be obtained in the same study that demonstrates bioequivalence since the demonstration of bioequivalence depends on the variability obtained in the study and that is the reason to widen the acceptance range in this study.
Line No: 638 to 639	"The bioequivalence study is of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30%." **Q.1** Can data of a study with less number of subjects (pilot) conducted with replicate design to demonstrate within subject variability for Cmax ≥30% be used to justify wider confidence interval limits for Cmax (75%-133%) in conventional two way cross over pivotal study?		Not agreed. The estimation of intra-subject or within-subject variability has to be obtained in the same study hat demonstrates bioequivalence since the demonstration of bioequivalence depends on the variability obtained in the study and that is the reason to widen the acceptance range in this study.
640 4.1.10 Highly variable drugs or drug products	Extension of the acceptance range for partial AUC should be included as an option as it is probably more variable than AUC(t). The same criteria as for Cmax should be applied, ie, extension should only be possible if within-subject CV of partial AUC is >30%. As outlined in the comment to lines 556-557, depending on the outcome of a critical review of available data, it might even be necessary to consider only the T/R ratio instead of the confidence interval for partial AUC or to use t(max) for assessment of early exposure	CHANGE: This possibility should be added to this paragraph.	Partial AUC are not going to be implemented.
4.1.10:638-641	Replicate design needed to be done in case wider Cmax is adopted	2X2 cross over should suffice provided drug is shown highly variable from	Not agreed. The estimation of intra-subject or within-subject variability

		literature	has to be obtained in the same study hat demonstrates bioequivalence since the demonstration of bioequivalence depends on the variability obtained in the study and that is the reason to widen the acceptance range in this study.
641	When the term "3-period cross-over study" is used, is it meant as a semi-replicate study or a study where 2 references and 1 test is used?	Suggestion of a scaling approach with more details.	Agreed in SABE. Either a semi-replicate study or a study where 2 references and 1 test is acceptable in a 3-period cross-over study.
Line 641	Suggest to put this sentence in section "alternative design"		Not agreed. This issue needs a different section due to its importance.
641 4.1.10 Highly variable drugs or drug products	Alternate designs should not be excluded. The preferred replicate design should be specified as there are several ways to conduct a 3 or 4-period cross over study. The implication that these (alternate designs) are substandard should be avoided.	CLARIFICATION: Please specify the preferred replicate design.	Not agreed. We require a replicate design. We are not excluding alternative replicate designs. As we are not restrictive we do not need to give details about a preferred design. It is the responsibility of the sponsor to select the best one or an acceptable one.
Line 641:	It should be "encouraged" instead of "acceptable".		Agreed, but we do not see the need for a change since specifying these two designs they are encouraged and both are acceptable.
4.2.1 In-vitro dissolution tests complementary to bioequivalence studies (line 644-652)			
4.2. In-vitro dissolution tests	The presentation of section 4.2 In-vitro dissolution could be more reader-friendly: Several aspects are put into appendices without a clear reference in the main text where to find it. e.g. - main details on test performance (number of tablets, time points, etc. are in appendices I and III	Please introduce appendices and briefly their content in the main text of section 4.2	The guideline text has been partly revised including references. It should be noted though, that in vitro dissolution is considered a side aspect in this guidelineand therefore not addressed comprehensively and

	- Appendices II and IV and V are not introduced in the main text - criteria and calculation options for "similarity" are provided in appendix I, however there is no reference in the main text		in great detail.
Lines 643-652	Depending on the physicochemical properties of the product, the pH range could be chosen between 1 and 6.8 and not set up at 1.2, 4.5 and 6.8. Furthermore, pH requirements are not the same in all international countries. Also, performing dissolution within the proposed 3 pH (1.2; 4.5; 6.8) can be difficult for weak base or weak acid having very low solubility at proposed pH.	Please change as follows: "The results of in vitro dissolution tests at least at pH **ranges from 1** ~~1.2, 4.5,~~ **to** 6.8 (**if applicable)** and (…)"	The requirement has been reworded to give more flexibility. However, the generally used three media are still mentioned in line with comparable documents.
644	The pH values 1.2, 4.5, 6.8 should be considered as a standard, but with the option to deviate from those, if justified. Therefore, the wording in appendix I (line 762) could also be used here.	Change the sentence to "The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended …"	Agreed – see above comment
644, 4.2.1	It is not always possible to test in the proposed media, e.g. instability of the drug substance or solubility limitations (sink conditions not given).	Please change: "The results of in vitro dissolution tests…should be reported unless otherwise justified".	The test is always possible, though not meaningful in certain situations which are then obvious. The comment is covered by the revised wording.
4.2.1. Line 644:	It appears 4 pHs should be applied sometimes: 3 pHs plus the media intended for drug product release (QC media). Is it sufficient to use 2 pHs plus the QC media since QC media is usually within the pH 1-8 range? pH 1.2, 4.5 and 6.8 are at least requested, could another pH within the range 1-8 be used?	The company asks for a clarification on the pH to be used for the in-vitro dissolution tests.	The comment is covered by the revised wording.
Lines 644-645	Some parameters of in vitro dissolution tests are defined. Refer to dissolution appendix for other factors such as temperature ranges	Add cross reference to Appendix I in addition to Appendix III	This is considered not necessary and beyond the scope of this guideline. Apart, the wording has been revised.
Line 644-646 Paragraph	*"The results of in vitro dissolution tests at least at pH 1.2, 4.5, 6.8 and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were*	Please, clarify – in case the *in vivo* BE study demonstrates bioequivalence -	Please see the revised wording of the guideline text. However, it is considered beyond

4.2.1	*used in the bioequivalence study should be reported."* It is unclear why comparative dissolution experiments (under overdiscriminating conditions) are required in addition to the *in vivo* BE study as the data of the in vivo study would overrule any differences in *in vitro* profiles. Please, clarify – in case the *in vivo* BE study demonstrates bioequivalence - whether differences in *in vitro* profiles would provide an acceptable "dissolution window, guaranteeing bioequivalence" in view of waiving future BE studies.	whether differences in *in vitro* profiles would provide an acceptable "dissolution window" in view of waiving future BE studies in case of post-approval changes.	the scope of this guideline to conclude on the relevance of particular results. If bioequivalence is not reflected in in vitro dissolution results this outcome does not necessarily provide any "dissolution window" unless an ivivc could be established.
Lines 644 to 647, para 3 page 16/29	Douglas Pharmaceuticals Ltd consider it is unnecessary to compare in-vitro dissolution profiles in 3 different media of the test and reference batches to be used in the BE study. One media (usually the QC media) is sufficient. The reason for this is that dissolution is usually more discriminatory than bioequivalence. This means that time may be wasted in product development overcoming differences noted in the dissolution profiles that have no relevance to clinical availability. If bioequivalence between formulations is shown, differences in *in-vitro* dissolution are irrelevant.	1). Delete lines 644 to 647	Not agreed, as explained with the revised wording of the guideline. The requested in vitro dissolution tests should facilitate a meaningful method, since this is eventually used to justify waiving an in vivo study. However, it is acknowledged that this is not always possible, which is now addressed by the revised wording.
648-652	It should be clearly stated that the main objective of dissolution testing for quality control purposes is to detect small differences in formulations. "Bio-relevance" of these quality control procedures should be of secondary importance and may not be achievable sometimes.	Change the wording at the beginning of the paragraph to: "Main objective of the dissolution procedure used for quality control purposes is to detect small differences in the formulations. If possible, specifications of in vitro dissolution tests used for quality control of a generic product should be derived from the dissolution profile of the test batch which was found to be bioequivalent to the reference product."	The current modified wording would not change the importance to develop a product specific in vitro dissolution method.
4.2.1. Lines 648-652:	It is understand that the dissolution specifications should be based on the dissolution results of the test product batch in the QC media and in this way the biorelevance of the dissolution method may be demonstrated.	It would be beneficial if some explanation of the type of data required to claim the biorelevance of the dissolution method is given.	In general, the in vitro dissolution should have been developed prior to performing an in vivo bioequivalence study. Accordingly, taken all data together this will

			demonstrate the usefulness of a certain experimental method. However, the wording has been revised.
Lines 648-652:	It is ideal to develop a dissolution method for quality control purpose that shows correlation to the favorable bioequivalence study. However, there are occasions where no correlation can be achieved using any method for a product that demonstrates bioequivalence. On the other hand, the dissolution performance using this specific method demonstrate "reproducible" and "ideal" dissolution profile that can be used a quality control method. Such method should be selected, even if the method shows no bio-relevance.		The comment is considered correct and acknowledged and covered by the revised wording. There is always the freedom to justify why specific methods have been employed.
Line 650, para 4 page 16/29	The use of one sentence only in this line is poor English	Change: "…to the reference product, which would be expected to…" to: "…to the reference product. The specifications for the quality control of the product would be expected to…".	The wording has been changed since specifications of reference products are not addressed here.
653, 4.2.2	A biowaiver of lower strengths should only be based on comparable dissolution profiles between the test product of the different strengths. It makes no sense to require that the dissolution between test and reference of the additional strengths is comparable, as there may be situations where this is not the case for the strength of the biobatch, however the in vivo result outweighs the in vitro result.	Please delete: "between additional strengths of the applied product and corresponding strengths of the reference product."	The initial request has been misunderstood by readers. The comment is covered by the revised wording.
Line 653, Paragraph 4.2.2.	The SIG submits that for biowaiver-based **approval of generic drug products**, only the similarity between originator and generic drug product needs to be demonstrated at each dose strength, since generic substitution may only occur between products of the same molar dosage strength. The SIG further submits, that when **additional** dose strengths are to be considered for approval on the basis of a bioequivalence study at one dose strength, similarity of dissolution profiles needs to be demonstrated between the additional dosage strength product(s) and the product for which the bioequivalence study was run.	***Proposed replacement text starting on Line 657 and continuing through Line 662:*** **Similarity of *in vitro* dissolution should be demonstrated at all conditions between additional strengths of the applied product and corresponding strengths of the reference product, where these are available.**	The comment is acknowledged however, the wording of the guideline has been slightly changed even though the proposed wording would be ideal. Similarity between additional strengths of the applied product and corresponding strengths of the reference product can not be required in general since details of the reference product are not available for the generic applicant.

	Rationale for proposed change: When a reference product, of the same strength is available, this is always the best choice as comparator. "Bridging" different strengths is only acceptable if there is no reference product, i.e. a line extension situation. In the case of "bridging", biowaiving is only acceptable if the new strength has the same composition with respect to excipients; the manufacturing process is the same, and the in vitro dissolution is equivalent. *[Note that if the product is available in widely differing strengths, the range of dose:solubility ratios represented may lead to sink conditions applying at some dosage strengths but not others, which would in turn lead to different % released vs. time profiles.]*	**When no reference product is obtainable at the corresponding strength, similarity within the applied product series i.e. between the additional strength and the strength used for bioequivalence testing should be demonstrated. This proof of similarity is only permissible when the composition with respect to excipients and the manufacturing process is the same for the products compared.**	Hence differences between T and R strengths may occur simply because the reference series is not proportional but the test product series. In these cases the differences are difficult to interprete. Accordingly, similarity of the test product strengths and the T and R biobatches is requested.
4.2.2 653 to 667	Differences in dissolution profiles at various dose strengths may appear in cases where the dissolution conditions move from sink to non-sink conditions within the dosage range. For approval of generic drug products, only the similarity between originator and generic drug product needs to be demonstrated at all dose strengths. In this case it is not necessary to demonstrate similarity of dissolution profiles at all dose strengths, since this may be simply impossible, depending on the range of dose:solubility ratios within the dosage range under consideration. On the other hand, when additional dose strengths should be considered for the biowaiver procedure on the basis of a bioequivalence study at a given dose strength, then similarity of dissolution profiles needs to be demonstrated for all dose strengths.	Line 662: At end of second bullet point, insert: "unless otherwise justified."	The comment is covered by the revised wording. However, in case of solubility problems an additional in vivo study may be required using the highest strength (acc. to sect. 4.1.6).
4.2.2. Lines-653-667	This section needs to be clarify as regards the possibility of waiving in-vitro dissolution tests as regards BCS classification: In cases of highly soluble drug substances: - Could the comparative dissolution of all strengths at 3 pHs and in comparison with the reference product be waived? If the highest strength of test and reference products are rapidly dissolving in three pHs the probability that the lower ones are not is very small and practically impossible	This section needs to be clarified as regards the possibility of waiving in-vitro dissolution tests as regards BCS classification. Could the Authorities please indicate the position in these cases mentioned?	Not agreed. Here the question of comparability of formulations is addressed rather than solubility of a drug substance. Usually, it can not necessarily be judged whether a certain pH is completely irrelevant or not unless respective data are available. Moreover, the revised version already gives some

	if it is a proportional formulation. In these cases could the dissolution tests of the lower strengths be waived based only on the results in QC media? In cases of low soluble drug substances: - Could the comparative profiles at an irrelevant pH be waived for the additional strengths? An irrelevant pH would be defined based on the results of the bioequivalence study. If two products are bioequivalent but have different dissolution characteristics at a given pH that pH could be considered irrelevant. For example, product test is faster than reference product at pH 6.8 but this trend is not observed in the in vivo T/R ratio and the products are bioequivalent. We would conclude the results at pH 6.8 are irrelevant for the waiver of the other strengths. Would this type of rationale be sufficient to justify not performing comparative dissolution of the additional strengths in these conditions?		flexibility as required.
Lines 654-667	Please add clarifying statements for similarity factor (f2) or appropriately reference subsections on page 20 in Appendix I with regards to the conditions necessary for IR products to qualify for biowaiver.		See revised wording making reference to App. I
Lines 655,656 para 5 page 16/29	Assuming lines 644 to 647 are deleted, this line needs to be amended to include reference to use of different pHs.	Change: "…values as outlined in the previous section…" to: "…values such as pH 1.2, 4.5 and 6.8 unless otherwise justified	The comment is covered by the revised wording.
Line 657	With regards to statement, "*Similarity of in vitro dissolution should be demonstrated at all conditions…*"	please add a reference to the similarity conditions outlined in Appendix 1.	The comment is covered by the revised wording.
Lines 657-662,	*"similarity of in vitro dissolution should be demonstrated at all conditions… between additional strengths of the applied product and corresponding strengths of the reference product."* However, how could we demonstrate the similarity of the profiles if the corresponding strength of the reference product is not available? Does it mean that similarity should be demonstrated at the same	Please clarify.	The comment is covered by the revised wording.

	molar dose?		
Line 657 para 5 page 16/29	As written there is uncertainty as to what the sentence beginning: "Similarity of in vitro…" is referring to. It needs to be linked to the previous sentence to ensure clarity of understanding that the subsequent information is referring to particular dosage forms and not solid oral dosage forms in general.	Change: "Similarity of in vitro…" to: "In such cases similarity of in vitro dissolution…"	The comment is covered by the revised wording.
4.2.2. Line 657:	It is very likely that in many generic applications similarity of in-vitro dissolution between the test and reference product cannot be achieved as per example the in-vitro method used by the applicant has not been validated for the reference product and in vitro methods tend to be over-discriminative.	Should the request of similarity with the reference be considered irrelevant?	The comment is covered by the revised wording.
4.2.2 In-vitro dissolution tests in support of biowaiver of strengths (line 654-667)			
	Similarity in the dissolution profiles between strengths within a drug product line should be tested using f2 value (similarity factor).		Partly agreed. As stated in Appendix I the f2 factor is recommended, but other methods may also be acceptable.
659-662 4.2.2 In-vitro dissolution in support of biowaiver of strengths	The guideline introduces a new requirement which requires showing similarity between additional strengths of the applied medicinal product and the corresponding strengths of the reference medicinal product. Similarity may not be achieved in all pH conditions, sometimes not even in one pH value. It should be clear that even in the case of differences in dissolution profiles between test and reference products, a generic medicinal product can be approved on the basis of the bioequivalence study because of the higher relevance of *in vivo* data. (see line 644). As it is the responsibility of the originator to demonstrate *in vivo* proportionality of different strengths (innovator SmPCs usually do not require the use of specific strengths in order to achieve a recommended dose), it is not justified to request similarity neither between dissolution profiles of different strengths of the reference product nor in dissolution profiles between test and reference products for a given strength from a generic medicines company.	CHANGE: Lines 661 & 662 should be removed.	The comment is covered by the revised wording.

	Otherwise, in situations where *in vitro* similarity between different strengths of the innovator product is not observed, the dissolution profiles of the different strengths of the test product can be similar, but some dissolution profiles may be different when comparing test and reference at different strengths. Therefore, the comparison of test and reference products at different strengths is of no relevance to the quality of the generic product.		
659-662 4.2.2 In-vitro dissolution in support of biowaiver of strengths	On the basis that the dissolution method is discriminatory, this represents unnecessary additional dissolution testing. There is currently no guidance on how to approach products with poor dissolution at one or more pH or labile products where degradation at specific pHs is found. For example: **(a)** If the different strengths of the reference product are not similar amongst themselves *in-vitro* (do not pass f2 test among themselves), what is more important in order to gain a waiver: similarity between different strengths of the test product or between the test and the reference (for the same strength)? **(b)** If the test and the reference products are bioequivalent *in-vivo* but not similar *in-vitro* (f2), and there is similarity between different strengths of the test product but not with respect to the reference product, would biowaiver still be applicable?	CHANGE: Requirement to measure dissolution at 3 pHs should be waived if justified eg, drug products where solubility is low at one or more pH.	The comment is covered by the revised wording. Moreover, there is always the possibility to (scientifically) justify specific situations (i.e. 'unless otherwise justified')
4.2.2. Lines 659-662	Comparative dissolution profiles to be performed in order to show similarity should be better defined. For example, should all strengths and all batches produced of the test product be compared to the strength of the reference product used for the bioequivalence study? Is it said at "different pH values"	Comparative dissolution profiles to be performed in order to show similarity should be better defined. Clarification on pHs to be performed needs to be given. Please refer to previous comment on line 644.	The comment is covered by the revised wording.
661-662	The request of in vitro similarity between additional strengths of the applied product (i.e. strengths for which no biostudy has been performed) and corresponding strengths of the reference product should be removed for the following reasons: - According to the current wording, this criterion would	Remove lines 661-662. *Alternative: "In cases where similarity between the different strengths of the test product cannot be demonstrated, this deviation might be justified by*	The comment is covered by the revised wording.

	apply for all 3 to 4 media in which dissolution tests have to be performed. As such in vitro similarity is not requested even for the strength investigated in the biostudy, this requirement will hardly be achievable in the other strengths. - Even if in vitro similarity between test and reference for the strength tested in the biostudy could be demonstrated in a certain medium, similarity between other strengths of test and reference for can only be achieved if the different strengths of the reference also show in vitro similarity which is not always the case (and cannot be influenced by the applicant). - The concept for extrapolation of BE results is established on the assumption that the various strengths of the reference product behave proportionally in vivo. There are however cases, where pharmacokinetic proportionality has been shown for the originator strengths which does not necessarily comply with in vitro similarity of these strengths. For the test product, in vitro similarity between strengths has been a requirement already in the current guideline and it definitely makes sense to maintain this requirement for extrapolation of biostudy results. In vitro similarity between all strengths of test and reference however should not be a requirement in cases of differences between reference strengths.	*confirmation of similar in vitro performance of each strength of test and reference product.*	
661-662, 4.2.2	It is not justified to request similarity in dissolution profiles between test and reference products for the strengths in which no separate biostudy has been performed. Even for the biobatches, no similarity between test and reference can be found in some conditions. Furthermore, there might be no in vitro similarity of the different strengths of the reference product (even if there is no difference to reach a final dose with different strengths in vivo) making it impossible to meet both the requirements for similarity between the different strengths of a test product and between test and reference for each of the strengths.	The requirement for similar dissolution profiles between test and reference products for the strengths in which no biostudy was performed should be removed. Such a comparison should be used only as supporting argumentation if no similarity between the different strengths of a test product can be demonstrated (e.g. due to low solubility)	The comment is covered by the revised wording.
Lines 661-662	If BE has been shown for the highest dose strength of the test formulation, in vitro data are used to compare lower dose strengths	This gives no additional information if proportionality between dose strengths	The comment is covered by the

	of the test to the highest dose strength of the test. The text as it stands right now can be read in a way that in vitro dissolution data would need to be obtained for the lower dose strengths of the reference product as well and then performing in vitro comparisons between test and reference on lower dose strengths. This doesn't make sense.	is demonstrated; contradicts 4.1.6 and should therefore be rewritten.	revised wording.
663, 4.2.2	It makes no sense to record dissolution profiles if sink conditions are not given because the results are hardly to interpret.	Please change: "At pH values where sink conditions may not be achievable for all strengths… the amount of dissolution profiles may differ between different strengths. In addition the applicant… "	The comment is correct in general. However, this passage is to facilitate justification of a waiver in case of certain differences between test product strengths.
4.2.2. Lines 663 to 665:	In cases where sink conditions can not be achieved at a certain pH comparison of the test product with the reference product should confirm that the observations are drug substance related and not drug product related. The company believes that dissolution results in these conditions are usually variable and inconclusive. The variation in the results does not allow the calculation of f2 factors.	Taking this into account the company ask for a position of the authorities on what the degree of similarity with the reference product would be required in this case.	The guideline recommendation is meant to propose a possibility how differences could in certain cases be justified. It is acknowledged that sink conditions are important although this is not indispensable in all cases.
Lines 663-667:	Even if the formulations for different strengths within a product line are proportional, often the dissolution profiles of dose equivalent different strengths do not show similar dissolution profile because different number of units of the drug product is used in the dissolution testing.		Usually one unit is used since in vitro dissolution is expressed as percentage. The use of more than one unit may help in certain cases where solubility changes with dose only.
Line 666	The hydrodynamic and shear forces impacting disintegration controlled dissolutions of single tablet in a dissolution vessel may differ from those forces experienced by two tablets. The comparison of dissolution profiles in this manner should not be presented without rationale.	The appropriateness of selected dissolution methodology should be discussed where comparisons are made involving single to multiple tablet numbers.	The use of more than one unit may help in certain cases only.
Lines 666 - 667	….could show **similar** profiles at the same dose (e.g. two tablets of 5 mg versus one tablet of 10 mg). A dissolution test is typically designed to compare single dose units. Due to differences in hydrodynamics introduced by dissolving more than one unit profile similarity is unlikely. There	Deletion of " In addition, the applicant could show similar profiles at the same dose (e.g. two tablets of 5 mg versus	The use of more than one unit may help in certain cases only. The comment is covered by the revised wording.

	may be other methods more suitable to show that the effect is drug substance rather than formulation related (e.g changing the volume of the dissolution medium or spiking the medium with the drug substance in question. We would therefore like to propose to delete the sentence "In addition, the applicant could show similar profiles at the same dose (e.g. two tablets of 5 mg versus one tablet of 10 mg)".	one tablet of 10 mg)".	
4.3 Variations (line 669-685)			
Line 668, Variations	Consideration should be made of the incorporation of product specific knowledge in line with pertinent ICH guidelines to permit biowaivers for formulations made which fall within established design space parameters (where CQAs are not adversely impacted).	Products within an established design space do not require provision of additional supportive data.	Not agreed.
669 – 673, 4.3	It may well be that the change of manufacturing site may result in an altered pharmacokinetic profile. Thus, if BE has been demonstrated with batches produced at manufacturing site A and the commercial batches are produced at a different manufacturing site B, it should be demonstrated that BE is still maintained.	A change in manufacturing site should be considered a major change, which necessitates a BE confirmation.	Not accepted This matter is discussed above in relation to the significance of the manufacturer (line 388-89). In addition, as far as this section is concerned a change in manufacturer that would lead to the need for a BE study would be associated with a change to the manufacturing process. Consequently, for clarification a slight amendment to the text has been made
674-679, 4.3	This paragraph is not clear and should be further explained. It might be understood that a bioequivalence study is always needed for a variation, in case an IVIVC cannot be demonstrated.		It is the intention of the text to require a BE study unless a valid justification is provided (e.g. IVIVC or BCS- biowaiver) whenever a change in formulation or manufacturing method that may affect bioavailability is made.
675 4.3	The requirement of an “acceptable correlation between *in-vivo* performance and *in-vitro* dissolution” is not clear. In many cases a	CLARIFICATION: Clarification should be introduced as a	An IVIVC is considered acceptable if it is a Level A IVIVC.

Variations	formulation is optimised during development on the basis of *in-vitro* profiles and then tested in a BE study. Can a positive study in such cases lead to the conclusion of an acceptable correlation?	means to establish "an acceptable correlation between *in-vivo* performance and *in-vitro* dissolution".	
Line 675-679	Reference is made to waivers of in vivo bioequivalence studies if in vitro dissolution rate of new product is equivalent to approved product. Reference is also made to correlations between in vivo and in vitro performance.	Provide additional text to clarify that the results of IVIVC modelling may be used to support the claim of equivalent dosage forms.	Not agreed. This section deals only with variations.
Line 680 /4.4 see also 741	A major problem of BE testing in Europe is the lack of Europeanwide reference formulation. Especially for drugs not centrally approved in the EU, different products of the same drug may be registered in different countries of the EU, which makes a rational selection of the reference product nearly impossible.	Provide a list of EU-wide agreed upon reference drugs (comparable to FDA "orange book")	Not agreed. This problem occurs rarely with very old drugs.
4.3 Variations Lines 684-685	*"When variations to a generic product are made, the comparative medicinal product for the bioequivalence study should be the reference medicinal product."* However, if the reference medicinal product chosen in the initial generic application does not exist anymore, what will be the recommendation for the choice of the comparator product: another acceptable reference product? The currently registered generic formulation? Other?	Please clarify.	This topic has been addressed in the section about test and reference product above. However, the guideline cannot address all the possible cases, it is the responsibility of the Applicant to justify its selection. For example, the reference may disappear from some countries (e.g. omeprazole capsules) but not in others. Therefore, it is still available in EU. Or it may be sold to another MAH. It is still available under a different name and MAH, but it is the preferable one. The same generic product should be the last option.
684-685 4.3 Variations	It should be clarified that for variations to a generic product on the basis of dissolution profiles, the comparative medicinal product for *in-vitro* testing is still the currently registered and marketed generic medicinal product.		This is agreed. However, it is out of the scope of this guideline to provide recommendations in this situation.

	Indeed, after registering the generic medicinal product, the reference product can undergo changes which are not communicated to the general public.		
4.4 Study report (line 687-706)			
688 4.4 Study report	In cases where the sponsor of a study works in partnership with a CRO, the whole report is not exchanged with the Principal Investigator (PI). The PI is generally not competent to do so and is usually only required to sign the clinical part of the report. According to the CTD structure, the *in-vitro* study of similarity between reference and test product is already included in Modules 3 and 5. Accordingly, the EGA feels it is unnecessary to include it once more in the study report. A cross-reference to Module 3 and/or 5 can be made. In addition, it should be noted that, contrary to the case of Phase III studies, this is not usually shared with the contracted CRO in the case of bioequivalence studies for reasons of confidentiality.	CHANGE: Request signature of the PI on the Clinical Report only. Do not require documentation on comparative dissolution testing as part of the biostudy report.	Not agreed. According to Annex I of the Directive 2001/83/EC, the report should be attested by the the PI. Agreed. Documentation on dissolution testing is not requested in the bioequivalence study report.
Section 4.4., line 695		Please add " Expiry date" and delete "evidence of purchase including date and place of purchase and vendor" that are unnecessary information	Partly agreed.
Paragraph 4.4; lines 696-701	It should also be possible to provide this information in the Quality module (Module 3), e.g. in section 3.2.P.2 Pharmaceutical Development	(add sentence at end of paragraph). Alternatively, all or part of this information may be provided in the Quality Module (Module 3, e.g. section 3.2.P.2) and cross referred to from the bioequivalence study report.	Partly agreed. There are now 2 subheadings and it is not longer stated that the dissolution data etc should be included in the actual bioequivalence study report.
Line 697 para 7 page 17/29	Again assuming lines 644 to 647 are deleted (see above), this line should include reference to dissolution profiles of the products conducted in the QC media.	Change: "…comparative dissolution profiles should be…" to: "…comparative dissolution profile(s) conducted in the media intended for drug product release (QC media) should be…"	Partly agreed. "…comparative dissolution profile(s) conducted in the media intended for drug product release (QC media) should be…" has been included in section 4.2.1.

704, 4.4	It is stipulated that all individual data should be available in electronic format (concentrations, pharmacokinetic parameters, randomisation scheme **etc.**). It should be specified if this refers only to the concentration and PK data required to re-calculate the 90% confidence intervals or also to the safety data.		It has been clarified that this refers to data sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated. Safety data do not need to be included.
4.4:704	Data availability in electronic formats is ok	SAS XPT formats to be required too	You can read comma delimited text files and Excel files into SAS. There is no need to specifically mention SAS XPT to be available.

DEFINITIONS (line 707-724)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
707 ff	This section should be amended by Ae, the cumulative amount of drug eliminated in urine	Add in line 707: "Ae … cumulative amount of drug eliminated in urine"	Urinary parameters have been included.
Lines 708-725	Comment: Abbreviations/Definitions might be sorted in alphabetic order.		Agreed
723 Definitions	Should it be (Cmax,ss-Cmin,ss)/ Cav ?	CLARIFICATION: Please specify.	This is correct, however, fluctuation has been removed.

APPENDIX I (line 725-799)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Appendix I	Appendix I deals with several aspects of dissolution testing such as purposes, recommendations for certain classes of DS, aspects on biowaiver, similarity calculation test performance etc. without a crystal clear structure easy to follow while reading first or while looking for specific information.	The appendix might be complemented by sub headers and rearranged as appropriate.	The comment is acknowledged and covered by the revised version. However, the appendix is meant to address certain aspects rather than to give a comprehensive overview on

			the use of in vitro dissolution.
Line 726 – Dissolution testing	Recommend reference be made to the use of disintegration testing in this section.	Eg. Line 729 " As soon as the composition and the manufacturing process are defined a dissolution test, or disintegration test where appropriate, is used in the quality control of scale-up and ….." Ideally, appropriate reference would be made to disintegration tests throughout the guidance note where dissolution testing is referenced.	Disintegration is not addressed in this context ref. to bioequivalence.
726	To add "and similarity of dissolution profiles" to the title to be more precise	Dissolution testing and similarity of dissolution profiles	Agreed
730 Appendix I Dissolution testing	QC tests for dissolution often consist of one point (not a profile). In other words, commercial scale and development tools are often different.	CLARIFICATION: Please specify.	The general wording will not be more detailed since this is considered beyond the scope of the guideline. If a profile comparison is needed investigations beyond usual quality control tests may be required.
Appendix I Lines 734-739	The order of topics is information should be changed to: information on reference product, information on test batches and QC tool.	"i – Testing on product quality **• To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies** • To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control. • To be used as a tool in quality control to demonstrate consistency in manufacture ~~• To get information on the reference product used in~~	Not considered necessary.

		~~bioavailability/bioequivalence studies and pivotal clinical studies"~~	
742, Appendix I	The applicant of the generic product has no information about the manufacturing process, specification and quantitative composition of the reference product.	Please delete "provided that the manufacturing process, composition and specifications are similar."	The comment is covered by the revised version
748 Appendix I Dissolution testing	There are instances where product monographs are not available whilst generic medicines are undergoing pharmaceutical development.	CLARIFICATION : This scenario should be taken into consideration	The comment is covered by the revised version.
Appendix 1 Lines 750-752	Alternative methods can be considered if discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo.	What type of data would be required to support these characteristics?	State-of-the-art methods should be developed and justified. It is considered beyond the scope of this appendix to give specific details in this respect.
Lines 753-762	A statement is made regarding an assumption that excipients do not 'affect' the dissolution, stability and absorption processes.	We recommend a rephrasing to read" excipients are known not to <u>negatively</u> affect the dissolution, stability and absorption process" We recommend it be acceptable to provide an indication that the excipients have been used in other marketed formulations and have not been found to negatively impact upon bioavailability. If more information is required we also recommend the provision of some examples of the type of data expected.	The comment is partly covered by the revised version.
Appendix I Lines 753-762	1. Please add clarifying statements in the appropriate sections that clarify under what circumstances dissolution profiling and testing would be required on all strengths for dosage forms that could be considered as qualifying for biowaivers (waivers of in vivo bioequivalence studies). 2. Please add appropriate reference to the statements on the subject of dosage strength that are made on page 16, section 4.2 (lines 653 to 667). In Appendix I, the statement on Lines 761 and 762 indicates		This request is not clear, however, the section has been revised and is considered clear now.

	the dissolution testing conditions that are necessary to justify similarity in profiles. However, as written, the statement does not clearly address if it is required to demonstrate any strength-dependent relationship between the dissolution profiles under such conditions		
753-762 Appendix I Dissolution testing	On line 762: *"The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH 1.2, 4.5 and 6.8)"*. Three "normally" fixed pH values are listed here. It would be desirable to leave this open to a broader range of pH values (between 1-8) to be studied as is stated in the current version of the guidelines to provide greater operative flexibility to the development.	Please see section 644-647 4.2 *In-vitro* dissolution tests	The comment is covered by the revised version.
Lines 753-799:	This section deals with various aspects of dissolution. It deals with high solubility, low solubility drugs and comparison of the dissolution profiles by estimating the similarity factor f_2. The first two paragraphs deal with high and low solubility drugs. A lot of information is provided in these two paragraphs in a rather confusing manner. The reader is likely to be confused as to what is the principal theme of these paragraphs. This doesn't come out for a reader. It should be clear as to under what conditions the similarity factor, f_2 should be estimated and what the f_2 values mean.		The comment is covered by the revised version. Agreed
Lines 758-762	Where very rapid dissolution release criteria are met (>85% dissolved within 15 minutes), dissolution profile equivalence should not be necessary	Clarify this discussion with respect to very rapidly dissolving drug products. "Samples of the product from batches of post-change drug product should be compared with those of the test/pre-change drug product. For very rapidly dissolving drug products confirmation of >85% dissolution at 15 minutes should be shown. For rapidly dissolving drug products (>85% dissolution at 30 minutes) similarity of in vitro dissolution profiles should be shown (reference Appendix I for	The comment is covered by the revised version.

		suitable dissolution conditions)".	
Appendix I Lines 758-760	"*A bioequivalence study may in those situations be waived based on similarity of dissolution profiles which are based on discriminatory testing*, (…)".	Please clarify as to when testing can be regarded as discriminatory.	The comment is considered a general statement since the GL does not primarily focus on in vitro dissolution details.
Appendix I Lines 761-762	It is stated "*the similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH 1.2, 4.5 and 6.8)*." To be in accordance with section 4.2.1, we recommend to add, if relevant, the media intended for drug product release (QC media) for dissolution testing. Please also make the appropriate corrections as regards pH range.	Please change as follows: "The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH **ranges from 1 to** ~~1.2, 4.5 and~~ 6.8) **and, if relevant, at the media intended for drug product release (QC media)**."	The comment is covered by the revised version.
761-762	We find that Appendixes I and III would be clearer with detailed information related to dissolution testing and similarity of dissolution profiles only in Appendix I and to refer in Appendix III to the detailed dissolution conditions displayed then in Appendix I. Therefore, we propose to transfer text from Appendix III § IV.1.1. after line 762 in Appendix I.	To add text from lines 976 to 1001 after line 762.	The comment is partly covered by the revised version. However, AppI and III are partly overlapping though addressing particular and different issues. In vitro dissolution for BCS based biowaiver are specific and are therefore addressed in App III.
Line 762	Occasionally, for newer products, data show an *in-vivo/vitro* correlation that strongly supports the dissolution media. For example with one of our products a bioequivalence failure was obtained and this failed batch was used to help develop the dissolution method that could discriminate this batch. In this situation we feel that it would be unnecessary to perform comparative dissolution testing in the 3 pH media Therefore if we have data to show that the QC dissolution test is clinically relevant (a clear *in vivo /in vitro* correlation) it is more appropriate to use the QC media for comparative testing rather than testing in 3 pHs	The similarity should be justified by dissolution profiles, covering at least 3 time points, attained at three different buffers, (normally pH1.2,4.5 and 6.8). In cases where data are available to show an in vivo/invitro correlation, only the media intended for drug product release (QC media) needs to be used'	The comment is covered by the revised version. Moreover, the topic of iviv correlation is not specifically addressed in this guideline, but establishing an ivivc is always appreciated. However, the provided example does not seem to dexcribe a valid correlation.
Lines 766-767	*"In those cases a variety of test conditions is recommended and adequate sampling should be performed until either **90%** of the drug is dissolved or an asymptote is reached."* The criterion "> **85%** dissolved" is usually recommended to characterize the quality of a product.	Change form "…either 90 % of the drug isdissolved…" into "…either **85%** of the drug is dissolved…"	The comment is covered by the revised version.

Lines 767-769	We understand in the discussion of dissolution requirements that dissolution data should be provided in cases where in vivo BE studies are conducted. We seek clarity on this interpretation and suggest that an in vivo BE study should provide the definitive performance data/result and that additional in vitro dissolution testing should not be required when in vivo BE has been demonstrated.	Please re-word	The comment is covered by the revised version. However, the already existing requirement to provide both in vivo and in vitro data has not been changed.
Appendix 1 Lines 767-770:	For low soluble drug substances it is stated that different dissolution conditions (ionic strength, surfactant, pHs, etc) should be explored. Is it therefore possible to use the dissolution QC media as developed for release for the biowaiver? Is this to be understood as an exception to perform the studies at the different pHs values?	For clarity to reader the authorities are asked to provide a more precise explanation would be helpful.	The comment is covered by the revised version.
768 Appendix I Dissolution testing	It could be made clear that the use of surfactants in dissolution testing is not generally discouraged, and that this only applies in case of highly soluble drugs where a BCS based biowaiver approach is used (lines 997-998).	CLARIFICATION	The comment is covered by the revised version.
Line 772	We recommend keeping recommended methods as simple as possible so that the key aspect, i.e. what magnitude of difference is important, can be defined in a manner that is understood by all and may be related to the practical consequence of failing to meet this requirement. Our preference is to calculate a 90% confidence interval for the mean difference at the key time-points and declare equivalence if the limits are within pre-defined acceptance limits (e.g. +/-10%). This has various advantages: Taking account of variability in units Equivalence limits have an interpretable scientific value – ie. One can relate to disso specifications more easily than any model parameters The model-dependent approach (e.g. fitting a Weibull) or more complex multivariate distance based approaches, while statistically valid, have the drawback of interpretation. How does one interpret or set acceptance criteria for what is a meaningful difference between parameters of a Weibull equation?	We believe this is a complex topic requiring further discussion for consideration in future revisions of this guidance note.	Basically agreed. Obviously, the f2 test is currently mostly used. However, it has been shown that other tests may be useful although there is currently no widely used alternative option.
Line 779	Definition of constants leaves out “t”	R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation	The comment is agreed, a definition of (t) is included as proposed.

		of the study. For both the reference and test formulations, percent dissolution should be determined at the same t values.	
Appendix 1 Lines 772-791:	Evaluation of the similarity factor. What is the relevance of the dissolution testing if the resulting RSD is too high to calculate f_2 similarity factor (according the requirements of this draft guideline)? How should these profiles be treated (i.e. should they be disregarded)?	This requires further clarification	There must be a reason for such a high variability and this should be adequately addressed
Lines 782 and 784	Line 784 is a little confusing. We believe it would be clearer to combine lines 782 and 784 and express the condition as follows: "The time points should be the same for the two formulations and should be selected such that not more than one mean result of > 85% is obtained"	Delete line 784. Amend line 782 to read as follows: "The time points should be the same for the two formulations and should be selected such that not more than one mean result of > 85% is obtained"	See the following comment
784 Appendix I Dissolution testing	The fourth condition for calculating the f_2 value, namely "not more than one mean value of >85% dissolved for any of the formulations", is not the same as the second recommendation fixed in the FDA guideline entitled, "Dissolution Testing of Immediate Release Solid Oral Dosage Forms", namely "only one measurement should be considered after 85% dissolution of both products." The expressed differences in the conditions for the calculation of the f_2 values may lead to various values of the calculated similarity factors, since according to the FDA guideline the measured means used for calculation are in general collected for a longer time period (both profiles over 85%) in contradiction to any of the profiles over 85% (presented draft guideline). A rationale for this would be to harmonise the conditions of calculation of the similarity factor f_2 or to assign the similarity factor indicated in the draft guideline differently.	CHANGE: Definition of f2 value.	The wording has been partly revised
Line 786	In early in vitro dissolution time points the relative standard deviation might exceed 20%. It should be mentioned that in this case more than 12 individuals might be used to reduce the relative standard deviation. For very fast dissolving tablets especially at early time points of the		The requirements incl. the sample size of 12 have been shown to be reasonable. There is always the possibility to use other tests to compare the similarity of profiles, if

	in vitro dissolution, no convection conditions are present anyway and therefore from a physico-chemical point of view this is not a suitable approach. N=12 is questionable for all those products where with n=6 the requirements for the RSD are already fulfilled, (since requirement of the EP is n= 6 at S1 level).		sufficiently justified. A modification of the stated requirements is considered not necessary.
787-799 Dissolution testing	It was useful to clarify the number and timing of sampling times needed to test similarity of dissolution curves. In particular it is stated that, in the case of gastro-resistant formulations, the concept of rapid dissolution does not apply and frequent sampling is required (e.g. every 5 minutes) during the rapid dissolution phase. It is also clear that these suggestions apply to all circumstances where dissolution test is used for purposes of bioequivalence surrogate inference (see lines 740-47). Reference is made in the text to immediate release formulations and also to gastro-resistant formulations.	It is understood that appendix I Dissolution testing applies in general to all solid oral dosage forms even though the present guideline refers mainly to immediate release dosage forms. In this respect, it would be beneficial to specify under what circumstances the similarity concept applies in the case of gastro-resistant formulations, since they do not belong to the category of immediate release formulations and therefore cannot be granted a biowaiver. Some examples of applicability in my understanding are different strengths,: formulation changes during development, different strengths, similarities between reference products from different countries, generics, variations, ..).	The request is not completely clear since it is correctly stated that App.I applies not only to IR products. However, there seems to be a misunderstanding reg. 'biowaiver' which is a general term if an in vivo study could be waived, i.e. not only based on the BCS concept. More details on gastro-resistant formulations will be given in the respective guideline which is still to be revised.
Appendix I Lines 788-791	"*In cases where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation except in the case of gastro-resistant formulations where the dissolution takes place in the intestine and the 15 minutes for gastric-emptying lacks of physiological meaning*." This final part of the sentence does not concern immediate release formulations (see also above "General comments")	Proposal to delete the final part of the sentence and replace by: "In cases where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation ~~except in the case of gastro-resistant formulations where the dissolution takes place in the intestine~~	The comment is covered by the revised version.

		~~and the 15 minutes for gastric-emptying lacks of physiological meaning~~ **for immediate release formulations**."	
Line 788 Line 1003 Line 794 Lines 917 and 923	"In cases where **more than 85%** of the drug is dissolved within 15 minutes…." "….when **more than 85 %**...." "In case **more than 85%** is not dissolved at…" "…very rapid (**> 85 %** within 15 min)…"	The term "more than 85%" should be changed to "no less than 85%" and the term "> 85 % within 15 min" should be changed to "≥ 85 % within 15 minutes" in order to be harmonised with other guidelines.	No change.
790, Appendix I	The 85% in 15 min criteria should be applicable to the dissolution in the alkaline medium for gastro-resistant dosage forms.	Please change: "…except in the case of gastro-resistant formulations **where the criterion is applicable for the dissolution in the alkaline medium."**	The comment is included and now covered by the revised version.
Appendix I line 791	It would be helpful for Industry if text could be included to acknowledge that in certain instances, well reasoned clinical arguments can be presented to circumvent an f2 failure.	After line 791 add **'In cases where an F2 value of below 50 is obtained it may be acceptable to present a clinical rationale in supporting the similarity of the two dissolution profiles'**	Not agreed. A clinical rationale can hardly be given for in vitro dissolution results unless there is an obvious correlation. Otherwise the f2 simply indicates a difference and an additional in vivo study may be required.
Lines 792 - 797	It is suggested for formulations having complete release within 30 min to generate one dissolution value before 15min. This recommendation is both unpractical and irrelevant. The dissolution values obtained before 15 min for IR formulations providing complete dissolution within 30 min are often very variable by use of standard methods and thereby not useful for quantitative assessment (f2-test). It is also not meaningful to put extensive development efforts to develop dissolution tests specially designed to address such variability since the dissolution variation within these early times are not considered to have any in vivo significance (in analogy with no f2 test requirement for complete dissolution within 15 min).	It is suggested that first time point for dissolution sampling should be 15 min.	The requirement relates to the fact that f2 testing requires at least three timepoints unless complete dissolution has been achieved within 15 min. In case a BCS based biowaiver is attempted these three timepoints have to be within 30 min since this is considered the maximal measurement period in which complete dissolution must be reached. Hence, it is reasonable to have three timepoints in cases where the f2 testing has to be used independently from the dosage form.

792-797 Appendix I Dissolution testing	Line 796: "For gastro-resistant formulations frequent sampling (eg, every 5 minutes) is required during the rapid dissolution phase." For gastro-resistant formulations, dissolution in the buffer stage should be left open in the same way as for an immediate release. However, should gastro-resistant formulation be addressed in the context of this guideline (immediate release oral dosage forms)?	CLARIFICATION: Please clarify the scope of the guideline.	The comment is removed.
Line 794-779, Appendix I	In Lines 794 – 797, it is required that when formulations have complete release within 30 min, a dissolution value before 15min be generated. This recommendation is impractical for many formulations. Dissolution values obtained before 15 min for IR formulations providing complete dissolution within 30 min are often highly variable and therefore cannot be used for quantitative assessment (f2-test). It is also not meaningful to put extensive development efforts to develop dissolution tests specially designed to address such variability, since the dissolution variation within these early times are very unlikely to have any in vivo significance (in accordance with dropping the f2 test requirement when dissolution is complete within 15 min). Therefore it is suggested that sufficient samples are taken to conduct an f2 analysis.	***Proposed replacement text for sentence starting on Line 794 and continuing to the middle of Line 796:*** **In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required. Data with less than 20% variance at the first time-point and less than 10% variance at subsequent time-points can be used for the f_2 calculation, noting that one, but only one, time point should be considered after 85% dissolution of both the reference and test products has been reached. A minimum of three time points (zero time-point excluded) is required for the calculation of f_2 .**	Not agreed. The requirement relates to the fact that f2 testing requires at least three timepoints unless complete dissolution has been achieved within 15 min. In case a BCS based biowaiver is attempted these three timepoints have to be within 30 min since this is considered the maximal measurement period in which complete dissolution must be reached. Hence, it is reasonable to have three timepoints whenever f2 testing is required, independent from the dosage form.
796, Appendix I	There are practical limitations to perform sampling every 5 minutes.	Please change: **"…sampling intervals should be not less than every 10 min."**	Even though it is acknowledged that frequent sampling every 5 min is a challenge there are tools available that can be used for this purpose. It is also not considered an unreasonable hurdle since in many cases an in-vivo study will be waived based on in vitro data.
Appendix I Lines 796-797	It is mentioned "*For gastro-resistant formulations frequent sampling (e.g. every 5 minutes) is required during the rapid dissolution phase."*	Please delete the whole sentence: ~~For gastro-resistant formulations~~	The comment is covered by the revised version.

	So, it does not concern immediate release formulations (see also above "General comments")	~~frequent sampling (e.g. every 5 minutes) is required during the rapid dissolution phase~~.	
Line 798	5-8 sampling points over a 60 minute interval appear excessive. Five to eight sampling points before 30 minutes might not be practical if complete release is achieved relatively fast, i.e., in 30 minutes.	We would recommend 3-8 with appropriately chosen time-points to define the curve. **'***In general* **three** *to eight sampling times within a 0-60 minutes interval are recommended to achieve meaningful dissolution profiles* **unless complete release is achieved relatively fast i.e within 30 minutes.'**	The comment is covered by the revised version. The wording now is less detailled.
798, Appendix I	5-8 sampling times within 0-60 min make only sense if dissolution is slow. 5-8 sampling points are not necessary to obtain meaningful profiles.	Please change: **"Sampling points should be so often that meaningful profiles are obtained."**	The comment is covered by the revised version.
Line 799	Suggest adding to the end of the sentence "(…../unless complete release is achieved relatively fast, i.e., in 30 minutes)" Five to eight sampling points before 30 minutes might not be practical in these instances.	'In general five to eight sampling times within a 0-60 minutes interval are recommended to achieve meaningful dissolution profiles unless complete release is achieved relatively fast i.e. within 30 minutes.'	The comment is covered by the revised version.

APPENDIX II (line 800-893)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Lines 804-808:	These statements have been described elsewhere in the document in some part. Furthermore difference between "appropriate bioavailability study" and "in vivo bioequivalence study" should be clearly explained.		This paragraph is meant to emphasize when a biowaiver may not be granted. The wording has been slightly changed.
BE Study requirements for different	Specific Comments on BE study requirements for different dosage forms : • For ODT formulations, the new guideline asks for a 3-period BE study with the test formulation being dosed with	This requirement would present a major challenge for drugs with early Tmax even if they are BCS class I. Please specify if BCS class I drugs are	Appendix II and III have been revised and allow BCS based biowaivers for ODTs provided there is no absorption from the oral

dosage forms	AND w/o concomitant fluid intake. This requirement would increase the risk and cost etc as well.(lines 819-822) • Lines 860-862: Please clarify the requirements for bilayer tablets? Are the requirements for tablets as a whole, or for each layer? • Lines 865-876: We agree with guidance provided in the injectable section of parenteral solutions and the local delivery section. However, the sustained release formulation section raises some questions for discussion/ consideration: o For a sustained release formulation switch from one clinical phase to another for IM/SC delivery, are bioequivalence (systemic PK) studies required if in vitro release is demonstrated to be equivalent to comparator? (line 865) o For sustained release formulation for local delivery (e.g. eye), are bioequivalence studies (pharmacodynamic or comparative clinical studies) required if in vitro release is demonstrated to be equivalent? (line 876)"	out of scope with regard to this requirement. In addition, for non-BCS class I drugs with very early Tmax (e.g. 30min), recommended the minimal number of subjects in order to have a meaningful comparison of PK parameters, especially for Cmax. For sustained release formulations intended for local delivery, in vitro release should be considered as an alternative to demonstrate BE.	mucosa. In a bioequivalence study the minimum number of subjects is 12, as stated in section 4.1.3. Requirements for bilayer tablets are the same as tablets as a whole. Additonal wording has been added to section 4.1.6. It is out of the scope of this guideline to provide further detail on requirements for locally applied products with local action.
Excipients	Overall the guideline appears to put much emphasis on the role of excipients. "Active" excipients are mentioned for e.g. in BCS Class III waivers (lines 1016-1027), and BE of oral solutions (lines 844-849). Some of them are what sponsors would normally consider inactive. We are concerned that excipient changes during clinical trials should not be leading to higher BE requirements or be undergoing more scrutiny.		Partly agreed. “Active” excipients has been clarified in both Appendix II and III.
Appendix II	To avoid any confusion, we recommend to focus on immediate release dosage forms with systemic action, which is the scope of this guideline (see also above “General comments”). To delete the following sections: “modified release and transdermal dosage forms”, “Gases” and “Locally acting locally applied products”.	Please delete the following sections and their content: ~~Modified release and transdermal dosage forms (Lines 854-857)~~ ~~Gases (Lines 874-875)~~ ~~Locally acting locally applied products (Lines 876-893)~~	It is agreed that it is out of scope of the guideline to provide extensive recommendations on these formulations. However, some information on other than immediate release formulations is considered of value. The following has been added in the beginning of the appendix as clarification: *Although this guideline concerns*

			immediate release formulations, Appendix II provides some general guidance on the bioequivalence data requirements for other types of formulations and for specific types of immediate release formulations
Appendix II Lines 809-873	We suggest to re-organize the sections "oral immediate release dosage forms with systemic action" versus "non-oral immediate release dosage forms with systemic action."	Proposal (order of the paragraphs): Section "oral immediate release dosage forms with systemic action" : - Orodispersible tablets - Oral solutions - Fixed combinations dosage forms Section "non-oral immediate release dosage forms with systemic action": - Rectal formulations - Parenteral solutions	Partly agreed. A more logical structure will be adopted.
Appendix II Line 810	It is stated "*This section pertains to dosage forms such as tablets, capsules and oral suspensions*." We propose to add oral solutions as mentioned further in lines 843-853.	Please change as follows: "This section pertains to dosage forms such as tablets, capsules, oral **solutions and** suspensions."	See above
813, Appendix II	Do the same rules as outlined for orodispersible tablets also apply to oral dispersible films?		Orodispersible films may be handled in a similar way as ODTs. Bioequivalence studies should be conducted according to the recommended use of the product.
Line 813, Appendix II	The Special Interest Group would like to propose that, when absorption through the oral mucosa can be ruled out on the basis of suitable data, formulations such as orodispersible tablets and oral suspensions containing BCS Class 1 and III compounds be deemed eligible for a BCS-based biowaiver.	***Proposed replacement text for sentence starting on Line 814 and continuing to Line 818:*** **Placement on the mouth and time of contact may be critical in cases where the active substance also is dissolved in the mouth and can be absorbed directly via the buccal mucosa. Depending on the**	This is reasonable as in this case it can be considered an immediate release oral dosage form, as long as there is no coating of any kind.

		formulation, swallowing of the e.g. coated substance and subsequent absorption from the gastrointestinal tract will also occur. If it can be demonstrated that the active substance is not absorbed through the oral mucosa, but rather must be swallowed and absorbed through the gastrointestinal tract, then the product might be considered for a biowaiver. If this cannot be demonstrated, bioequivalence must be evaluated in human studies.	
Lines 823 838:	In order to conduct either a 3-way or a 2-way study it should depend on the recommended dosing procedure described in the product labeling. If the product is to be administered with or without water, two 2-way studies would be preferred to demonstrate bioequivalence under two dosing conditions. A 3-way study would be appropriate as head to head comparison with the reference drug is necessary under the two dosing regimen.		The current wording adequately covers the different possibilities
Line 839 Appendix II	Non-oral immediate release dosage forms with systemic action	If formulation contains excipients that promote absorption a BE waiver should not be considered – see conditions oral solutions. If formulation is alternative to parenteral administration then a BE would be required.	Agreed A reference to the section on oral solutions has been added at the end of the sentence: "conditions under oral solutions may apply in this case"
Appendix II Line 840		Please revise the first sentence to read, "This section applies to **non-oral immediate release dosage forms with systemic action,** e.g. rectal formulations"	No need to change. This section will be restructured
843, Appendix II	The possibility to waive a bioequivalence study should not only be restricted to oral solutions where all ingredients (active substance and all excipients) are completely dissolved.	Please add in line 851: "For oral suspensions where the active ingredient is completely dissolved in	Not agreed. There is no such requirement! The only requirement is that the API

	There are situations where the active ingredient is completely dissolved but some excipients, e.g. flavours are not completely dissolved. Therefore the dosage form of the product is an oral suspension by definition. Since the active ingredient is completely dissolved, the absorption is independent from formulation properties, provided there is no interaction between the dissolved active ingredient and undissolved components. Therefore, a bioequivalence study can be waived.	an aqueous medium at the time of administration the same principle as described above is applicable."	has to be dissolved; not the excipients. In the case there is a suspension where the API is dissolved then the applicant has to show exactly that.
848-849, Appendix II	The sentence "Any differences in the amount of excipients should be justified either by reference to other data or by a bioequivalence study." is not clear. It makes sense only if it refers to such excipients (mentioned in the previous sentence) which might have an impact on bioavailability. Even qualitative changes are allowed in the reformulation of oral solutions, therefore it seems not to be necessary to justify any quantitative changes.	Modify the sentence: "Any differences in the amount <u>of such excipients which might influence bioavailability</u> should be justified…"	Agreed. The text has been modified based on this and other comments.
848, Appendix II	Even if there is a difference in excipients, oral solutions should be exempted from biostudies in normal cases.	Please delete: "Any differences in the amount of excipients should be justified either by reference to other data or by a bioequivalence study."	It should be clear that the requirement on "same excipients" only refers to those excipients that affect GI transit or absorption. See above.
848, 872, Appendix II 1013, Appendix III	The applicant does normally not know the quantitative composition of the reference product.	Please delete: "Any differences in the amount of excipients should be justified either by reference to other data or by a bioequivalence study" (line 848). Please change: "…and the same excipients as the medicinal product currently approved" (line 872). Please change: "… it is advisable to use the same excipients …"	See previous comment Not agreed, see other comments on line 872 below
852 and 853	*"In those cases where the test product is an oral solution which is intended to be bioequivalent to another immediate release oral formulation, bioequivalence studies are required".*	To write: "In those cases where the test product is an oral solution which is intended to be bioequivalent to another	Not agreed. According to Appendix III, BCS based biowaiver is only applicable when excipients are

	Why is an excipient-based justification not acceptable any longer?	immediate release oral formulation, bioequivalence studies are required, **unless an exemption can be justified**."	similar. Excipients for solid are different from excipients for liquid dosage forms.
Line 852 / Appendix II	Waiver for oral solution may be granted if the reference oral IR product is dissolved by ≥ 85 within 15 min and is a BCS class I product.		Not agreed, see above
Appendix II Lines 852-853	Please clarify if the statement, "*another immediate release oral formulation*" in this context refers specifically to solid dosage forms.	Please change as follows: "In those cases where the test product is an oral solution which is intended to be bioequivalent to another immediate release **solid** oral formulation, bioequivalence studies are required.	Not agreed. It already states "another", meaning that it is not an oral solution. For clarity, we could replace "formulation" with "dosage form". "Solid" not accepted. Could be a suspension
Appendix II Lines 855-857	We very strongly recommend rewording to indicate that biowaivers are appropriate for modified release products for example when supported by development of an in vitro/in vivo correlation (IVIVC) Please add a clarifying statement that for modified release, a biowaiver may be applicable.	Please change as follows: "**Biowaivers are appropriate for modified release products when supported by development of an in vitro/in vivo correlation (IVIVC).** Bioequivalence studies are required…"	This is already stated in the modified release guideline. No need to repeat it here. Moreover, an ivivc does not replace bioequivalence testing between a generic and originator product but facilitates the application for variation and further strengths based on proportionality.
Line 860 Line 1031	BE testing for FDCs is a controversial topic and many questions are still open and a more detailed description on FDC BE would be helpful. Specifically the "reference" should be specified. Is the reference the simultaneous administration of the "mono products" or would a three-way crossover be required giving the mono products in two different periods? If for one compound of an FDC a biowaiver applies, how would the BE study be designed?	Please clarify.	This is clarified in the PK section of the new FDC guideline. A reference to the FDC guideline has been added.
Appendix II Lines 863-864	It is stated "*For generic fixed dose combinations, the reference product in the bioequivalence study should be the originator fixed combination product*." The wording "generic fixed-dose combinations" and "originator fixed combination product" should be clearly defined.	To define the wording ""generic fixed-dose combinations" and "originator fixed combination product" and to add in the proposed annex-glossary.	Agreed. This has been clarified in section 4.1.2

	In particular, it should be clarified whether the originator fixed-dose combination product is a FDC authorized in the Community on the basis of a complete dossier.	Please change as follows: "For generic fixed dose combinations, the reference product in the bioequivalence study should be the originator fixed combination product **which has been authorized in the Community on the basis of a complete dossier.**"	
Line 860, Appendix II	What is the recommended study design for fixed-dose combinations: two-fold crossover of fixed-dose combination (A+B) vs. loose combination (A) + (B) or threefold crossover of fixed-dose combination vs. single components: (A+B) vs. (A) vs. (B)?	The design of BE studies for fixed-dose combinations needs to be clearly defined.	This is clarified in the PK section of the new FDC guideline. A reference to the FDC guideline has been added.
Appendix II Lines 865-873	When reading this paragraph, there could be the misleading impression that for all parenteral products no bioequivalence studies are necessary. It should be mentioned that for parenterals with modified release a bioequivalence study is mandatory.		Recommendations regarding emulsions and micellar forming formulations have been added as well as modified release intramuscular or subcutaneous dosage forms.
Lines 866-869:	Unless the test drug and excipients are qualitatively and quantitatively same as those in the reference product, bioequivalence study requirement should not be waived. This requirement should be strictly recommended.		The paragraph has been revised based on this and other comments.
Lines 868-869	Suggest more clarification regarding parenterals to avoid varied interpretation.	Please add, for example: where the drug is not ionizable, small variations in excipients, pH or osmolality could be acceptable.	The paragraph has been revised based on this and other comments.
Lines 868-869	It is stated that BE studies are not required for parenteral solutions administered as an aqueous i.v. solution if the excipients, pH, osmolality are the same or at least comparable and should not interact with the drug substance. If the excipients do not interact with the drug substance, why do they need to be the same? Provided the drug substance is in solution, which is assumed in the first sentence of the paragraph, pH, along with osmolality, has no impact on bioavailability. By definition i.v. administration gives absolute bioavailability. The	Delete sentence: "Moreover, the excipients, pH and osmolality have to be the same….."	Agreed

	excipients, pH and osmolality are irrelevant. Many drug products for i.v. administration are diluted before administration. Thus, excipient concentrations of the solution administered are being different from the drug product anyway, and pH and osmolality can either be not controlled (e.g. in case of dilutions with normal saline) or are determined by the diluent.		
868 Appendix II Parenteral solutions	As 100% bioavailability can be assumed for intravenous solutions, it is not necessary to request the same or comparable excipients in the test and reference product. If the requirement remains, the term "comparable" should be specified. Examples could be given for each type of excipient: • solubilisers (eg, are Tween vs Pluronic, different?), • cyclodextrines, • preservatives, • antioxidants. However, should intravenous formulation be addressed in the context of this guideline (immediate release oral dosage forms)?	CHANGE: Delete "the excipients," in line 868.	The paragraph has been revised based on this and other comments.
868-869	Intravenous solution: Is it necessary to perform a bioequivalence study when the active substance interacts with an excipient forming a complex? Even if the excipient is the same or very similar in test and reference formulations? Please, clarify. From the text it seems that the bio study is required always when a complex is formed.		The paragraph has been revised based on this and other comments.
868-869, 870-873, Appendix II	Regarding aqueous solutions, the excipients, osmolality and the pH need not be same since it is not necessarily relevant in vivo.		Agreed
Lines 868-869	Suggest more clarification regarding parenterals to avoid varied interpretation by regulators.		The paragraph has been revised based on this and other comments.
870-873, Appendix II	The use of the same excipients by generic companies in case of i.m. or s.c. parenteral solutions might sometimes not be possible for patent reasons. It is questionable if BE studies are necessary in	"Comparable excipients" should be acceptable if it can be justified that the formulation will most likely not have	Not agreed. In solutions intended for im or sc administration, either aqueous or oily, the main parameter controlling the rate of absorption

	each of these cases in order to demonstrate equivalence.	an impact on bioavailability.	may be viscosity. Slight differences in composition may cause significant variations in viscosity. Therefore, the word "comparable" is not adequate. In order to assure the same viscosity, it would be better to state "the same excipients in similar amounts". If it can be demonstrated that the excipients have no impact on the viscosity of an aqueous parenteral solution, then comparable excipients in similar amounts may be used.
Lines 870-873	For s.c. and i.m. routes of administration, again it is not required to test BE provided the test product contains the same or similar excipients in "similar"amounts as the approved reference product. It is curious that there is no condition about interactions between the drug substance and excipients, as is the case for an i.v solution.	Modify text to "*In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and* **contains the same or similar excipients** *as the medicinal product currently approved, bioequivalence studies are not required*.	See above
872 Appendix II Parenteral solutions	The request for the "same excipients" between a test and a reference product cannot be justified in any case of intra-muscular or sub-cutaneous parenteral solutions as differences in bioavailabilty are not likely in many cases. Additionally, the term "in similar amounts" should be specified. Use of the same excipients is sometimes not possible due to patent reasons.	CHANGE: Allow "comparable excipients" in addition to the same excipients at least in case of high permeability active substances (BCS class I or II). CLARIFICATION: Please clarify "in similar amounts".	See above
Lines 870 – 873:	For intramuscular depot dosage forms, sometimes it may become necessary to document bioequivalence by conducting in vivo study if the drug becomes insoluble or may precipitate in the micro environment under depot conditions. This is particularly important for lyophilized products meant for reconstitution with limited		Recommendations regarding modified release intramuscular or subcutaneous dosage forms have been added.

	volume of fluid. There should be some recommendations for the non-solution parenteral drug products.		
Lines 877-893:	This section includes a list of locally acting drugs delivered via various routes. This section has been oversimplified as drug delivered through different routes of administration require different considerations. Furthermore many of these drugs could be metered, pressurized, with a device that would require additional considerations. It is recommended that either this section is deleted with a note that these products are outside the scope of this guideline because of their complexities. This section is over-simplified and is misleading. A new separate guideline for Locally Acting, Locally Applied Products should be considered by EMEA.		This section has been revised and refers to the Locally Acting, Locally Applied Medicinal Products guideline. This prevails over the statements in the BE guideline. EWP will consider revising the Locally Acting, Locally Applied Medicinal Products guideline
880-885	Particularly for topical products the efficacy and tolerability are determined not only by the active substance, but by also the formulation of the product including all of the excipients. This fact will be taken into account in a comparative evaluation of topically applied products. According to CPMP/EWP/239/95; 1996, none of these products can be considered “essentially similar”. Nevertheless, full toxicological and clinical data would not normally be necessary provided that the therapeutic equivalence is justified by expert reports. Regulatory authorities may have varying opinions on whether therapeutic equivalence is justified by comparability to a currently authorised topical product, or if the authorisation of a variation notification requires clinical data. For example, in the case of the authorisation of a generic eye drop product containing dexamethasone sodium phosphate, a regulatory authority required that clinical data should be presented to prove the therapeutic equivalence to the reference product. The excipient composition showed a difference only with respect to the solubilising component required to prevent turbidity of the solution, the	Change In the case of solutions for topical use, e.g. eye drops or cutaneous solutions, and if the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance *and the same excipients in the same amounts as the medicinal product currently approved*, *a biowaiver is acceptable. In certain cases quantitative differences in excipients may be acceptable for these products, if adequately justified.* To In the case of solutions for topical use, e.g. eye drops or cutaneous solutions, and if the test product is of the same type of solution (aqueous or oily), contains the same concentration of the	Partly agreed. The paragraph has been changed based on this and other comments.

	properties and specifications of the two products were, however, essentially identical and no difference in the bioavailability was to be expected. Consequently, the results of a double-blind, randomised, comparative clinical study on 210 patients showed no differences between test product and comparator (Gross and Struck, 2007*). This study illustrated that demands for clinical testing to demonstrate the comparability of topical products should be made strictly case-related and with a proper sense of proportion. If before the start of the clinical trial careful evaluation of the available data show a very high probability of equivalence of the products in question, the required effort to perform a clinical study according to GCP is in no relation to the knowledge gained. Minor differences in the composition of test product and comparator should not lead to requirements for clinical testing where available knowledge and expert evaluation supports a conclusion that bioavailability will not be affected. * Gross, D and Struck, H-G, *Arnzeimittel-Forschung (Drug Research)* 2007, **57**(5), 254-9	same active substance and the same **or equivalent established excipients** as the medicinal product currently approved**, resulting in comparable pharmaceutical specifications of the test product**, a biowaiver is acceptable. **Any qualitative or quantitative differences in excipients must be adequately justified.**	
880 to 885	Where topical solutions, particularly eye drops are concerned, slight differences in concentration of excipients or a change from a specific excipient to another excipient with similar properties are in most instances unlikely to have any significant influence on the efficacy or tolerability of the product, provided that the physicochemical properties of the formulation are essentially unchanged. Therefore, where therapeutic equivalence is justified on the basis of expert reports toxicological and clinical data should not be required. This is also supported by CPMP/EWP/239/95; 1996 that foresees the possibility, in case of minor variations, for an argument that these data are not necessary. In the case of solutions for topical use, the provision that a biowaver, is acceptable when a test product contains “the same excipients in the same amounts as the medicinal product currently approved” is unnecessarily restrictive. This can lead to excessive	**A biowaiver is acceptable in the case of solutions for topical use, e.g. eye drops or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties of the test product and reference product are identical or essentially similar. Any qualitative or quantitative**	Partly agreed. The paragraph has been changed based on this and other comments

	demands for clinical studies by regulatory authorities, even where no influence on bioavailability can be anticipated based on current knowledge and experience. For example, Gross and Struck (*Arzneimittel-Forschung (Drug Research) 2007; 57(5):254-259*) reported on a clinical study with a generic eye drop product containing dexamethasone sodium phosphate. This had been demanded by a regulatory authority although the excipient composition only differed in a minor respect to the reference product and the properties and specifications were essentially identical. No differences between test product and comparator were observed. On the other hand, for a generic eye drop product containing sodium cromoglicate, another regulatory agency did not require a bioequivalence study although, according to the declaration, the product contained an additional excipient (polysorbate 80) not present in the composition of the originator product (*MHRA:UKPAR PL 15872/0010*). This illustrates the need for clarification in the guideline that bioequivalence of products of this type can be reasonably argued even if the excipient composition is not fully identical. The level of likelihood that any significant differences in therapeutic efficacy or tolerability could be observed in a comparative study should be weighed against the need to avoid unnecessary clinical testing (see *Augsburger*, *Trans Am Ophthalmol Soc 2005;103:143-147)*. In the public interest, unreasonably high hurdles for marketing authorisation of equivalent products for reason of overly restrictive guidelines should be avoided.	**differences in excipients must be satisfactorily justified in relation to their influence on therapeutic equivalence.**	
881 Appendix II Locally acting locally applied products	Nasal sprays could be added as an additional example. However, should nasal sprays or eye drop formulations be addressed in the context of this guideline (immediate release oral dosage forms)?	Modify to "… eg, eye drops, nasal sprays or cutaneous solutions…"	Agreed to add nasal sprays

886	The guidance states 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.*" We believe that the term "*best*" could be interpreted differently, therefore we would suggest a more specific term.	*"If the extent of absorption and the bioanalytical method are such that a pharmacokinetic approach is reliable, then a bioequivalence study might be **more appropriate** for the approval of a locally applied/locally acting generic medicinal product.*"	The paragraph has been deleted
Line 886 Appendix II	*"If the extent of absorption and the BAN method allow for a PK approach then a BE study might provide the best data for approval"*	This is only a statement. Can this be made more formal e.g**. would require a BE study unless justified**	The paragraph has been deleted
889-893	Comment: This section is not very clear. Does it mean that for locally applied drugs with systemic exposure, the BE acceptance criteria is that the systemic exposure upper limit of 90% confidence interval should not exceed 125? Or is this an additional requirement in supplementing a PD study? Rationale: For clarification and interpretation.	Please add a separate paragraph for BE criteria the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit 125%.	This has been clarified
	extemption from the BE study for different strange of such a pharmaceutical dosage forms like: suspensions powders/granules for oral suspension is not discussed		The same applies as for other immediate release formulations.
Appendix 2, line 893		Please add that for these products having local action "A widening of the upper bioequivalence acceptance limit may be considered, if the applicant can justify it and demonstrate that the safety margin is not jeopardized"	Not agreed. If there is a safety concern related to systemc exposure, the upper limit should not exceed 125%.

APPENDIX III (line 894-1062)			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Appendix III III. Drug Substance	For the BCS classification of an active substance, it would be useful to mention and refer to the BCS classification for WHO essential medicines.	Proposal to add at the end of this paragraph: **"For drug substances on the WHO model list of essential medicines, BCS classification is available on the WHO prequalification guideline, annex 8, see http://healthtech.who.int/pq/"**	Not agreed, since maximum dose strengths may be different which may affect the final BCS classification. However, the applicant may be free to also use this information if applicable as literature may support the BCS classification acc. to lines 931 and 932.
Appendix III III. Drug Substance	For the BCS classification of an active substance, it would be also useful to mention and refer to the biowaiver monograph established by the International Pharmaceutical Federation (FIP) and published in the Journal of Pharmaceutical Sciences.	Proposal to add at the end of this paragraph: **"Some bioawaiver monograph have been established by the International Pharmaceutical Federation (FIP) and published in the Journal of Pharmaceutical Sciences (also downloaded form the FIP web site at http://www.fip.org/)."**	Not agreed – see comment above
Appendix III	In line with the WHO guideline further discussion may be needed to accept biowaivers for BCS class II weak acid drugs if the dissolution profiles at pH 6.8 support waiving the *in vivo* BE study, i.e., confirm that the dissolution of the 2 drug products is similar with respect to rate and extent.		Not agreed considering the current inconsistent acceptability of BCS-based biowaiver within the EU in general. Moreover, the predictability of comparative in vitro dissolution results for the in vivo situation of BCS class II drugs is not completely convincing and reliable. However, further steps may not be excluded in the future depending on available sets of data.
	This is an important concept that needs special consideration in the guideline. Putting it as an appendix may not be appropriate.		The authors are of the opinion that the topic has gained necessary

	Unless separate guideline on this approach is available, it would be appropriate here to describe the approach in a summarized manner for the benefit of the user of this guideline. Unless there is authentic or authoritative information available in the literature, a sponsor using this concept, should experimentally determine solubility, permeability, and as usual, in vitro dissolution. From BCS standpoint, dissolution in water should also be considered. Some caution is recommended while considering waiver for Class III drug products. Excipients should be carefully scrutinized and no literature data should be allowed to classify the drugs under this class. Line 1049 – WHO Guidelines has been finalized, WHO Technical Report Series #937, 2006, Annex 7, 347-390.		importance now by providing a separate App. rather than a short passage within the main guideline text. Moreover, the concept as such is described and used worldwide already within different jurisdictions since more than a decade, i.e. it is not new and numerous publications are available. Therefore using sound literature data for drug substance characteristics is deemed acceptable. Requirements for BCS class III drugs are quite strict and are therefore considered sufficient. References have been deleted.
BCS-based biowaiver Lines 895–1027	Specific comments on BCS-based biowaiver • Line 910-912: The second sentence in the paragraph could be clarified. Does this mean that a biowaiver may be appropriate in these situations? • Line 936: Please comment on applicability of biowaiver approach when comparing different crystalline forms. • Line 950: BCS guidance on absorption is different than FDA guidances as 85% of compound needs to be absorbed based on human data only (not in vitro data). Please clarify the scientific rational. • Lines 951-972: For the absorption part, the guideline really describes well only the criteria of 85% based on human data. It is not clear from the guideline whether non-clinical data would be acceptable for biowaiver purposes. It is only state at the end that "Well performed in vitro permeability investigations including a reference standard may also be considered supportive to in vivo data". • While the guidance opens the option for waivers for BCS III, the clauses around it are quite restrictive "excipients have to be qualitatively the same and quantitatively very	Excipients that are qualitatively similar and within the variation as provided in SUPAC should qualify for BCS waiver If the drugs are highly soluble and considered non-critical in terms of therapeutic range, rationale should be included why in vivo BE studies are not	- Yes - The applicability relates to solubility properties which have to be carefully investigated (see sect. III) - Different crystalline forms may be eligible based on their solubility characteristics; however, this is considered not a prominent issue since only highly soluble drug substances are considered. - It is acknowledged that permeability is not the same as absorption. However, permeability has been used to predict absorption. Referring to respective findings it is reasonable to require the most relevant data on human

	similar to exclude different effects on membrane transporters". • "Drugs for which tighter acceptance range of 90 -111 % would apply in in vivo bioequivalence studies are not eligible for BCS-based bio waiver approach" • Other comment – If the drug is anticipated to be given clinically as multiple dosage forms (i.e. given as 2 or more tablets at the same time), should the BE study be conducted with a single tablet or the number of tablets expected to be administered clinically?	eligible for BCS –based biowaiver approach for drugs with tighter acceptance range of 90 – 111%, otherwise the statement should be deleted. MSD proposes that BE should be tested with the dosage units recommended to be given as per the dosage and administration.	absorption. - Based on current experience and knowledge in vitro data have been shown to imply relevant limitations. Therefore, in vivo data should be available for the final conclusion regarding the BCS classification. - The reasons for requirements for BCS class III drugs are mentioned. - The dose is already introduced in solubility investigations.
Appendix III, page 24 Line 900-901	BCS-based Bio-waiver It is claimed that provided certain prerequisites are fulfilled, comparative *in vitro* dissolution could be even more discriminative than *in vivo* studies. It is fully understandable why BCS-based bio-waivers are restricted to highly soluble drug substances with known human absorption. But if comparative *in vitro* testing is even more discriminative than *in vivo* studies it is less understandable why this should be restricted to drug substances that are considered non-critical in terms of therapeutic range as stated on line 902-903.	Please comment on this.	It may be noted that the wording says 'could be' rather than 'is'. It is well known, that in certain cases – though not in all cases – in vitro dissolution test may be even overdiscriminating. However, the particular sentence has been deleted. Apart, it is acknowledged that the initial concept as published does not refer to the therapeutic range. However, the restriction is made in order to minimize possible risks.
Appendix III I. Intro-duction Lines 902-908	Please add statements that consider the impact of the definition of BCS-Biowaivers in terms of global development programs and paradigms. Therefore, as provided in the FDA Guidance on Biowaivers, please consider adding the conditions that should be met for which a biowaiver might be requested for a highly soluble and highly permeable drug substances (Class 1) in IR (immediate release) solid oral dosage forms that exhibit rapid in vitro dissolution.	The suggested conditions to be met are the following: (1) the drug substance must stable along the gastro-intestinal tract, (2) excipients in IR tablets and capsules should have no significant effect on the rate or extent of oral drug absorption, (3) the drug must not have a narrow therapeutic index and (4) the drug product is formulated such that the drug	Requirements are clearly and sufficiently stated. Repetition is considered not necessary.

		substance is not absorbed in the oral cavity (i.e. mouth or throat).	
Appendix III 905 ff	It is agreed that the BCS concept cannot be applied to drug products which demonstrate intraoral absorption of the active pharmaceutical ingredient. However, when such an absorption route can be excluded, formulations such as orodispersible tablets and oral suspensions containing BCS-class 1 compounds might well be eligible for a BCS-based biowaiver. Paracetamol suspension provides an example for which demonstration of BE should be acceptable based on comparative dissolution studies. It is acknowledged that in case of oral suspensions the risk of a non-correct bioequivalence decision based on a BCS-based biowaiver for a BCS-class III compound is elevated due to frequently higher excipient contents in these formulations. Consequently, oral orodispersible tablets and suspensions should be applicable for biowaivers only if their active pharmaceutical ingredients are not absorbed by the oromucosal epithelia.	Modify sentence in line 907 as follows: "However, it is not applicable for modified release formulations, as well as for sublingual, buccal, and orodispersible formulations, **provided that oromucosal absorption of the active substance has been observed or may be expected.**"	The proposal has been included.
Appendix III I. Intro-duction Line 906	Please clarify and define the use of the term "pharmaceutical equivalent" referenced in this case. In other words, as provided in the former document CPMP/EWP/QWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence, section 2.2, are medicinal products considered "pharmaceutical equivalents" if they "… contain the same amount of the same active substance (s) in the same dosage forms that meet the same or comparable standards." Please add the definition.		The wording has been slightly revised.
Line 907	In the previous version of the guideline it was stated (5.1.8 Locally applied products): "For locally applied products with systemic action a bioequivalence study is always required". In the draft guideline (line 907)it is stated: "BCS-based biowaiver is not applicable for sublingual, buccal, orodispersible, and modified release formulations." In our opinion the critical factor is that there is a relevant in vitro method available that is proven to correlate with in vivo data. A biowaiver should be applicable with such a relevant method present.		It is emphasized to separate the topics here. The BCS based biowaiver applies to IR oral dosage forms only. Required in vitro dissolution experiments provide some comparison of formulation properties leading eventually to the conclusion, that the formulation effects can be considered irrelevant (i.e. risk minimization) rather than

			providing any correlation to the in vivo situation. In addition, an ivivc would be useful for certain product variations but can not be used to prove bioequivalence between different products (T and R)
Appendix III 913 ff 917	**BCS-based biowaiver – Summary requirements:** The requirement that a BCS based biowaiver can be obtained for a BCS **class-I** containing drug product only when in vitro dissolution characteristics of **test and reference product** reveal complete (>85 %) dissolution within 15 minutes is challenged by the Expert Panel. The scientific justification for this requirement is not apparent. Immediate release BCS-class I drug products exist on the market that do not fulfil this overly conservative dissolution specification (e.g. some gelatine capsules and film tablets) but nevertheless should be eligible for a biowaiver. Consequently it is more important to demonstrate the similarity of the dissolution profiles between test and reference product as specified in the Guidance CPMP/EWP/QWP/1401/98. The dissolution specification for BCS class-I drug product should be set to >85% within 30 minutes which is in line with other relevant guidelines on this topic (FDA, WHO) and has demonstrated its robustness in the past.	Revise specification in line 917: "Not less than 85 % in 30 min"	Comment is covered by the revised draft version.
Lines 917-8 in Appendix III (II)	Requirement of very rapid dissolution is not in line with FDA guidance for industry: "Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage form based on biopharmaceutics classification system", WHO guidance "Multisource (generic) Pharmaceutical products: guidelines on registration requirements to establish interchangeability" and Pharmacopeial Forum vol. 34(4) (July – Aug. 2008). These references allow rapid dissolution (> 85% within 30 min) for BCS I classified products. Please see for more information in appendix 1.	Replace with "Rapid (> 85% within 30 min) in vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements	Comment is covered by the revised draft version.
917,918 and 923,924	• *'very rapid (> 85% within 15 min) in vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements*	• *very rapid (> 85% within 15 min) in vitro dissolution characteristics of the test and*	Comment is covered by the revised draft version. However to note, harmonization with

	(see Section IV.1)' We recognised that the definition of very rapid dissolution is newly described in the Draft Guideline. However, we miss the definition of rapid dissolution which is also not exactly described in the current Guideline. But, the current Guideline allows for rapid dissolution to demonstrate similarity of dissolution profiles as described in Appendix 1. Furthermore, we recognised that there is still no harmonisation with US guidance 'Waiver of in vivo BA and BE studies for IR dosage forms based on BCS' chapter II C: '*an IR product is considered rapidly dissolving when no less than 85% ... dissolves within 30 minutes ...* .' For proper definitions and harmonisation with the US Guidance, we propose to add a definition for rapid dissolution harmonised with the US Guidance: >85% within 30 min. We think that it is necessary to demonstrate additionally the similarity of dissolution profiles as described in Appendix I.	*reference product have been demonstrated considering specific requirements (see Appendix I)* **or** **rapid (>85% within 30 min) in vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements while demonstrating similarity of dissolution profiles as described in Appendix 1.**	the US-FDA guideline is not ultimately intended since this is the oldest document in this area and may not necessarily reflect the latest scientific discussion/findings.
Line 914-919, Appendix III, Part II.	The requirement that approval of a drug product based on a BCS-biowaiver can be obtained for a BCS class-I containing drug product only when both the **test and reference products** are "very rapidly dissolving" i.e. exhibit ≥85 % dissolution within 15 minutes is challenged by the Special Interest Group. Other similar bioequivalence documents (FDA, WHO) allow application of the biowaiver to Class I drugs when the products are "rapidly dissolving" (>85% release from reference and test product within 30 minutes). There is no clear rationale for this proposed tightening of requirements, since there are not, in the collective experience of this Group, any case examples where application of the present FDA and WHO guidelines has failed to correctly ascertain bioequivalence. Further, a too-restrictive dissolution requirement would inappropriately bar many film-coated tablet products and hard gelatine capsule products from consideration. For such products it is more important to demonstrate the *similarity* of the dissolution	***Proposed replacement text for Lines 917 and 918:*** • **rapid (≥ 85% within 30 minutes) *in vitro* dissolution characteristics of the test and reference product have been demonstrated considering specific requirements (see section IV.1) and ……**	Comment is covered by the revised draft version.

	profiles between test and reference product as specified in the Guidance CPMP/EWP/QWP/1401/98.		
Lines 917-924	The requirement of very rapid product in vitro dissolution for bio-waivers of class I drugs is restrictive compared to existing guidelines and guidelines from others like WHO, FDA and USP. There is no clear rationale for this proposed tightening of requirements since there are not to our experience any case examples where present guidelines have been failing to ascertain clinical efficacy and safety. BCS based biowaivers should also be possible for rapidly dissolving drugs e.g no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes in 900 ml or less in the buffers prescribed in the guidance. With this requirement profile comparisons using the f2 metrics would no longer be useful. Also it is not consistent with the §IV1.1., line 987 where 12 units are required to enable statistical evaluation ; but no statistical evaluation is needed if >85% is dissolved within 15 min. It should be mentioned that under certain circumstances BCS class biowaivers might also possible for BCS class II substances. (e.g. weak acids which show good solubility at intestinal pH).	The paragraph should be modified: " **rapid** (> 85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product have been demonstrated considering specific requirements (see section IV.1) and" Or **"Rapid dissolution: In vitro data should demonstrate the similarity of dissolution profiles between the test and reference product in each of three buffers within the range of pH 1 – 6.8 at 37°C**"	Comment is covered by the revised draft version. However, at the time being, BCS class II drugs including those having pH dependent solubility are not considered eligible for a BCS-based biowaiver
Lines 917-924	"…**very rapid** (> 85 % within 15 min) *in vitro* dissolution characteristics of the test and reference product have been demonstrated considering specific requirements (see section IV.1) and…" BCS based biowaivers should also be possible for rapidly dissolving drugs e.g. no less than 85% of the labelled amount of the drug substance dissolves within 30 minutes in 900 ml or less in the buffers prescribed in the guidance. With this requirement profile comparisons using the f2 metrics would no longer be useful. It should be mentioned that under certain circumstances BCS class biowaivers might also possible for BCS class II substances (e.g. weak acids which show good solubility at intestinal pH).	The paragraph should be modified: "**rapid** (> 85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product have been demonstrated considering specific requirements (see section IV.1) and"	Comment is covered by the revised draft version. Regarding biowaiver extension to BCS class II APIs is currently considered insufficiently substantiated by scientific data. Moreover, in many cases even with weak acids differences in rate of absorption may not be detectable based on in vitro dissolution. At the time being there is no common scientific view on the best and most sensitive experiments to be done to

			compare respective products.
Appendix III II. Summary Requirements Line 920-925	It is stated "*BCS-based biowaiver are also applicable…if excipients are qualitatively the same and quantitatively very similar."* However, since the quantitative composition of a medical product is confidential, it would not be possible to verify this requirement.	Please change as follows: "BCS-based biowaiver are also applicable…if excipients are qualitatively the same and ~~quantitatively very similar~~ **not suspect of having any relevant impact on bioavailability (see section IV.2)."**	The comment is well taken. Therefore, the particular wording has been chosen. However, in many cases 'reverse manufacturing' is not impossible and also not completely uncommon. In contrast, discussing 'relevant impact of excipients on absorption' is based mostly on assumptions since sound data are rare.
Lines 921-22	The inclusion of class III drugs for bio-waivers is very welcome and strongly supported. However, the request for qualitatively same and quantitatively very similar compositions seems to be overly conservative and more describe a situation where in vivo BE would not be required for an IR product irrespective of BCS class. Excipient limitations should focus on lack of effect on permeability including transporters and intestinal transit, which are the only known factors to potentially influence bioavailability given that dissolution is the same. There also a lot of data in the literature supporting such a more general bio-waiver approach for class III drugs, for example the bio-waiver monographs published by D Barends and others including several class III compounds.		See above comment. In addition the request aims to reach best possible risk minimization.
Appendix III Line 925 Page 24	This is not described in further detail in Section IV.2- . It would be useful to have some definition of excipient categories and allowable % changes so that application of this aspect by regulators is consistent.		The comment is considered valid. However, to define allowable % changes and excipient categories beyond the most critical that are mentioned is beyond the scope of this guideline. It is also considered a drug substance specific issue, i.e., changes may be relevant for one drug substance and irrelevant for the bioavailability of another.
Appendix II; line 925	During development of an innovator drug, it should also be possible to bridge changes for rapidly dissolving BCS 3 drugs by		This may be an option but has to be carefully decided on a case-by-case

	dissolution testing beyond that; e.g. for slight changes of the qualitative excipient composition (with well-established excipients in usual amounts).		basis.
Line 920-925, Appendix III, Part II.	The inclusion of class III drugs for biowaivers is very welcome and strongly supported by the Special Interest Group. The Special Interest Group agrees with the stringent dissolution specification for BCS Class III drugs, since low permeability compounds frequently show an absorption window in the upper small intestine. Thus it is very important to ensure complete dissolution of the drug product already during its residence in the stomach, and to assume, that the test and reference product essentially may be treated like a solution. However, the request for qualitatively same and quantitatively very similar compositions seems to be unnecessarily restrictive. Excipient limitations should instead focus on lack of effect on permeability (including transporters) and intestinal transit, which are the only known factors potentially influencing bioavailability (given that dissolution is the same). There also a lot of data in the literature supporting a risk/benefit biowaiver approach for class III drugs, for example the biowaiver monographs published by D. Barends and co-authors including several class III compounds (available at www.fip.org/www/?page=ps_sig_bcs: Acyclovir, Atenolol, Cimetidine, Chloroquine, Ethambutol, Isoniazd (I/III, Metoclopramide (I/III), Pyrazinamide, Ranitidine). Further, for reference products approved in the USA or Japan, neither the qualitative nor the quantitative excipient composition is disclosed to the public. So if the reference product is to come from one of those markets, the necessary information to fulfil this requirement would not be available to the sponsor of the test product. In practice, it is impossible to copy these innovator drug products. A further consideration is that qualitative and quantitative composition of an innovator formulation might be protected by formulation patents, which would preclude the	*Proposed replacement text for Line 925:* • excipients included in the formulation of the test product are well-established for products containing that drug substance, and it has been documented that the excipients used will not lead to differences between the reference and test product with respect to processes affecting absorption (e.g. via effects on gastrointestinal motility or interactions with transport processes), or which might lead to interactions that alter the pharmacokinetics of the drug substance. Evidence that each excipient present in the test product is well-established and does not effect gastrointestinal motility or other process affecting absorption, can be documented using appropriate part(s) of the following information: 1) the excipient is present in the reference product, or the excipient is present in a number of other products which contain the same drug substance as the test drug product and which have marketing authorizations in the EU, and 2) the excipient is present in the test	The comments are well taken. Reference is made to the excipient section for details regarding the requirements. However, the proposed wording seems to be rather vague, particularly the term 'typically used' and/or used in other registered products. This does not sufficiently answer the question of bioequivalence between specific products. Furthermore, past experiences show the very limited database on possible influences of excipients on transport and/or bioavailability of certain drug substances. Therefore, it is very difficult to draw firm conclusions. It is recognized that there is a number of examples indicating that BCS class III drugs can be good BCS Biowaiver candidates. However, based on current knowledge the authors consider the more restrictive view to be generally most adequate.

	sponsor from complying with this requirement.	product in an amount similar to that in the reference, or the excipient is present in the test drug product in an amount typically used for that type of dosage form. Generally, the closer the composition of the test product to that of the reference product with regard to excipients, the lower the risk of an inappropriate equivalence decision using a biowaiver based on the BCS.	
925	The requirement of qualitatively the same and quantitatively very similar excipients between test and reference product poses problems and questions. The quantitative excipient composition is generally not disclosed to the public in a drug product. In addition, it should be specified as to when a composition can be regarded as quantitatively very similar, also taking into consideration that qualitative and quantitative composition of an innovator formulation might be protected by formulation patents.	Revise line 925 as follows: "…excipients are qualitatively and quantitatively comparable"	The comment is well taken. Therefore, the particular wording has been chosen. However, in many cases 'reverse manufacturing' is not impossible and also not completely uncommon. In contrast, discussing 'relevant impact of excipients on absorption' is based mostly on assumptions since sound data are rare. Moreover, the term comparable bears too much room of interpretation and uncertainty.
933-938 Appendix III	If a drug substance is classified as BCS class I in the WHO Working document QAS/04.109/Rev1, this should serve as adequate reference for the BCS classification as well as for identifying the highest dose and strength.	CLARIFICATION: Please reword the paragraph to include that the WHO Working document QAS/04.109/Rev1 is an adequate reference for the BCS classification.	The WHO document is considered helpful but not necessarily sufficient. In particular, the highest dose strength may differ between WHO and other jurisdictions.
Line 939-940, Appendix Iii, Part. III	This text refers the reader back to section 4.1.9. Section 4.1.9 discusses the need for setting more narrow limits for AUC and/or Cmax in cases where a drug has a narrow therapeutic index (NTI). Thus in Lines 939 to 940 it is suggested that biowaivers only are unacceptable from NTI considerations if the in vivo BE study limits have to be tighter than usual. As this is very seldom the case, it would be possible for many more compounds with toxic	***Proposed replacement text for sentence on Line 939 and 940:*** **The biowaiver procedure is applicable only if the risk of an incorrect biowaiver decision in terms of risks to individual patients and public health (therapeutic index) can**	The proposed change is not agreed. A biowaiver is applicable for non-NTI drugs provided that the requirements given in Appendix III are fulfilled. The decision on NTI will be done based on clinical considerations on a case by case

	effects at concentration ranges not far from the therapeutic range to be considered for biowaiver. The draft text therefore represents a major relaxation of the world-wide accepted criteria. The proposed text from the Special interest group is in line with the position of the Code of Federal Regulations' definition on the subject of NTI and reflects currently accepted regulatory practice.	**be deemed acceptable. In this context narrow therapeutic index (NTI) is to be understood as a less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and/or when safe and effective use of the drug product requires careful titration and patient monitoring.**	basis.
Lines 944-6	The pH range should consider wide range from pH1.2 to 7.5, instead of pH6.	Change 'pH6.8 'to 'Ph 7.5'	There is no obvious reason to change the pH range.
946 and 947	*"A minimum of three replicate determinations at each pH condition is recommended …"* Why would 3 replicate determinations be necessary to determine the solubility of the drug substance?	We propose to delete this sentence as displayed in the current Guideline.	Agreed, a threefold replication may not always be necessary. The wording has been modified accordingly.
950 ff	It is recommended that the acceptable methods for permeability estimation are widened to include e.g. rat intestinal perfusion data and data using ex-vivo tissue studies in Ussing-type chambers, for which correlations to human absorption have been demonstrated, as supporting evidence.	The sentence in lines 971 to 972 should be modified as follows: "Well performed in *vitro, in situ* or *ex vivo* permeability investigations including a reference standard may also be considered supportive to *in vivo* data".	Currently not agreed. The interlab variability is usually pronounced which may also preclude the use of the same 'correlation' with absorption. Correlations to human absorption are considered limited and therefore interpretation of results is often difficult.
953 to 956 and 959 to 963	In some cases, such as drugs with pre-hepatic (bio)transformation, mass balance studies (usually 14-C) are not appropriate for assessing the completeness of DRUG absorption in humans. A urinary recovery of unchanged drug and metabolites (total radioactivity) of ≥85% of the dose is not an indication of complete drug absorption. Similarly, a recovery in urine and faeces (!) of ≥85% of the dose is not an indication of complete drug absorption even in the case of high phase I and II metabolism.	1) Revise line 955 to: "mass balance, **if appropriate**" and 2) amend lines 959-963 accordingly	The guideline has been revised to clarify how mass balance data can be used to support the claim for complete absorption
957 to 958	This sentence is adequate but not realistic. Mass balance and absolute bioavailability studies are usually conducted in the early	The sentence should be modified as follows: "Absorption of a drug with	This paragraph has been deleted.

	Phase I, far beyond from products to be marketed. It is proposed to modify that sentence. It is better to investigate two extreme doses than only one dose, at the upper and lower end of the predicted therapeutic range, irrespective of the underlying mechanism of the non-linearity and formulation-related factors.	nonlinear behaviour should be best assessed at the highest (safety considerations) and lowest dose of the predicted therapeutic range".	
Appendix III III.2 Absorption Lines 959-961	*"It has also been demonstrated that high Phase 1 (oxidative) and Phase 2 (conjugative) metabolism would support the evaluation of complete absorption if the recovery in urine and faeces account for > 85 % of the dose*." This statement is not correct; measurement of metabolite in faeces may lead to an overestimate of the amount absorbed due to microbial formation.	Please modify.	The guideline has been revised to clarify how mass balance data can be used to support the claim for complete absorption
Appendix III Line 970	We believe that *in-vitro* permeability studies by themselves, which are performed against a validated cell line, are sufficient to allow a definitive permeability classification rather than being merely supportive data.		Not agreed. There is enough evidence (e.g. lit. data) that in-vitro permeability may not be sufficient to ensure correct permeability classification and/or absorption assessment, i.e. variability and misleading results. However, if a drug substance is wrongly classified as a BCS class I instead of being a class III drug this has relevant consequences regarding excipients and in vitro dissolution comparison. Therefore, sound information on human absorption is preferred.
Lines 976-1001	This paragraph addresses general aspects of in-vitro dissolution testing, and not only in-vitro dissolution for BCS-based biowaiver.. As a consequence, we propose to move this entire paragraph to the appendix I on dissolution testing.	Please move section IV.1.1 to appendix I and indicate in appendix III: "**For dissolution testing and evaluation of in-vitro dissolution, refer to appendix I".**	Not agreed. The paragraph outlines 'general aspects' relevant to BCS-waiver related in vitro dissolution experiments.
976 to 1001	See comment on lines 761-762.		The dissolution related to the BCS-based biowaiver is considered a different and specific topic which can not be mixed with section 4.2 in the main guideline text.

Lines 979-980	"*The pH conditions to be employed are at least pH 1.2, 4.5, and 6.8. Additional investigations may be required at pH values in which the drug substance has minimum solubility*." It is not clear whether additional pH investigations are required within or outside the range 1.2 to 6.8.	Please change as follows: "Additional investigations may be required at pH values in which the drug substance has minimum solubility, **within the range 1-6.8**."	No change.
Line 981	The strict discouragement of addition of surfactant to dissolution media has no scientific justification since, the surface tension is much lower than water in the entire GI tract including both stomach (both fasting and fed conditions) as well as the colon. It has on the contrary been suggested by Dressman et al in several papers to add a small amount of surfactant below the critical micelle concentration to simulated gastric medium in order to increase in vivo relevance and it is well established to include bile acids/lecithin in simulated intestinal medium. Thus, potential addition of surfactants corresponding to in vivo conditions should be acceptable although not in excessive amounts providing too high solubility in relation to in vivo conditions.	Please modify.	Not agreed. The main reason is that the required in vitro dissolution experiments should serve as kind of worst case investigations not mimicking in vivo conditions (this is also not possible yet). It should be noted that only highly soluble drug substances in IR dosage forms are basically considered eligible for a BCS-based biowaiver, i.e. solubility and dissolution should 'per se' not bear any limitation for bioavailability. Accordingly, surfactants are simply not needed.
Lines 982 - 983	*"Test and reference products should meet requirements as outlined in the EU guidance on bioavailability and bioequivalence."*	Replace "EU guidance on bioavailability and bioequivalence" by "guideline on the investigation of bioequivalence"	Wording has been slightly revised.
Lines 983 - 984	*"It is advisable to investigate more than one single batch of the test and reference products in order to ensure that respective results are representative."* This requirement is sometimes interpreted to mean that multiple cross-over comparisons between batches are necessary. It should therefore be clarified a 1:1 profile comparison is made between the batches which have been found to be representative.	"*It is advisable to investigate more than one single batch of the test and reference to select* **one** *representative batch each for which profile comparisons are then performed.*	The text has been slightly revised.
983, 984	*'It is advisable to investigate more than one single batch of the test* *and reference products in order to ensure that respective results are representative.'* Is it useful to repeat costly and time consuming dissolution testing	We propose to delete this sentence	Not agreed. Costs can not be a valid argument in lieu of the fact that an in vivo study is waived.

	if batches are manufactured by the same representative process?		
Line 986	Validation data is requested for the comparative in vitro dissolution experiments. While we recognise the requirement for provision of analytical method validation data for release testing or stability indicating methods, we recommend that for these comparative dissolution methods it is sufficient to demonstrate a method is fit for purpose (absence of interference/bias for example).	We recommend clarification of the distinction between data provision requirements for validation of stability indicating and QC methodology vs data to demonstrate comparative dissolution methodology employed is fit for purpose.	Not agreed. Practical experts are expected to know what is relevant to reliably validate respective methods.
Appendix III. *IV.1* Lines 975-1001	It should be clarified the following questions: Which dissolution media and settings are to be used in the 3 pHs study? Same as for the QC media release? Or shall the method be adjusted to the new pHs? Is the use of different dissolution media/setting for the different pHs suitable? If surfactants are used in the dissolution media, should the same media be used for the 3 pHs test?	The section should be amended to clarify the interpretation of the above questions.	Reference is made to line 996 where PhEur buffers are recommended. Surfactants are generally discouraged (see line 997)
Appendix III. *IV.1* Lines 985-987	Comparative dissolution experiments should follow compendial standards. What is meant by the requirement of "validation data" in the context of different media used for comparative purposes? What items of validation are necessary? Would more than specificity be required?	The validation data required should be discussed in detail.	Not agreed. Usual validation requirements for in vitro dissolution experiments are considered well known: accuracy, precision, specificity, range, linearity. More details are deemed beyond the scope of this guideline.
Appendix III; line 990	Multiple companies commented on how, as the use of surfactants is discouraged, the use of 900 ml dissolution medium may be necessary to achieve adequate sink conditions. Therefore, it should be possible to use 900 or 1000 ml dissolution medium, where justified (for instance for product having a pH dependent solubility profile). Further, Ph Eur permits use of up to 1000ml, and FDA and Japanese guidances favour 900ml. In practical terms a larger volume can be more suitable, especially for low dose drug products where a cone effect can be observed in 500ml medium, which is not the case in 900ml of medium due to different hydrodymamics in the vessel. 900ml is therefore the	We recommend the provision of illustrative text providing acceptable experimental parameter ranges: Volume of dissolution media: 500 to 1000 mL Agitation – paddle apparatus: 50 to 100 rpm Agitation – basket apparatus: 75 to 150 rpm Buffer: pharmacopoeial buffers recommended, solubility enhancers	Partly agreed and covered by the revised version.

	harmonised volume meeting the majority of requirements.	may be permitted as required with scientific justification.	
Lines 989-998	The guidance provided on analytical methods and conditions provided are overly prescriptive.	We recommend inclusion of text to indicate that any scientifically justified dissolution method (including volumes and choice of media, paddle speeds) may be utilised.	Not agreed for this is in line with the BCS based biowaiver concept comparing different products for the purpose to conclude on bioequivalence (in contrast e.g. to quality control purposes)
Line 990; Appendix III, Part IV	The Special Interest Group would like to suggest that the Committee, in the spirit of harmonization with existing international documents (FDA, WHO), consider amending the volume of fluid to that specified by other biowaiver documents (FDA, WHO) where a volume of 900 mL or less is recommended, as well as in usual quality control tests for Class I and III drugs (USP, JP). For most Class I drugs sink conditions will apply at either 500 or 900 ml of dissolution media, and even in cases where D:S is very close to 250 ml, the final concentration in 500 ml will not exceed one-half of the solubility. Thus it is unlikely that the choice of volume within this range will have a strong impact on the outcome of the dissolution test – but it would help unnecessary proliferation of the tests needed to obtain approval in different jurisdictions.	***Proposed replacement text for Line 990:*** • **Volume of dissolution medium: 900 ml or less**	Covered by the revised version.
992	A modification of the agitation speed in the paddle apparatus from 50 rpm to 75 rpm is suggested. It has been shown that at 75 rpm less coning takes place than at 50 rpm, thus reducing the coning artefact (Strauch S., Jantratid E., Dressman J.B., Comparison of WHO and US FDA Biowaiver Dissolution Test Conditions Using Bioequivalent Doxycycline Hyclate Drug Products. J. Pharm. Pharmacol. in press).	Line 992: Paddle apparatus: usually 75 ppm	The recommendation is worded "usually" and therefore leaves at least some room for modification if justified. No changes in the proposed text.
Line 992, Appendix III, Part IV	The Special Interest Group suggests a modification of the agitation speed in the paddle apparatus from 50 rpm to 75 rpm. It has been shown in many dissolution workshop presentations and as well as in the published literature that at 75 rpm less coning takes place than at 50 rpm, thus reducing the coning artefact (e.g. Strauch S., Jantratid E., Dressman J.B., Comparison of WHO and	***Proposed replacement text for Line 992:*** • **Agitation: paddle apparatus – usually 75 rpm**	The recommendation is worded "usually" and therefore leaves at least some room for modification if justified. No changes in the proposed text.

	US FDA Biowaiver Dissolution Test Conditions Using Bioequivalent Doxycycline Hyclate Drug Products. J. Pharm. Pharmacol. 2009 Vol. **61**:1-7). Please also refer to the video on coning submitted with this response (kindly provided by Erweka GmbH, Heusenstamm, DE).		
Appendix III. *IV.1* Line 995	The sentence "pH 1.2 (0.1 N HCl or SGF without enzymes)" 0.1 N HCl normally has a pH of 1.0, should this be buffered to 1.2 or is pH 1.0 also possible?	Please consider a clarification at this point.	The wording has been slightly modified.
Line 997	The use of surfactant is stated to be 'not permitted'. We recommend this should be acceptable provided sound scientific rationale is presented	We recommend rephrasing to read 'Buffer: pharmacopoeial buffers recommended, solubility enhancers may be utilised as required with scientific justification'.	Not agreed. Solubility enhancers are basically considered not necessary since highly soluble drug substance in IR dosage forms are eligible only.
Appendix III; line 1003	*While the definition of the term "very rapidly dissolving" as more than 85% dissolution in 15 minutes is considered useful, it is noted, that it is in contradiction with ICH Q6A (where it is called "Rapidly dissolving"). Revision of ICH Q6A may* be considered in the future.		The differences are acknowledged. However, the definitions used here are in line with those generally used in the context of BCS based biowaiver recommendations and will therefore not be changed.
Lines 1003 - 1008	This paragraph addresses evaluation of in-vitro dissolution results, and not only evaluation for BCS-based biowaiver. As a consequence, we propose to move this entire paragraph to the appendix I on dissolution testing.	Please move section IV.1.2 to appendix I and indicate in appendix III: **"For dissolution testing and evaluation of in-vitro dissolution, refer to appendix I".**	Reference to App. I is included.
Line1009	As general comment on the concern on excipient effects on transporters and permeability it should be noted although this has been intense research area during the last 10 years almost no examples of effects has been shown so far in vivo except for a few excipients with surface active properties.	We recommend a balanced risk based approach should be applied also in this area more in line with view expressed on Lines 1016-17.	Acknowledged though not completely agreed regarding the consequences. Even though there may be little effects of single excipients, drug products are unique considering their composition and manufacturing. Therefore it is considered a matter of risk minimization to require similarity in

			excipients as far as possible. In particular this is considered relevant for BCS class III drugs.
Lines 1012-1013	"*even in the case of class I drugs, it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product*." Since the quantitative composition of a medicinal product is confidential, it will not be possible to verify this requirement.	Please change as follows: "*Therefore, even in the case of class I drugs, it is advisable to use* ~~similar amounts of~~ *the same excipients in the composition of test like in the reference product*."	It is acknowledged that the quantitative composition is confidential. However, practical experience has demonstrated that it is possible to determine respective quantities if needed.
Lines 1012-1015	"*Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product*". If a biowaiver is applied for a BCS-class III drug substance excipients have to be qualitatively the same and quantitatively very similar to exclude different effects on membrane transporters	This part should be deleted or restricted to critical excipients as it otherwise puts considerable limitations to the whole approach.	The different requirements regarding BCS class I and III drugs should be noted. No changes are proposed.
Line 1014	The draft guidance note states that the excipients "*have to be qualitatively the same and quantitatively very similar*" in BCS III biowaiver applications.	We recommend moderating this requirement to read "**Scientific rationale should be provided in support of excipient level changes demonstrating the absence of impact upon pharmacokinetics/pharmaco-dynamics**."	The requirement should ensure that the drug substance is available as a solution to avoid any formulation effect on absorption. Experience gained so far demonstrate that 'scientific rationale' is usually insufficient but should be supported by real data. However, these are available to a very limited extent only.
Lines 1014-1015	*"If a bioawaiver is applied for a BCS-class III…excipients have to be qualitatively the same and quantitatively very similar to exclude different effects on membrane transporters."* Where reference product is sourced from a third party it would be difficult for a sponsor to know the quantitative composition. We therefore recommend some flexibility This information is generally held by the innovator.	Please change as follows: *"If a bioawaiver is applied for a BCS-class III (…) excipients have to be qualitatively the same* ~~and quantitatively very similar~~ **where known,** *to exclude different effects on membrane transporters."*	Not agreed. See also above comments. The current data base is considered insufficient to justify more flexibility for BCS class III drug substances. 'Third party' is unclear.
Lines 1016 – 1021,	The application of restrictions of excipient amounts/ranges when known not to impact upon permeability/absorption appears very	We recommend deletion of lines 1016 through 1018 so that this section reads	Not agreed. See also above comments.

	conservative in particular when applied to products meeting the 'rapid dissolution' criteria.	**"A description of the function and levels of excipients is required with scientific rationale demonstrating absence of impact upon pharmacokinetics/pharmaco-dynamics."**	Experience gained so far demonstrate that 'scientific rationale' is usually insufficient but should be supported by real data. However, these are available to a very limited extent only.
1010 to 1027	The structure of this paragraph should be in line with what has been stated in the Summary requirements (lines 914 to 929). i.e. the requirement that "even in case of BCS Class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product" does not match the requirement that immediate release drug products for BCS-class I drugs are applicable for a BCS-based biowaiver if the excipients are not suspect of having any relevant impact on bioavailability" (ln. 919). From a scientific standpoint it may be justified to issue a BCS-based biowaiver even in the situation where test and reference product of a BCS-class I drug contain qualitatively and quantitatively different excipients, if it has been demonstrated that these are non critical excipients and thus do not interfere with gastrointestinal motility, intestinal permeability and membrane transporters. Furthermore, the expression for critical excipients should be harmonised, i.e. rename the expression "active" excipients (ln. 1020) to critical excipients.	Line 1012: Replace "it is advisable" by "optimum would be" Line 1020: Replace "active" by "critical"	Not agreed. The need for changes/modifications is not completely clear and may be a matter of correct English wording (e.g. 'advisable' does not express a compelling requirement) Both the words "cative" and "critical" excipients have been replaced by "Excipients that might affect bioavailability"
Line 1010-1027, Appendix III Part IV.2.	The structure and content of this paragraph (lines 1010 to 1027) should be brought in line with what has been stated in the Summary requirements (lines 914 to 929). i.e. the requirement that "even in case of BCS Class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product" does not concur with the requirement that immediate release drug products for BCS-class I drugs are eligible for a BCS-based biowaiver if the excipients are not suspected of having any relevant impact on gastrointestinal events.	***Proposed replacement text for Lines 1010 to 1013:*** **Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbed drug substances (i.e. BCS-class I) is considered rather unlikely, it cannot be completely excluded. Therefore, even in the case of class I drugs, the compositions of the test product that are *close to that***	The comment is covered by the slightly modified wording. The current wording has been proposed based on the overall discussion in order to get the most possible acceptance. Therefore, the flexibility regarding excipients is limited also in lieu of the limited data base. The red marked term may cause new

	For BCS Class III drugs substances, the Special Interest Group recognizes that the closer the formulations are between test and reference, the less will be the risk of an inappropriate bioequivalence decision when the biowaiver is applied. However, the Special Interest Group is strongly of the opinion that the requirement that the compositions be quantitatively similar is unnecessarily restrictive (except in the case of 'active' excipients). And in many cases a qualitative change in one or more excipients such as binders or diluents would also not be of concern, so long an 'active'excipient was not substituted. As a general comment on the concern about excipient effects on tranporters and permeability, it should be noted although this has been an area of intense research during the last 10 years, very few examples of excipient effects on permeability in vivo have been shown. These are typically excipients with surface active properties (SLS and Tween 80). *Although there are few published studies which conclusively show that other common excipients do not influence permeability, there is little suspicion of then causing problems.* Likewise, the culprits that hasten transit are largely identified (e.g. mannitol and sorbitol) or are unusual (e.g. sodium pyrophosphate). Therefore a more balanced, risk-based approach should be applied - more in line with the views expressed on rows 1016-17. Finally, the Special Interest Group prefers to have a standard nomenclature, which would necessitate choosing between 'active' excipient and 'critical' excipient for use throughout this section.	**of the reference product with regard to excipients are to be preferred, in order to minimize the risk of an inappropriate biowaiver decision.** ***Eliminate Lines 1014 and 1015*** ***Maintain text on Lines 1016 to 1025*** ***Proposed replacement text for Lines 1026 and 1027 – we suggest one of the following two versions:*** **1) In cases where 'active' excipients are relevant, the same amount should be used in the test product as in the reference product.** **2) In cases where an excipient is present in the test product for which there is a suspicion of an effect on the gastrointestinal permeability, such as a surface-activity , an *in vivo* bioequivalence study is needed, unless evidence is provided that the same amount of that excipient is present in the test product and in the reference product.**	questions since it is again imprecise. See also comment above
Lines 1012-3 in Appendix III (IV.2)	Requirement for similar quantitative compositions of test and a marketed reference product involves confidential data not available for the applicant.	Replace with "Therefore, even in the case of class I drugs it is advisable to use same excipients in the test product as are used in the reference product. The amounts need to be	See previous comments. (Pharmaceutical justification would not necessarily meet bioequivalence requirements)

		pharmaceutically justified."	
Lines 1032 - 1062	A set of referenced material is provided in this section however it is not clear where they are referenced throughout the guidance note		References have been deleted
Line 1043, Appendix III references	Author is missing from Reference	**Gupta E, Barends D, Yamashita E. Lentz KA, Harmsze AM, Shah VP, Dressman J, Lipper RA**	References have been deleted
General Comment	Concluding statement The FIP Special Interest Group is confident that the thoughts and suggestions expressed in this response will stimulate further and fruitful discussions at the EMEA level. This will enable a balanced and practical approach to biowaiver-based drug product approvals in the EU to be implemented, contributing to improved public health and rational use of resources in the health care system.		

APPENDIX IV			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Appendix IV	Dotted lines lead to confusion as it is not clear in which cases the following steps are requested.	Change dotted into solid lines.	Given that section 4.1.5 has been simplified, there is no need for a decision tree regarding choice of parent or metabolite. The decision tree has been deleted.
	These are made rather in a complicated way and could be simplified. The question is whether to use (i) parent, (ii) metabolite, or (iii) parent and metabolite for BE determination and which strength to use in the bioequivalence study to demonstrate bioequivalence for the whole product line.		The decision tree has been deleted, see comment above

Page 28	Formation should be formulation		The decision tree has been deleted, see comment above
Pages 28+29	In Appendices IV and V dotted lines are used next to solid lines: the difference in meaning was not very clear at first sight.	Please add clarification to the figure.	The decision tree has been deleted, see comment above
	As per decision tree on measurement of parent compound or metabolite, if the parent compound is active, and possible to reliably measure, and then BE should be demonstrated on parent compound **only.** At the same time the decision tree specifies that if the active metabolite contributes to major clinical activity then BE on both parent compound and metabolite is required. In such scenario kindly clarify what does the word "**Only**" signify? In what percentage the active metabolite should contribute to clinical activity to demonstrate BE on active metabolite?		The decision tree has been deleted, see comment above
Appendix IV and Appendix V (Decision trees)	The meaning of the dotted lines is not clear.	CHANGE: Should be clarified.	The decision tree has been deleted, see comment above
Appendix IV (Decision tree)	The dotted line on the right hand side originates from the question "Possible to reliably measure parent compound" instead of the answer associated with "Yes".	CHANGE: Should be modified.	The decision tree has been deleted, see comment above

APPENDIX V			
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
Appendix V	It is mentioned in the decision tree, for some cases, to "conduct BE at highest dose using highest strength and at lowest dose using lowest strength". Please clarify if one BE study or two BE studies are necessary: - to conduct one BE study with 3 arms (test product A: highest dose with highest strength, test product B: lowest dose using lowest strength, reference product) - or to conduct two BE studies (BE n° 1: product A vs reference product A, BE n°2: product B vs reference product B)	Proposal: To illustrate the decision tree by an example of a test product concerned by a biowaiver based on dose-proportionality of formulations.	Given that section 4.1.6 has been simplified, there is no need for a decision tree for selection of dose and strength. The decision tree has been deleted.
	Similar to the Appendix IV, this decision tree could be simplified to decide on which strength to select and dose to apply for bioequivalence study and which strength or strengths to select for waiver request. This could be prudently simplified once the few simple important selection criteria are identified on scientific grounds.		The decision tree has been deleted, see comment above
Appendix V/ p29	If comparing two 50 mg tablets versus one 100 mg tablet (which have quantitatively identical tablet cores), would it not be possible to avoid BE if the following data were available:		Yes, if the criteria in section 4.1.6 are fulfilled

	- Linear pK across the dose range - Similar dissolution profiles in 3 relevant media Rapid disintegration		
	The decision tree on selection of dose and strength in BE studies is inconsistent. Requirements when PK linearity is known along with fulfilment of Section 4.1.6 criteria a, c, and e are greater than those when PK linearity is unknown.	The same requirement of conducting BE study at highest dose using highest strength and at lowest dose using lowest strength (bracketing approach) may be better for consistency.	A bracketing approach has been introduced in section 4.1.6
	Too complicated	Please simplify	The decision tree has been deleted, see comment above
Appendix V (Decision tree)	The decision tree after the answer "No" to the question "Linear PK (criteria b fulfilled)?" does not take into account proportionality of the formulation.	CHANGE: Should be modified. However, even in case of deviations from proportionality according to the left hand side (under the "<5% rule"), deviations from linear PK should be possible without performing a study for each strength (see comment to line 418).	The decision tree has been deleted, see comment above