



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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CPMP/EWP/4151/00 draft 1

Overview of comments received on 'Guideline on the Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)' (CPMP/EWP/4151/00 Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
	<u>General comments on the draft Guideline and comments on the requirements for studies in adults</u>
1	Orion Corporation Orion Pharma
2	ANDI-VENTIS LTD
3	EFPIA (European Federation of Pharmaceutical Industries and Associations)
4	EGA (European Generic Association)
5	EPAG (European Pharmaceutical Aerosol Group)
6	Innovata Biomed Limited
7	IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)
8	Pari Pharma GmbH
9	Pfizer
10	Roche Products Limited
11	Siegfried Pharma Development GmbH
12	Vectura Limited.
13	TEVA Pharmaceuticals Europe
14	Schering Plough
	<u>Comments on the requirements for studies in children and adolescents</u>
15	EFPIA (European Federation of Pharmaceutical Industries and Associations)
16	EGA (European Generic Association)
17	EPAG (European Pharmaceutical Aerosol Group)



Stakeholder no.	Name of organisation or individual
	IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)
18	IPAC-RS
19	Orion Corporation Orion Pharma
20	Siegfried Pharma Development GmbH
21	TEDDY (Task-force in Europe for Drug Development in the Young)
22	TEVA Pharmaceuticals Europe

Table 2:
Discussion of comments

GENERAL COMMENTS - OVERVIEW	
Orion Pharma	
1.)	<p>The concept of therapeutic equivalence needs to be clarified. At present, only a general definition of therapeutic equivalence is given (lines 288-9). In particular, it should be clarified whether therapeutic equivalence is substantiated when both non-inferior efficacy and non-inferior safety is demonstrated [as suggested by the NfG <i>Replacement of CFCs in metered dose inhalation products</i> (CPMP/III/5378/93)], or whether two-sided equivalence actually needs to be demonstrated for both efficacy and safety (as suggested by several of the present draft provisions). It seems superfluously restrictive to rule out products that could demonstrate an improved benefit–risk profile. [This idea may stem from the bioequivalence analogy, where the lower limit of the equivalence range (often 0.80) controls inferior efficacy (but superior safety too, unnecessarily) and the upper limit (often 1.25) controls inferior safety (but superior efficacy too, unnecessarily). This analogy of bioequivalence with a systemically-acting product, however, is not applicable to locally-applied locally-acting products, since measures of bioavailability at the sites of action for the intended and unintended effects are dissociated (whereas for systemically-acting drugs they are the same).]</p> <p>EWP comment: <i>TE should be a two-sided approach in accordance to the BE. In general, the definition of TE will be not completely fulfilled with this non-inferiority-proceeding. Efficacy and safety should always be considered jointly. In case of improved efficacy and/or reduced safety we see open issues with the recommended doses. Normally, if efficacy was improved a dose-reduction would be needed. The informative texts of the test product can't be adapted for those of the reference product. In the case that an orally inhaled product is non-inferior to the originator for efficacy and provides clear evidence of comparable safety the product would be approvable.</i></p>
2.)	<p>Once there is conceptual clarity on therapeutic equivalence, it should be clarified whether the studies should primarily aim to demonstrate <i>therapeutic equivalence</i> (which by definition is always on the “response” scale, i.e. measures of efficacy or safety used as outcome parameters) or <i>bioequivalence</i> (equivalence on the “dose” scale; i.e. measures of dose delivery to the site of action used as outcome parameters; therapeutic equivalence is then assumed). The latter is suggested by several of the draft provisions, although the term therapeutic equivalence is consistently used throughout the text. For effective implementation of the guideline, an explicit differentiation between bioequivalence [equivalent bioavailability of the active substance/moiety at the site(s) of action; “dose” equivalence] and therapeutic equivalence (non-inferior/equivalent efficacy and safety; “response” equivalence) is a must, and the specific term should be used appropriately.</p> <p>EWP comment: <i>A definition of “therapeutic equivalence” is given within the guideline. The aforementioned comment concerning the corresponding parameters for testing therapeutic equivalence on one hand and bioequivalence on the other hand cannot be agreed with. Therapeutic equivalence can also be confirmed by comparison on the x-axis. The conclusion that the same dose is needed to reach a defined response is also a statement of therapeutic equivalence.</i></p>

3.) A related issue is whether orally inhaled products are considered **generic** or not. The move towards requiring demonstration of equivalent bioavailability at the site(s) of action (rather than direct demonstration of therapeutic equivalence) in the present draft suggests that even orally inhaled products will be regarded as “essentially similar” or generic. This is against the view given in the *NfG on the clinical requirements for locally applied, locally acting products containing known constituents* (CPMP/EWP/239/95), which clearly states that “[n]one of these products can be considered essentially similar”. A clear standpoint on this issue needs to be taken, to avoid controversial interpretation of the guideline provisions.

EWP comment: *Orally inhaled products are definitely not “generics” but “hybrids”. Therapeutic equivalence testing in OIPs is a stepwise approach. The simple bridging to the bioequivalence model is mostly not sufficient. Due to the specialities of this administration route all influencing factors have to be considered and addressed in the development plan.*

4.) If the guideline aims to prioritise demonstration of dose equivalence, which the approach is taken in North America, consideration should be given to its implications for the flow of new products based on abridged applications. It is likely that fewer products will actually meet the dose equivalence requirements than would meet response equivalence requirements. (After all, it is no accident that some vocal proponents of the “therapeutic equivalence on the x-axis” approach are employed by companies that produce “originator” products.) Does this serve the best interest of European patients using orally inhaled products? Are there examples where the current approach has failed and a hazard to public health has been imminent? Are North-Americans better served by a more versatile and/or safe product assortment on the market? Unlike medicinal products, guidelines are not subjected to empirical testing of their intended and unintended effects, so there should be a clear understanding of the potential implications before enforcement.

EWP comment: *It has been shown in the recent procedures that most of the studies, conducted with the previous study design, lack sensitivity to distinguish between different doses/strengths. It is not doubted that OIPs have a flat dose response curve so that comparisons in the x-axis are more likely to show differences than comparisons in the y-axis.*

EFPIA / Pfizer:

The overall guidance is a welcome progression of the existing PtC on Requirements for Clinical Documentation for Orally Inhaled Products and clarifies a number of aspects of clinical development and related pharmaceutical development topics.

1.) As similar initiatives to clarify requirements are underway in the US and other regions (notably Canada), EFPIA do encourage harmonisation of such guidance with other regions.

EWP comment: *This guideline should primarily give a clear advice for the development of new inhaled products with known active substances in Europe. To which extent a world wide harmonisation seems to be possible can not be stated at the moment.*

2.) The scope of the guideline is somewhat unclear, as well as the title since the proposed draft guideline combines development of a NCE and demonstration of therapeutic equivalence in the context of abridged applications or variations/extensions to a marketing authorisation.

EWP comment: *From EWP point of view the scope is clearly stated in the ‘executive summary’. An additional hint is also addressed in the section ‘scope’. Fact, the guideline deals with ‘follow up’ products only. In case of NCE it is referred to other guidelines.*

3.) The title and scope refer to COPD whereas all other sections seem to only consider asthma except section 4.5 that includes a vague comment that “the above may not be appropriate in patients with COPD”. It is therefore recommended that clear identification of requirements for both concepts be made in the final document.

EWP comment: *There was a general consensus that it is unlike more difficult to conduct a sensitive pharmacodynamic study for a ‘hybrid’ product in COPD patients than in asthmatic patients. Therefore for currently marketed, inhaled products that are indicated both on asthma and COPD the usual way would be to conduct the pharmacodynamic study in asthmatic patients. For the whole marketing authorisation TE might only be demonstrated in one of the claimed patient population.*

4.) *In vitro* data alone may be sufficient to establish equivalence in some cases. However, both *in vitro* and clinical data should be taken into consideration on a case-by-case basis.

EWP comment: *If in vitro data is sufficient, no further clinical data (in vivo data) will be necessary. If in vitro data is not sufficient, in vivo data (pulmonary deposition studies and/or PD) is necessary to evaluate the influence of in vitro differences at clinic. From EWP point of view this point has already adequately reflected in the present version.*

5.) There is no specific statement (Section 4.2.2) that the test product must meet the same specifications that the reference product for delivered dose or particle size distribution, for a known active substance. Without these criteria it is possible to demonstrate *in vitro* comparability as defined but the test product parameters would not meet the reference product specifications.

EWP comment: *This issue has been clarified.*

6.) A requirement for safety standards in terms of impurities, extractables/leachables and microbiological testing should be included.

EWP comment: *The requested requirements have already been included in the Quality guideline (EMA/CHMP/QWP/49131/2005corr). A corresponding reference has been given in the final version of the guideline.*

7.) Different statistical limits for bioequivalence are used: in some cases a 95% CI is suggested and in others, a 90% interval. Classically a two-sided 90% CI is used to allow equivalence to be declared in bioequivalence evaluations. It is suggested that a two-sided 90% CI and the limits 0.8 to 1.25 is used throughout the document for *in vitro*, PK imaging and pharmacodynamic comparisons. However, it is to be noticed that this range is taken from standards for oral bioequivalence studies and could be considered very tight for oral inhalational products; currently even the FDA guideline does not state this requirement. It is thus debatable whether a new range with broader limits could be considered provided strong justification.

EWP comment: *The EWP partly agrees. For analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here it is expected that the 95% CI lies within the acceptance range of 0.8 to 1.25, unless other justified. One exemption has to be raised. For calculation of the relative potency the CI can be widened (please compare final version of the guideline).*

EGA:

1.) The EGA has already contributed to the public consultation on the "Recommendation on the need for revision of (CHMP) Points to Consider on the requirements for Clinical Documentation for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00)".

We therefore welcome the revision of the "Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)" (CHMP/EWP/4151/00 Rev.1).

Before discussing specifics of the guideline, EGA member companies would like to outline a very significant and pressing issue which would deserve careful evaluation by the EMEA CHMP or the CMD(h). In re-drafting this guideline a noticeable effect has been to undermine the confidence of assessors in assessing current applications and indeed for assessors to predict the outcome and pre-emptively implement changes.

It is worth noting that assessors have also begun to defer assessments and to hold back on completing assessments already begun, pending the outcome of this review. This is likely to leave applicants in a "regulatory vacuum" until Q3-2008 at the optimistic earliest.

EWP comment: *We are astonished about this modus operandi. Fact is most of the applications within the last two years have been rejected. Most of the rejections had been justified by lack of assay sensitivity. Therefore the CHMP recognised the need of action.*

2.) The EGA would urge the EMEA to provide the necessary guidance to assessors within the agencies on how best to manage the interim "vacuum" in guidance when assessing applications, as this has now become of paramount importance to the industry.

EWP comment: *The requested guidance to assessors within the agencies on how best to manage the interim "vacuum" is no matter of this revision process. In case of different opinions and addressed 'major objections' the further procedure should be discussed in the corresponding boards and commission case by case.*

3.) In addition to this important remark, the EGA would like to highlight five (5) areas where clarification is sought:

- The guideline suggests a stepwise approach and in effect a hierarchy of equivalence testing, i.e., from in vitro, PK, PD and TE studies.
It is to be acknowledged that this approach runs completely contrary to the current thinking whereby agencies have suggested that locally acting respiratory medicines needed TE (i.e., lung function endpoint studies) to show patient-delivery interaction.
In practice it remains to be clarified whether all agencies will pursue recognising the former studies as being capable of proving clinical equivalence or whether questions will be repeatedly raised whereby the clinical package will in effect become a combination of all the studies suggested. Particular attention should be given to the choice of words employed in order to limit the degrees of interpretation. The interesting emphasis in lines 262-263, for instance, presents an illustration of this: "[PK studies] **might** be considered as sufficient demonstration of therapeutic equivalence." EGA member companies believe acceptance of PK equivalence for safety and efficacy is fundamental and that requirements for long term safety studies in particular need to be reconsidered.

EWP comment: *We agree. This wording opens space for interpretation. However, equivalent lung deposition, which can be shown via PK studies as well as imaging studies, does not simultaneously imply equivalent safety. Additional investigations will be necessary. Furthermore, the final decision depends on the study. It is not possible to say 'is considered' (instead of 'might be considered'), because there are a lot of gaps and possibilities for major objections.*

TE has to be shown with regard to efficacy and safety and then there will be no basis for further requirements.

- As such, the guideline as it stands needs significant revision and editing to steer applicants judiciously rather than, as at present, consisting of a 'catch-all' document, listing non-validated studies that have been used in the past, such as scintigraphy or knemometry for example, but which are believed not to be commonly accepted by most agencies or assessors. The EGA suggests that specific reference to non-validated studies be removed from the guideline until their application has been proven. In the meantime, a reference to “a validated study methodology” could be considered in order to maintain a degree of flexibility in approach and to favour future advances from industry in this area.

EWP comment: *We do not really share this opinion. There is a lot of experience both with scintigraphical studies and knemometry surveys. Rejection would have been justified if the presented study/investigation has had major concerns.*

- It is also important to note that the existing originator medicinal products were registered based on study designs now considered potentially invalid by this guideline. This would place recent registrations of products such as Foster/Forair in question. Questions have also been raised about the potency of EU reference products. For example Foradil is a one-strength product that has been registered on the recognised plateau of dose-response curve and, as such, equivalence to this product cannot be demonstrated by a generic entrant where the guideline requires 'sensitivity' demonstration via a dose-response approach.

EGA member companies would welcome the EMEA position on this latter point.

EWP comment: *We agree. However it should always be considered the complete situation. Foradil is available in one strength, but there are other Formoterol powder formulations, which are marketed in several strengths. Therefore, the task of the company is to look for an adequate reference product. In special situations a national or European advice should always be sought. The basis of the mentioned new combination product (composed beclometasone and formoterol) was sensitive studies.*

- A decision tree (or flow chart) to suggest possible studies and approval routes under various situations would be a useful addition to the revised guideline. This is perceived as an essential tool to prevent differences in interpretation of the guidance by the various stakeholders.
A summary of each study type and clear rationale of their objectives would be useful.

EWP comment: *The EWP has discussed to add a decision tree to the course of action. Thanks for this hint. However, in the final version of the guideline, the main relevant aspects seem to be addressed. A summary of each study type and a clear rationale of their objectives would be beyond of the scope of this guideline. The final guideline has been created as precise as possible.*

EPAG:

1.) We believe that it would be most helpful and consistent if harmonisation with GINA guidance could be established.

Proposed change: It is important that these guidelines be harmonised with the GINA guidelines, e.g. age range and types of devices that can be used.

EWP comment: *We completely agree with this comment. However, GINA guidance is intended to give therapeutic recommendation. The here discussed guideline is intended to address requirements for the development of inhaled products with known active substances. Therefore, some differences may be possible. In general, the final version of the guideline should be in line with GINA guidance.*

2.) We note that the guidance does not refer to breath actuated pressurised metered dose inhalers.

Proposed change: The annex should refer to use of Breath-actuated pMDIs and that they may be used.

EWP comment: *This raised issue is solved in the final version of the guideline (please compare).*

3.) If a pressurised metered dose inhaler',

Proposed change: We recommend a change to If a non-breath actuated pressurised metered dose inhaler. Later in paragraph change to non-breath actuated pressurised metered dose inhaler.

EWP comment: *The terminology has been changed in the final version of the guideline.*

Innovata Biomed Limited:

1.) The CFC guidance on TE is of limited relevance due to its narrow scope (only applies to a change in propellant in pMDIs). IBL agrees that this new guideline covers wider range of recent formulation advances for inhaled products.

EWP comment: *Agreed.*

2.) The PtC contains partial guidance on the issues of TE, but also refers to the CFC guidance which will be of little relevance within a few years. The reference in the PtC to the CFC guidance should be removed. IBL agrees that the scope of the new guideline has been changed from the original focus of replacement of CFC propellants.

EWP comment: *Agreed.*

3.) Design recommendations in the current guidance are insufficient and contradictory: The study duration stated in the two documents is contradictory. The requirements for demonstration of TE should be more detailed. There is now evidence that some designs used in the past for demonstration of TE lacked assay sensitivity, but were compliant with current guidance. New guidance should contain specific recommendations for demonstrating assay sensitivity. Moreover, in situations where multiple indications are sought, the guidance should contain recommendations for these situations. More specific recommendations should be considered in relation to different drug classes (e.g. a distinction between short- and long-acting beta2 agonists, inhaled corticosteroids, anticholinergics) and combination products. Recommendations are necessary for products, where the dose strengths of the reference product are non-linear.

Innovata Biomed Limited believes the new draft guidance is still contradictory. The guideline and the Scientific Advice received by IBL suggest that a Bioequivalence (BE) approach is preferred for clinical trial design. IBL notes that the paediatric Appendix 1 refers to a demonstration of therapeutic equivalence (TE) as part of its criteria. It appears that the main body of the guideline and Appendix 1 were written from two differing perspectives, which do not agree with each other. Innovata Biomed believes this inconsistent approach in the two documents requires clarification.

EWP comment: *The EWP can not really share this view. However, based on all received comments, the guideline was intensively updated. The paediatric topic has been included in the main part of the guideline. It was tried to remain as concrete as possible / necessary in the final version of the guideline. Therefore, we hope that any confusion is avoided now.*

4.) There is a need for updating the requirements in relation to the use of spacers in specific populations. For example, a named spacer should be used in the clinical studies in accordance with the guideline on pharmaceutical documentation of inhalation products. Whilst this point does not directly affect Innovata Biomed Limited, as developers of dry powder inhalers, it is acknowledged that this is confusing in the market place and is addressed in the draft guideline.

EWP comment: *Agreement. No further comment to this statement.*

5.) The title should reflect the main issues of the guideline (i.e. considering a restriction of the guideline for hybrid applications of OIPs in the treatment of asthma and COPD). Whilst the title has been amended, this is not clearly reflected within the main body of the draft guideline. IBL believe the guideline would be improved by separately addressing each application type (i.e. new products, line extension, variations within the guideline).

EWP comment: *The guideline is not intended to address recommendations for new active substances. This is clearly stated in the guideline. This guideline gives recommendation on the testing for therapeutic equivalence, the different requirements for the different types of line extensions, variation etc. are explained elsewhere and are beyond the scope of this guideline. Therefore, the scope of this guideline should be clearly defined.*

6.) The PtC should clearly distinguish between requests for hybrid applications, variations and line extensions. As noted in the section above, IBL believe this aim has not been achieved. IBL believes that a clear summary table, based upon the degree of pharmaceutical match, would be a useful addition to section 4.2 of the guideline. In our Scientific Advice procedure, the CHMP agreed with our interpretation as presented in this summary table, that the revised draft OIP guideline appears to provide a stepwise approach to clinical study design and MAA route based on the level of pharmaceutical equivalence demonstrated to the reference product. We believe this can be summarised as:

Option	Match to Pharmaceutical Equivalence Criteria Presented in OIP Guideline (4.2.2)	Type of <i>in vivo</i> data to be presented	MAA
1	All criteria met	Only comparative <i>in vitro</i> data required. No <i>in vivo</i> data required.	According to Directive 2004/27/EC, Article 10(2b) "Generic".
2	Most, but not all, criteria met	Comparative <i>in vitro</i> data and results from <i>in vivo</i> studies of PK/PD based "Bioequivalence" type design, abridging to the efficacy data of the reference product.	According to Directive 2004/27/EC, Article 10(3) "Generic hybrid".
3	Fewer criteria met	Comparative <i>in vitro</i> data and results from <i>in vivo</i> studies of PK/PD type design supplemented with traditional "Therapeutic Equivalence" type designed to assess the differences highlighted in both the pharmaceutical and PK/PD assessments.	According to Directive 2004/27/EC, Article 10(3) "Generic hybrid".
4	Limited criteria met	Comparative <i>in vitro</i> data and results from <i>in vivo</i> studies of traditional "Therapeutic Equivalence" type designed to compare the product against the individual substances and placebo (in line with fixed combination guideline).	According to Directive 2004/27/EC, Article 10(b) "Fixed Combination".

In summary, an assessment of the pharmaceutical data should be performed in the first instance, followed by investigation of the extent of pharmacokinetic (PK) equivalence. Additional clinical studies should then only be performed after the PK data are available and only in order to address any specific issues raised where differences in the *in vitro* or PK equivalence occur. We believe this simple summary removes ambiguity.

EWP comment: *EWP agrees that the guideline recommend a stepwise approach. However, the tabled summary does not quite reflect what is concluded in the guideline. The question of the corresponding legal basis has been not finally solved.*

7.) Finally, it is clear from our Scientific Advice letters that matching the reference medicinal product closely in terms of *in vitro* parameters is key to influencing the clinical study design i.e. CHMP expect if both products are an *in vitro* match then *in vivo* equivalence should be observed with PK/PD studies. Whilst this is desirable for the patient and regulatory agencies patents and Intellectual Property may hinder this aspiration.

EWP comment: *Agreed.*

IPAC-RS:

1.) The recommendations in the guideline are quite stringent regarding ICS bridging, especially in light of the lack of clinical assay sensitivity for ICS dose-response. Moreover, the recommended approaches [e.g., the selection of patients that have demonstrated an ICS dose-response at screening; and the need to demonstrate dose-response in the same study for different strengths of LABA/ICS combinations] have no precedent in the literature. These CHMP proposals may, therefore, be premature to include in a guideline.

EWP comment:

Some such studies were conducted successfully in the past. The main challenge in this matter is the method of patient's recruiting, however we discuss about a frequent and chronic disease. Furthermore, clinical studies would be the last step. At the beginning, the applicant should try to show equivalence in vitro and/or in vivo via Imaging/ PK studies. If this procedure was not successful, PD studies would be necessary.

2.) Some of the terminology used in the guideline is not consistent with existing regulatory documents. Instances of inconsistent terminology are highlighted at the end of these Comments.

EWP comment:

Many thanks for this comment. We have been thinking about this. Please compare the final version of the updated guideline.

Pfizer:

1.) Some of the terminology used in the guideline is not consistent with existing regulatory guidelines. Instances of inconsistent terminology are included within our comments.

EWP comment:

Many thanks for this comment. We have considered this concern.

2.) There appears to be an opportunity to introduce a decision tree as a part of the guideline. The use of a decision tree would be a benefit to sponsors.

EWP comment: *The EWP has discussed to add a decision tree to the course of action. Thanks for this hint. However, in the final version of the guideline, the main relevant aspects seem to be addressed. A summary of each study type and a clear rationale of their objectives would be beyond of the scope of this guideline. The final guideline has been created as precise as possible. The EWP got similar comments from some other institutions.*

3.) Pfizer welcomes the opportunity for further discussion on this subject, particularly the Key Comments (below), and respectfully requests an Interested Parties meeting led by the EWP.

EWP comment:

We understand the need of the proposed meeting by the industry. However was not possible to manage such one within the tight timeline of this revision process. However, members of the group are open for participating on meetings and on relevant congresses. Hopefully, crucial points can be discussed and clarified. Furthermore, in case of concrete questions to a certain procedure there will be always the possibility to seek for a central or national scientific advice.

Roche Products Limited:

1.) Demonstrating therapeutic equivalence is a difficult problem in terms of trial design and statistical issues yet no consideration seems to have been given to the statistical aspects. No references to important statistical guidelines (including one specifically on choosing equivalence margins) is given and, indeed, the way the acceptable margin is specified seems to contradict guidance on specification of margins (CPMP/EWP/2158/99).

EWP comment: *A reference to the choice of non-inferiority guideline has been added. However, it should be kept in mind, that the guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99) can not primary transferred to TE with OiP's, because the OIP guideline requires equivalence and not non-inferiority. However, the guideline on choice on non-inferiority margin is relevant to the choice on equivalence margins.*

2.) When listing other relevant guidelines, the document should include ICH E10 and the Guideline on the choice of the non-inferiority margin. It is suggested to add: CPMP/ICH/364/96 Choice of control group and related issues in clinical trial; CPMP/EWP/2158/99: Guideline on the choice of the non-inferiority margin.

EWP comment: *Both guidelines have been added in the final version of the guideline.*

TEVA:

1.) There are a number of recommendations made in the guideline on demonstration of therapeutic equivalence (e.g. *in-vitro* data only, or pulmonary deposition using imaging and PK studies only, or pharmacodynamic studies). However, the overall decision path is not very clear and a decision tree describing the overall recommendations including each of the criteria applied would be highly recommended.

EWP comment: *The implementation of a decision tree for determining which studies are needed under which circumstances was intensively discussed by the EWP. A decision tree does also open the possibilities of confusing, because not all pros and cons can be reflected simply in such a decision tree. Therefore, it was tried to be as concrete as possible/necessary in the final version of the guideline.*

2.) With respect to demonstration of sensitivity of a study, the guideline requires a minimum of two dose levels to show dose-response, but it is not clear what is considered to be an acceptable demonstration of a dose response and if other alternatives could be considered especially since demonstrating dose response has been challenging for both ICS and beta-agonists.

EWP comment: *The guideline based on the experiences and critical considerations of the European assessors. The proposed approaches are deemed the only possibility to ensure sensitive studies. However the relevant sections have been comprehensively modified (please compare). Please take also into account the hierarchical system.*

Vectura Limited:

It is clear that matching the reference medicinal product closely in terms of *in vitro* parameters is key to influencing the clinical study design i.e. CHMP expect if both products are an *in vitro* match then *in vivo* equivalence should be observed with PK/PD studies. This approach is desirable for the patient and regulatory agencies and Vectura Ltd is in favour of it.

We believe that the guideline should include additional clarification on each application type, i.e. new products, extensions, variations and follow on/generic applications separately. In particular the degree of pharmaceutical match and the requirements for a supporting clinical package would be a useful addition.

EWP comment: *The guideline is not intended to address recommendations for new active substances. This is clearly stated in the guideline. This guideline gives recommendation on the testing for therapeutic equivalence, the different requirements for the different types of line extensions, variation etc. are explained elsewhere and are beyond the scope of this guideline.*

2.) We would welcome a diagrammatic representation of the recommendations in the guideline in order to emphasise the stepwise approach to product development.

EWP comment: *The implementation of a decision tree for determining which studies are needed under which circumstances was intensively discussed by the EWP. A decision tree does also open the possibilities of confusing, because not all pros and cons can be reflected simply in such a decision tree. Therefore, it was tried to be as concrete as possible/necessary in the final version of the guideline.*

3.) We are concerned that the guideline appears to support exact *in vitro* matching to a reference product. This approach does not allow for development of a product with a more favourable risk/benefit profile, e.g. a follow-on DPI that is less flow rate dependent than the reference product; or one where the *in vitro* differences may not have a therapeutic or safety implication. In addition Vectura Limited disagree that follow-on products should be adapted to a non-linear reference product if a linear product range is more therapeutically appropriate.

EWP comment: *The EWP likes to draw the attention to the fact that the guideline is addressing requirements for hybrid applications. Efficacy and safety should always be considered jointly. In case of improved efficacy and/or reduced safety we see open issues with the recommended doses. Normally, if efficacy was improved a dose-reduction would be needed. The informative texts of the test product can't be adapted for those of the reference product. Therapeutic equivalence would not be given. If it is the intention of the company to apply for a superior product an application with reference to Art.8 of the directive 2001/83/EC will be an option.*

4.) The guideline suggests that both 8 and 12 weeks study durations would be acceptable with suitable justification. Clarification is sought on which study duration might usually be expected together with the type of justification that would be considered acceptable.

EWP comment: *Sensitive studies are required. For example, if an 8 weeks bronchodilating study is sufficient to show TE in a sensitive way then the study will be accepted.*

5.) With regards to the safety designs included, Vectura Limited believes that use of knemometry and the synacthen test are not sufficiently sensitive to use for comparison purposes for follow-on products. The ability to detect differences between products /doses using knemometry is questioned. In addition, the use of the synacthen test requires repeated venepuncture, which may not be acceptable for many patients.

EWP comment: *There is a lot of experience with knemometry surveys. The paragraph with regard to ICS safety has been intensively amended.*

6.) Vectura Limited support comments by EPAG agreed at a meeting held in Cambridge in March 2008 which will be submitted separately.

EWP comment: *The EWP took this comment into account.*

Schering Plough:

1.) There is a disconnect between the stated scope of the document and some of the content. The draft includes guidance that is not related to the demonstration of therapeutic equivalence of two inhaled products and although there is some 'soft' wording in both the scope and title, the document is confusing and difficult to read because of the different types of guidance that it contains.

EWP comment: *The EWP took this comment into account. The draft version of the guideline was revised.*

2.) Since the Scope makes reference to existing guidance documents for OIPs containing NCEs, it should be ensured that the guidance documents are consistent, and the new guidance does not raise the barrier for NCEs.

EWP comment: *This guideline is dealing with hybrid products only. The requirements for NCE are not discussed within this guideline. Furthermore any barrier for the approval for NCE can not be realised. The scope of this guideline is clearly stated.*

3.) Should have consistent use of terms 'reference product' vs. 'comparator' vs. 'authorised product'. We prefer Reference Product - which should be defined

EWP comment: *The EWP took this comment into account. The term 'reference product' has been explained in the annex 'definition'.*

SPECIFIC COMMENTS ON TEXT		
EXECUTIVE SUMMARY		
Line no. ¹ + paragraph no.	Comment and Rationale	Outcome
2	<p>EFPIA / Pfizer:</p> <p>Whilst it is clear that the main focus of the guidance is clinical strategies for abridged applications it should be recognised that the approaches presented are equally applicable to supporting pharmaceutical and device changes that occur during development of new oral inhalation products.</p>	<p>EWP comment:</p> <p><i>The scope of this guideline is clearly addressed. The development of NCE is not included.</i></p>
2-7	<p>EFPIA:</p> <p>EMA/CHMP/QWP/49313/2005corr references ‘Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products’. However, since CPMP/EWP/4151/00 will supersede the points to consider document and will not cover nasal products. EMA/CHMP/QWP/49313/2005corr will need to be updated when this one (CPMP/EWP/4151/00) is finalised.</p>	<p>EWP comment:</p> <p><i>The EWP sees your point. However it is not the matter of the current discussion in frame of this guideline.</i></p>
4	<p>EFPIA:</p> <p>“For abridged applications”: this term is not an official term for classification of applications in EU. Therefore it is strongly recommended to use in addition, the terminology as used in the Directive 2001/83/EC, throughout the whole guideline.</p> <p>Proposed change: “e.g. Art.10(1), Art. 10(3) and Art. 10(4) applications, Directive 2001/83/EC, as amended”.</p> <p>IPAC-RS:</p> <p>“...abridged applications” is not an official term for the classification of applications in the EU. It is strongly recommended to use the terminology used in the Directive 2001/83/EC.</p>	<p>EWP comment:</p> <p><i>The legal basis is adequately mentioned. Furthermore, ‘abridged application’ is a well-known accepted terminology. There is no need of any change.</i></p>

¹ Where applicable

	Proposed change: Use the terminology of Directive 2001/83/EC: Art.10(1), Art. 10(3) and Art. 10(4) applications.	
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1. INTRODUCTION (background)		
Line no. ² + paragraph no.	Comment and Rationale	Outcome
9-10	<p>EFPIA: This guideline is stated to describe the clinical requirements for inhalation products further to the pharmaceutical considerations laid down in EMEA/CHMP/QWP/49313/2005corr. Nasal products are not covered by CPMP/EWP/4151/00. Thus, it is recommended to update lines 9-10 to clarify the scope. Proposed change: “This guideline describes the clinical requirements for inhalation products <u>for orally inhaled products (OIP) used in the treatment of asthma and chronic obstructive pulmonary disease (COPD)</u>, further to the pharmaceutical considerations laid down in the CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products EMEA/CHMP/QWP/49313/2005corr.”</p> <p>IPAC-RS: This guideline is stated to describe the clinical requirements for inhalation products further to the pharmaceutical considerations laid down in <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u>. However, nasal products are not covered by CPMP/EWP/4151/00. Proposed change: Change lines 9-10 to: “This guideline describes the clinical requirements for inhalation products <u>for orally inhaled products (OIP) used in the treatment of asthma and chronic obstructive pulmonary disease (COPD)</u>, further to the pharmaceutical considerations laid down in the CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</p>	<p>EWP comment: <i>This would be an unnecessary repetition. Therefore the proposed wording will not be taken over.</i></p>

² Where applicable

	EMA/CHMP/QWP/49313/2005corr.”	
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2. SCOPE		
Line no. ³ + paragraph no.	Comment and Rationale	Outcome
21 - 24	<p>EFPIA/ IPAC-RS / Pfizer:</p> <p>The guidance states that it “will address specific issues of relevance to inhaler devices but may not be able to offer complete guidance on every aspect of the clinical documentation for the product.” However, no indication is given to the pathway an applicant should take where an approach is out with the guidance. A suggested addition is thus recommended.</p> <p>Proposed change: <i>“In cases where an approach other than that outlined in the guidance is proposed then an applicant is encouraged to seek scientific advice”.</i></p>	<p>EWP comment:</p> <p><i>Agreed. A corresponding wording has been implemented.</i></p>
30 - 36	<p>EFPIA:</p> <p>It is not clear why pMDIs are separated into pMDIs, pMDIs with spacers in this list. The same comments apply as well to DPIs. The term “non-pressurised, pump activated, liquid reservoir metered dose inhalers” is not identical to the term used in “<i>EMEA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</i>”, where such products are named as “non-pressurised metered dose inhalers”. It is thus recommended for consistency reasons to use the wording of “<i>EMEA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</i>”.</p> <p>Proposed change: It is thus suggested to reword as proposed:</p> <ul style="list-style-type: none"> • pressurised metered dose inhalers, <i>with spacer devices and holding chambers</i> • pressurised metered dose inhalers with spacer devices and holding chambers • breath-operated inhalers 	<p>EWP comment:</p> <p><i>Agreed. Proposed wording have been implemented in a slightly modified version (please compare final version of the guideline).</i></p>

³ Where applicable

	<ul style="list-style-type: none"> • non-pressurised, pump activated, liquid reservoir metered dose inhalers • dry-powder inhalers using a reservoir and metering mechanism <u>or a pre-dispensed dose</u> • dry powder inhalers using a pre-dispensed dose solutions and suspensions for nebulisation 	
32	<p>IPAC-RS: “Breath-operated inhalers” is a confusing category. Proposed change: Either delete or replace with “breath-triggered inhalers” and provide a definition, e.g., “an inhaler for which the patient needs to generate a minimum (trigger-point) airflow value in order for the inhaler to release aerosol”.</p>	<p>EWP comment: Thanks. Breath-operated inhalers are defined in the glossary.</p>
33	<p>IPAC-RS: The term “non-pressurised, pump activated, liquid reservoir metered dose inhalers” is different from the term used in <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u>, where such products are named as “non-pressurised metered dose inhalers” Proposed change: Use the terminology of <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u> for consistency reasons.</p>	<p>EWP comment: Agreed. An amendment has been implemented.</p>

3. LEGAL BASIS		
Line no. ⁴ + paragraph no.	Comment and Rationale	Outcome
40; 47-8 + 3.	<p>Orion Pharma: The present guideline is proposed to be seen as additional to the NfG <i>Replacement of CFCs in metered dose inhalation products</i></p>	<p>EWP comment: There are pros and cons for implementation of a reference to the CFC directive. Currently, the CFC-replacement guideline is still active, and</p>

⁴ Where applicable

	<p>(CPMP/III/5378/93-Final). The latter guideline is 15 years old, somewhat outdated, and several provisions are discrepant with those given in the present guideline. Therefore it should no longer be maintained as “active”. Rather, the provisions that are still relevant should be included in the present guideline (excluding the pharmaceutical requirements now detailed in EMEA/CHMP/QWP/49313/2005corr).</p> <p>Proposed change: We propose that CPMP/III/5378/93-Final is superseded by the present guideline; lines 47-8 should be deleted.</p>	therefore the reference is legal.
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4.1 INHALATION DEVICES AND CLINICAL REQUIREMENTS		
Line no. ⁵ + paragraph no.	Comment and Rationale	Outcome
56-57	<p>EFPIA/ IPAC-RS:</p> <p>Non-pressurized metered-dose inhalers should also be mentioned in this sentence, as they constitute a distinct class of inhalers in “<i>EMEA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</i>”. Also, the flow dependent deposition pattern does not only differ among inhaler classes, but also among different inhaler types and formulations (i.e. products) within one class.</p> <p>In order to avoid a definitive statement, the word “have” should be replaced by “typically have”.</p> <p>It is thus suggested to reword as proposed: Change to read: “Propellant-containing pressurized <i>and non-pressurized</i> metered dose inhalers, dry powder inhalers and nebulisers <i>typically</i> have different flow-dependent pulmonary deposition patterns, <i>as well as different products within the same inhaler class.</i>”</p>	<p>EWP comment:</p> <p><i>Agreed. Proposed wording has been implemented in a slightly modified version.</i></p>
56-59	<p>EFPIA/ IPAC-RS:</p> <p>Section 4.1 describes factors which impact the patient use of a device</p>	<p>EWP comment:</p> <p><i>The aspect has been already changed. Please compare the final version.</i></p>

⁵ Where applicable

	and hence require addressing in the clinical documentation. A suggested rewording is thus proposed: “Therefore some general considerations concerning the requirements for clinical documentation in respect of <u>to support patient handling of new/ different</u> these devices are presented below”.	
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4.1.1 Pressurised metered dose inhalers		
Line no. ⁶ + paragraph no.	Comment and Rationale	Outcome
61-62	EFPIA/ IPAC-RS: It is suggested that the scope be wider than just the valve as the whole delivery system or the container closure system may influence performance. Proposed change: “Pressurised metered dose inhalers (pMDIs) contain different propellants and other excipients, and may use different valve systems <u>delivery systems or container closure</u> systems, all of which may result in differing clinical outcomes.”	EWP comment: <i>Agreed. Proposed wording has been implemented in a slightly modified version.</i>
64	EFPIA / Pfizer: Do spacers really <i>remove</i> the need for coordination or just mitigate it? The use of breath-operated devices does not completely “remove” the need for coordination of breathing during the use of an inhaled product. It is suggested to change “remove” to “mitigate” or “lessen” or “reduce”. Proposed change: “Breath-operated devices and spacing devices remove <u>reduce</u> the need for such co-ordination.”	EWP comment: <i>Agreed. Proposed wording has been implemented in a slightly modified version.</i>
64	Pfizer: Are spacing devices really considered <i>necessary</i> for all pMDIs or just for those which are indicated for populations which require spacers? The scope of this statement seems to be too broad and, as such, should be qualified.	EWP comment: <i>All in all, “spacers are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.” There is no need of any major amendment.</i>

⁶ Where applicable

	<p>Proposed change: Add details around specific situations where spacers are actually necessary i.e., high dose ICS, paediatrics and elderly population.</p> <p>Schering Plough: “Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.” This statement is not supported by evidence or clinical practice. while spacers may be useful in particular circumstances e.g. for patients who have difficulties with coordination or patients trying to reduce the probability of topical side effects from inhaled corticosteroids, there is no evidence that spacers increase efficacy in general. Some spacers increase systemic absorption for certain drugs, e.g. inhaled corticosteroids with high first pass metabolism. Spacers can be bulky and interfere with the desire of many patients to use their inhaler without making it obvious to surrounding people.</p> <p>Proposed change: The line should be amended to “Spacing devices are used with MDIs when use by patients who have difficulty coordinating the actuation with inspiration of breath (e.g., younger children and some elderly patients).”</p>	
64-65	<p>EFPIA: The term “spacing devices” is used throughout the guideline. We suggest using “spacer” rather than “spacing device” to be consistent with EMEA/CHMP/QWP/49313/2005corr. The statement “Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.” is inconsistent with the CHMP Reflections Paper on Paediatric Formulations which indicates that children can be taught to use breath operated MDIs. In addition, we do not the requirement to always use a pMDI in children to be relevant especially as the ages are not defined. A large proportion of children, particularly older children have a similar ability as adults to use a pMDI without a spacer. It should also be taken into consideration that portability and on demand/rescue use of pMDIs is more convenient if a spacer is not used. Finally, it is difficult to see</p>	<p>EWP comment: <i>EWP agrees with the benefit of a spacer outlined in the proposed wording. The EWP has also noticed slight differences between the mentioned Appendix III of the Guideline on Pharmaceutical Quality of Inhalation and Nasal Drug Products and the here discussed guideline. However the use of spacers in relevant populations is deemed necessary. However, the raised aspect has been rewritten in the final version of the guideline (please compare).</i></p>

	<p>how/why this requirement should be included for breath-actuated devices, which normally would be used without a spacer. A rewording is thus proposed.</p> <p>Proposed change: “Spacing devices <i>Spacers</i> are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child. <u><i>Recommended for patients who find coordination of actuation of the pMDI with inspiration of breath difficult, for example younger children and some elderly. They may also reduce the amount of medical product deposited in the mouth and pharynx.</i></u>”</p> <p>IPAC-RS: The statement “<i>Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.</i>” is inconsistent with the <u>CHMP Reflections Paper on Paediatric Formulations</u> which indicates that children can be taught to use breath operated MDIs. While spacers may be useful in particular circumstances, e.g., for patients who have difficulties with coordination or patients trying to reduce the probability of topical side effects from ICS, there is no evidence that spacers increase efficacy in general. Moreover, some spacers increase systemic absorption for certain drugs, e.g., inhaled corticosteroids with high first pass metabolism.</p> <p>Proposed change: Ensure consistency between this guideline and the <u>CHMP Reflections Paper on Paediatric Formulations</u>. The need for a spacer should only be required where a specific product type (e.g., a high-dose steroid) is indicated for specific patient populations (e.g., children), as recommended in Appendix III of the <u>Guideline on Pharmaceutical Quality of Inhalation and Nasal Drug Products</u>. Change to “<i>Spacing devices are recommended for use with pMDIs and should be especially considered when a pMDI is used by a child.</i>”.</p> <p>Pfizer: The statement “Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.”</p>	
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	<p>is inconsistent with the CHMP Reflections Paper on Paediatric Formulations which indicates that children can be taught to use breath operated MDIs.</p> <p>Proposed change: Ensure consistency between this guideline and the <i>CHMP Reflections Paper on Paediatric Formulations</i>. The need for a spacer should only be required where the product is indicated for specific patient populations (e.g. children, high dose steroids) as indicated in Appendix III of the <i>Guideline on Pharmaceutical Quality of Inhalation and Nasal Drug Products</i>.</p> <p>TEVA:</p> <p>Assertion that all pMDIs must be used with spacers is too broad and restrictive. Spacers are of demonstrated benefit for reducing oropharyngeal deposition of corticosteroids to limit side effects and for helping patients unable to coordinate inhalation with actuation. Spacers are both inconvenient for the patient to carry in addition to the inhaler, as well as being a disincentive to inhaler use (more complicated, bulky, draws more attention to the patient who may be self-conscious about using an inhaler in public, and costly). Apart from the evaluation of corticosteroids and perhaps other inhaled products in paediatric populations, it should be explicitly stated that spacers are not necessary for evaluating inhaled products in the adult and adolescent populations.</p> <p>Proposed change: “Spacing devices are only considered necessary for evaluating a specific pMDIs (e.g. containing steroids) in a particular patient population (e.g., children).”</p>	
65-68 (as well as 101-103)	<p>EFPIA:</p> <p>It is stated that “spacing devices are considered necessary for use with all pMDIs”, and that “development of all pMDI-s should always include the testing of at least one specific named spacing device”. It is difficult to see how/why this requirement should be included for breath-actuated devices, which normally would be used without a spacing device.</p> <p>Proposed change: Remove these requirements, or change line 101-103 to “development of <u>a non breath-operated pMDI</u> should always include the testing of at least one named spacing device”</p>	<p>EWP comment:</p> <p><i>Agreed. The nomenclature has been changed.</i></p>

	Change line 66 to “ <i>For non-breath-operated pMDI-s</i> , appropriate data to support use of a specific named spacing device...”	
69-74	<p>EFPIA / IPAC-RS:</p> <p>This paragraph outlines the requirements when a new propellant or excipient is introduced. New (‘novel’) propellants or excipients should be fully characterised.</p> <p>Reference should be made in the Introduction to the guideline on replacement of CFCs.</p> <p>An additional statement is thus proposed.</p> <p>Proposed change: “In the event that the replacement contains a new propellant (excipient) not previously authorised, the provisions of Directive 75/318/EEC as amended, apply.”</p>	<p>EWP comment:</p> <p><i>The EWP can not agree in this aspect. If all European countries finalize the replacement process (e.g. Germany had been finalized this process for 2 years), the mentioned ‘Replacement Directive’ will be removed. This is expected in near future.</i></p>
69-74	<p>EGA:</p> <p>If the new excipients are well known and have been used in other inhalation products without any documented problems, extended safety data in animals or patients should not be needed.</p> <p>Proposed change: “Generation of extended safety data may be necessary, <u>unless the new propellant or excipient are well known and have been used in other inhalation products without documented problems. When applicable</u>, in respect with safety [...] must be sought.”</p>	<p>EWP comment:</p> <p><i>Please read the complete paragraph. ‘When a new propellant or excipient is introduced into a pMDI the possible impact on clinical efficacy and safety must be studied in addition to any toxicological and preclinical programme (see section 4.7).’ We do not demand toxicological data about well-known excipients.</i></p> <p><i>Furthermore, it should be distinguished between new excipients (see section 4.7) and differences between test and reference product with regard to the excipients. However, adequate data are always expected</i></p>
72	<p>IPAC-RS:</p> <p>The term “<i>inhalation induced bronchoconstriction</i>” may be preferable to “<i>paradoxical bronchospasm</i>” since the document covers also non-bronchodilator drugs.</p> <p>Proposed change: More clarity is needed around the definition and required tests for this condition.</p> <p>Schering Plough:</p> <p>The term “<i>inhalation induced bronchoconstriction</i>” may be preferable to</p>	<p>EWP comment:</p> <p><i>The term “‘paradoxical bronchospasm’ is well accepted. Furthermore this side effect is observed not only after inhalation of bronchodilator drugs but also after inhalation of non-bronchodilator drugs. The proposed wording “inhalation induced bronchoconstriction” reflects the cause of bronchoconstriction, correctly. However the current version is generally accepted and has been used in all informative texts/dossiers.</i></p>

	<p>"paradoxical bronchospasm", in particular since the document covers also non-bronchodilator drugs.</p> <p>Proposed change: Revise "paradoxical bronchospasm" to "inhalation induced bronchoconstriction."</p>	
72-74	<p>TEVA:</p> <p>The reference to bronchial hyper-reactivity (paradoxical bronchospasm) and mucociliary clearance has been carried over from the old guidelines on replacement of CFC by HFA propellants in pMDIs and BOIs but information on well-validated methods to test these phenomena is needed, as well as their relevance to clinical situations. There is considerable uncertainty over the relevance of these statements as they stand and, of equal importance, no guidance on how they are to be evaluated has been provided.</p> <p>Proposed change: A more specific definition and more specific guidance on what tests are to be carried out is required. If the reference product does not show the evidence of bronchial hyper-reactivity (paradoxical bronchospasm), with respect to local tolerability, is it really necessary for a generic product to show the evidence, assuming the formulation, including excipients have not changed?</p>	<p>EWP comment:</p> <p><i>Please count the cough attacks immediately after inhalation.</i></p>
73-74	<p>EFPIA:</p> <p>It is unclear how "any effect that the new propellant or excipient may have on mucociliary clearance" should be assessed.</p> <p>Proposed change: Add clarification on how to assess this.</p>	<p>EWP comment:</p> <p><i>The EWP can not see a need of further clarification. This aspect would be beyond the scope to guideline and has been already clarified elsewhere.</i></p>

4.1.1.1 Breath-operated inhalers		
Line no. ⁷ + paragraph no.	Comment and Rationale	Outcome
76	IPAC-RS:	EWP comment:

⁷ Where applicable

	<p>The European Respiratory Society recommends the terms PIF and PEF instead of PIFR and PEFR.</p> <p>Proposed change: Consider harmonizing terminology with that used by ERS.</p> <p>Schering Plough:</p> <p>The European Respiratory Society recommends the terms PIF and PEF instead of PIFR and PEFR.</p>	<p><i>Could be amended, however it seems to be only a stylistic matter. Other institutions and stakeholders talk about PEFR and PIFR. This should be not a matter of discussion.</i></p>
76-91	<p>IPAC-RS:</p> <p>Clarity is needed around the minimum PIF rates applicable and acceptable in different situations (e.g., children, the elderly, asthma or COPD, acute emergency use / prophylactic use). (see also line 130-147)</p> <p>Proposed change: This topic is one that would benefit from further discussion and consensus by industry and regulatory experts. We recommend the use of an Interested Parties meeting, led by the EWP, to discuss this topic and others before finalization of the guideline.</p>	<p>EWP comment:</p> <p><i>Minimal PIF is dependent on the device that is used. Therefore no generally applicable PIF can be outlined in a guideline.</i></p> <p><i>We understand the need of the proposed meeting by the industry. However was not possible to manage such one within the tight timeline of this revision process. However, members of the group are open for participating on meetings and on relevant congresses. Hopefully, crucial points can be discussed and clarified. Furthermore, in case of concrete questions to a certain procedure there will be always the possibility to seek for a central or national scientific advice.</i></p>
76-91 (& 130-147)	<p>TEVA:</p> <p>What are the minimum PIF rates applicable and acceptable in different situations? (E.g. children, the elderly, asthma or COPD, acute emergency use / prophylactic use). PIFR will vary widely in all these situations and to be able to guarantee that a BOI / DPI will always work in all members of a patient subgroup cannot be predicted from a clinical trial. In addition, this has not been an approval requirement for any existing inhaled product. Such parameters need to be specified in advance of any clinical development programme (if necessary based on a consensus of literature sources and the <i>in vitro</i> flow rates necessary to trigger the specified BOI / DPI device). These PIFR need to be agreed between a regulatory authority and a pharmaceutical company in advance of any clinical trial to avoid misunderstandings later.</p> <p>Since the effect of the relevant flow rate on individual stage particle size</p>	<p>EWP comment: <i>This issue has been comprehensively covered in the guideline! (Submit in vitro data about clinically relevant pressure drops/flow limits and define the appropriate patient population.)</i></p> <p><i>It should be noted that a small amendment has been implemented. (MA for DPIs with high flow rate dependency can only be granted for use in the patient populations studied in the clinical programme.)</i></p>

	<p>distribution and the delivered dose is fully investigated as per the guideline (EMA/CHMP/QWP/49313/2005 Corr), is it still necessary to demonstrate the minimum PIFR in a clinical study?</p> <p>Proposed change: The clinical relevance of the minimum PIFR should be discussed and there is a need to specify exactly what is required to address the issue.</p> <p>In order to establish the minimum PIFR, the following approach should be considered :</p> <p><u>First step:</u> an <i>in-vitro</i> study (on aerodynamic particle size distribution, fine particle dose and the delivered dose) is fully investigated with a range of flow rates (e.g. typically 30L/min, Q and 90 L/min). This should ensure the performance of the device by across the patient populations intended to use the device.</p> <p><u>Second step:</u> only when the <i>in-vitro</i> study results show that there are differences between the test and the reference products, and there is a high flow-rate dependency in their performance, would a patient study designed to establish the achievable flow rates in different patient groups be appropriate.</p>	
76-91	<p>Siegfried Pharma Development GmbH:</p> <p>As also dry powder inhalers may be breath triggered it may be better that section 4.1.1.1 is not a subsection of 4.1.1 MDIs.</p> <p>Proposed change: Make section 4.1.1.1 a section of its own (after 4.1.2 DPIs) and clarify what types of devices it applies to.</p>	<p>EWP comment:</p> <p><i>A small amendment has been implemented.</i></p>
76-91	<p>Siegfried Pharma Development GmbH:</p> <p>Since the patient's ability to trigger the BOI is independent of the formulation (as no formulation is delivered before the release of the trigger) these studies may be performed with empty/placebo devices.</p> <p>Proposed change: Clarify that use of empty/placebo devices is acceptable.</p>	<p>EWP comment:</p> <p><i>A small amendment has been implemented.</i></p>
84-86	<p>EFPIA:</p> <p>The statements on lines 84-86 are not clear. While it is important to demonstrate that patients can generate a flow rate needed to activate a</p>	<p>EWP comment:</p> <p><i>The wording has been changed (please compare final version of the guideline). The contestable sentence has been removed.</i></p>

	<p>breath-operated inhaler (BOI), the ability to generate a specific flow rate does not seem applicable to the pMDI. It is not clear why a patient would need to generate the same flow rate for a BOI as for a pMDI. The last part of the sentence refers to triggering of the BOI, and is covered by the preceding paragraph; “triggering” of the pMDI is not relevant in this context.</p> <p>Proposed change: “....that the target populations can generate the same flow rate through the BOI and <u>as through</u> the pMDI and therefore that all patients can trigger both devices successfully.”</p>	
85	<p>Pfizer:</p> <p>The term “generate the same flow rates through the BOI and pMDI” is confusing. Do we really generate flow rates <i>through</i> a pMDI.</p> <p>Proposed change: Remove reference to pMDI.</p>	<p>EWP comment:</p> <p><i>The wording has been amended.</i></p>
87-91	<p>EFPIA / Pfizer:</p> <p>The intent of this paragraph is unclear and should be re-worded to clarify the CHMP position.</p>	<p>EWP comment:</p> <p><i>This paragraph has been re-worded (please compare final version of the guideline).</i></p>

4.1.1.2 Spacing devices and holding chambers		
Line no. ⁸ + paragraph no.	Comment and Rationale	Outcome
94-97	<p>EFPIA / Pfizer:</p> <p>The statement that spacers are recommended for all patients in principle should be removed, as it is contrary to the current situation where patients receive adequate therapy using pMDIs without spacers. The guidance should focus on use of spacers for specific patient populations. It is thus suggested to delete the sentence: “The use of a spacing device is recommended for all patients in principle, but particularly for those who find coordination of actuation of the pMDI with inspiration of breath difficult (for example children and the elderly) and for patients treated with inhaled glucocorticosteroids”</p>	<p>EWP comment:</p> <p><i>This general aspect should be kept in the guideline. In general, we expect data with and without spacer.</i></p>
102	<p>EFPIA:</p> <p>In the discussion of the “specific named spacing device for use with the particular pMDI” we suggest clarification of what is intended by use of the word "named". For example, is the purpose of using a "named" spacing device so that the spacing device would be listed by name on the SPC? Will there be unintended difficulties in conducting global clinical trials if a specific spacing device is available in some countries but not others? Is the intent of this section to encourage the use of an approved / marketed spacing device or to encourage a sponsor to develop a new spacing device as part of the inhalation drug development program?</p>	<p>EWP comment:</p> <p><i>The question how can a spacer be developed can not be solved by this guideline. The agencies only want to see data to efficacy and safety with and without spacers in comparison to a licensed product which can be used with a special spacer and/or without. It is also possible to develop more than one spacing device in adoption on the divergent European marketing situation. In consequence, the tested spacing device has to be namely listed in the informative texts and should ideally be available in the corresponding market.</i></p>

⁸ Where applicable

106	<p>EFPIA: The paragraph stating requirements on <i>in vitro</i> testing is not directly relevant to the scope this guideline as it relates to pharmaceutical characterisation tests and should be removed. Proposed change: Remove paragraph or update according to intent/context.</p> <p>IPAC-RS: The paragraph stating requirements on <i>in vitro</i> testing is not directly relevant to the scope this guideline as it relates to pharmaceutical characterisation tests. Proposed change: Update the paragraph according to intent/context. Alternatively, update/clarify the scope of the guideline. Consider adding a reference to Appendix 1 (http://www.emea.europa.eu/pdfs/human/ewp/4850108en.pdf) which provides recommendations for clinical studies in children.</p> <p>Pfizer: The paragraph stating requirements on <i>in vitro</i> testing is not directly relevant to the scope this guideline as it relates to pharmaceutical characterisation tests and should be removed. Proposed change: Remove paragraph or update according to intent/context. Alternatively, update/clarify the scope of the guideline. Consider adding a reference to Appendix 1 (http://www.emea.europa.eu/pdfs/human/ewp/4850108en.pdf) which provides recommendations for clinical studies in children.</p>	<p>EWP comment: <i>In general, when <i>in vitro</i> testing is required for clinical reasons these tests are within the scope of this guideline and should definitely not be deleted.</i> <i>The guideline describes a step by step approach to test inhaled products with known active substances. The first step is always an <i>in vitro</i> investigation. However, it should be pointed out that the <i>in vitro</i> data requested in this guideline is reflecting the clinical position. Because spacing devices can modify the efficacy and safety of inhaled products, the <i>in vitro</i> aspect has also to be covered in this paragraph.</i> <i>However, the concerned section has been intensively updated. In addition, paediatric issues have been implemented in the main part of the guideline. Please compare the final version of the published guideline.</i></p>
114	<p>IPAC-RS: In vitro data with or without a spacer may not correlate with clinical data with respect to exposure and clinical safety. Proposed change: Clinical data (and not just <i>in vitro</i> data) should be required with and without a spacer to assess differences in exposure and any associated safety implications.</p>	<p>EWP comment: <i>We do not see the need to require always clinical <i>in vivo</i> data. The hierarchical principle is also valid for metered dose inhalers used with spacer.</i></p>
115/125-126	<p>IPAC-RS: Lack of consistency in the use of terminology.</p>	<p>EWP comment: <i>The point has been considered. The guideline has been changed</i></p>

	Proposed change: Replace “device” with “spacing device” or “spacer”.	<i>adequately.</i>
120	<p>EFPIA / Pfizer:</p> <p>The statement “If there are no specific recommendations for the use of a specific spacing device with the reference product, the test product used both with and without a spacing device should be compared with the reference product used without a spacing device; otherwise the reference product should be used in accordance with the spacing device as stated in its own Summary of Product Characteristics (SPC).” requires clarification. In such cases it is assumed that use of a spacer may be supported by <i>in vitro</i> data only otherwise clinical studies may be required to be conducted for products containing existing substances to support the use of a spacer, simply because the originator did not provide adequate information, which contrasts with the philosophy of section 4.2.2.</p> <p>Proposed change: Develop consistency between sections 4.1.1.2 and 4.2.2.</p>	<p>EWP comment:</p> <p><i>The raised inconsistency between 4.1.1.2 and 4.2.2 can not be followed. However, the paragraph dealing with spacers has been modified (please compare the final version of the guideline).</i></p>
121	<p>EGA:</p> <p>In general, the requirement of studying spacing devices would require further clarification.</p> <p>When two products demonstrate <i>in vitro</i> equivalence on spray pattern, plume geometry, and particle size distribution, there is no logical reason to believe that they will not perform the same when used with the same spacing device.</p> <p>Hence, no extra testing should be needed.</p> <p>However, if the SmPC specifies the use of a particular spacer for the reference product, only that spacer should be tested <i>in vitro</i> and compared between the test and reference products.</p> <p>On line 121, it is unclear as to why the test product used both with and without a spacing device should be compared with the reference product used without a spacing device.</p> <p>Finally, if there are no specific recommendations for the use of a specific spacing device in the SmPC of the reference product, no additional testing should be needed.</p>	<p>EWP comment:</p> <p><i>The EWP has already discussed this argumentation. The EWP has also considered the special European situation using the medical product ‘spacer’ in this context. It has been recognised that spacers are often sold by other companies than the inhaled products. Furthermore, it has been noticed that not all spacers are available in all European countries. On the other hand, spacers may have an important influence on efficacy and safety of inhaled medicinal products. Despite of this known influence, spacers has not been comprehensively discussed so far. Therefore, any hint on appropriate and tested spacer is missing in most of appropriate reference products. This situation is not acceptable, and now it is tried to change this situation in stepwise approach.</i></p> <p><i>In context with the spacers, possible in vitro methods are also discussed. In adoption to the marketing situation, it might be necessary to test more than one spacer in frame of European approval procedure.</i></p>

	<p>This could also be clarified through a decision tree.</p> <p>Proposed change: “If there are no specific recommendations for the use of a specific spacing device with the reference product, the test product used <u>both with and without a spacing device</u> should be compared with the reference product used without a spacing device; otherwise <u>both the test and</u> the reference products should be used in accordance with the spacing device as stated in <u>its own</u> the Summary of Product Characteristics (SmPC) of the reference product.</p>	
124-126	<p>EFPIA:</p> <p>It is not fully understood why the “active substance” is the only determinant of whether clinical testing of a new spacer would be needed.</p> <p>A suggested rewording is thus proposed: “However, depending on the active substance <u>the properties of the pMDI and spacers in question</u>, this may not be appropriate....”</p>	<p>EWP comment: <i>We agree that the development program does not only depend on the active substance but also on the device. Therefore a modified wording has been implemented in the final version of the guideline (please compare).</i></p>
129	<p>EFPIA / IPAC-RS / Pfizer:</p> <p>The requirement to indicate the name of spacer on product labelling is in excess of that required by Article 54 of Directive 2001/83/EC. Inclusion within the SmPC and PIL should be sufficient.</p>	<p>EWP comment: <i>The use of an adequate spacer is a relevant aspect for the patients. Therefore, from our point of view, this hint should be included in all relevant informative texts.</i></p>

4.1.2 Dry powder inhalers		
Line no. ⁹ + paragraph no.	Comment and Rationale	Outcome
section 4.1.2	<p>EFPIA / IPAC-RS:</p> <p>This section does not address breath-operated (i.e. breath-triggered) DPIs. Thought should be given to include these DPIs or to write a separate, general section on breath-operated inhalers.</p>	<p>EWP comment:</p> <p><i>Different kinds of DPIs have already been covered by the guideline. Further subdivisions seem to be misleading, unclear and redundant.</i></p>

⁹ Where applicable

130-147	<p>IPAC-RS: see comment to line 76-91</p>	<p>EWP comment: <i>The EWP would like to refer to the aforementioned statement (see above).</i></p>
131-133	<p>EFPIA: Non-pressurized metered dose inhalers are similar to pMDIs with respect to flow dependence. In addition, it is assumed that pMDIs are not flow dependent. This is however not entirely true. The inhalation flow rate will not affect the quality of the generated aerosol cloud from the pMDI but the degree of impaction in the oropharynx will affect the dose reaching the lungs as has been discussed by Newman et al., Eur J Respir Dis suppl 119, vol 63, 1982:57-65. Proposed change: “In contrast to <u>pressurized and non pressurized metered dose inhalers</u> to the pMDI dry powder inhalers often show a high flow dependency in their <u>in vitro particle size distribution characteristics</u> deposition characteristics. Therefore characterisation of <u>in vivo</u> flow rate dependency in the patient populations in whom the DPI is to be used must be presented”.</p> <p>IPAC-RS: Non-pressurized metered dose inhalers are similar to pMDIs with respect to flow dependence. Proposed change: Change to: “<i>In contrast to pressurized and non pressurized metered dose inhalers ...</i>”.</p>	<p>EWP comment: <i>We see the point of the EFPIA and the IPAC-RS, however flow rate dependency can also be investigated in vitro. Therefore the emphasis of in vivo studies seems to be misleading.</i></p>
132-133	<p>Siegfried Pharma Development GmbH: The statement “Therefore characterisation of flow rate dependency in the patient populations in whom the DPI is to be used must be presented” needs to be clarified. The flow dependency of drug deposition characteristics is determined by <i>in vitro</i> assessments, because it cannot be reliably ascertained <i>in vivo</i> in all patient populations in whom the DPI is to be used.</p>	<p>EWP comment: <i>A small amendment has been implemented.</i></p>

	<p>Proposed change: We propose the sentence to be replaced with the following: „Therefore the <i>in vitro</i> characterisation of flow rate dependency should cover the entire clinically relevant flow range of the patient populations in whom the DPI is to be used. In addition, the dossier should demonstrate with data from inspiratory profile / ease of use studies, that the relevant patient population concerned is able to use the device appropriately and release the drug.”</p>	
134	<p>EFPIA: A rewording is proposed to clarify the statement. Proposed change: “...has to include sufficient in-vitro data such that the <i>in vitro</i> flow-dependent deposition characteristics of the products ...”.</p>	<p>EWP comment: <i>The current statement should be kept.</i></p>
134-136	<p>Innovata Biomed Limited: <u>line 134-136</u> “The dossier submitted has to include sufficient <i>in vitro</i> data such that the flow deposition characteristics of the products within the range of clinically relevant pressure drops/flow limits can be described.” <u>as well as line 298-300</u> “If clinical studies are needed and the reference product has an authorized indication which includes both asthma and COPD, therapeutics equivalence studies may only be needed in one of the patient populations in order to obtain a marketing authorization. Generally such studies are easier to carry out in patients with asthma. However, if therapeutic equivalence to the reference product is demonstrated (in respect of both efficacy and safety) in one clinical indication, say asthma, comparative <i>in vitro</i> data must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range which are clinically applicable to all patients in whom the test product will be used, in order that a marketing authorization can be granted which will include all therapeutic indications as listed for the reference product. ” Proposed change: Inhalation devices differ for a number of reasons, such as patent and design restrictions. These differences mean that it</p>	<p>EWP comment: <i>EWP agrees that a completely identical particle size distribution may be unrealistic due to several reasons. Therefore it is stated in the guideline (compare section 5.2 of the final guideline): “The maximum allowable <i>in vitro</i> difference should be indicated and justified, e.g. +/- 15% may be justifiable.” If the <i>in vitro</i> criteria were not met the next step would be to compare the lung deposition of test and reference product.</i></p>

	<p>may not always be possible for a development company to create an absolutely identical deposition profile match over all stages of the Andersen Cascade Impactor at all flow rates. IBL believe that a certain amount of difference should be acceptable providing that it is demonstrated that it does not have any impact on safety or efficacy parameters. Subtle differences in deposition profile should not preclude the conduct of clinical trials in one study population only.</p>	
137-142	<p>EFPIA: How is high flow rate dependency defined? This paragraph seems highly speculative. Why would “Pulmonary deposition and subsequent systemic exposure be much higher” for inhalers with a high flow rate dependency than for inhalers with a low flow rate dependency? Higher flow dependence will not always lead to higher pulmonary deposition and systemic exposure as suggest in the text. More prominently, higher flow dependence will lead to higher variability of pulmonary deposition and systemic exposure. In addition, the wording “subsequent systemic exposure” suggests that systemic exposure is a consequence of only the pulmonary deposition. For example, oropharyngeal deposition is typically also highly flow-rate dependent and thus the resulting systemic exposure. It is suggested to revise the paragraph to reflect the comment. Proposed change: “Marketing authorisations for DPIs with a high flow rate dependency where pulmonary deposition and subsequent systemic exposure may be much higher than is seen with inhalers with a low flow rate dependency can only be granted for use in the patient <i>will be restricted to those</i> populations studied in the clinical programme, <i>or proven to be able to generate a sufficient PIF to use the product.</i>”</p> <p>IPAC-RS: A higher flow dependence will not always lead to higher pulmonary deposition and systemic exposure as suggest in the text. More prominently, a higher flow dependence will lead to a higher variability</p>	<p>EWP comment: <i>Agreement in principle. A modified wording has been implemented.</i></p>

	<p>of pulmonary deposition and systemic exposure.</p> <p>The wording “<i>subsequent systemic exposure</i>” suggests that systemic exposure is a consequence of only the pulmonary deposition. For example, oropharyngeal deposition is typically also highly flow-rate dependent and thus the resulting systemic exposure.</p> <p>Proposed change: In line 138, delete “<i>subsequent</i>” and replace “<i>much higher</i>” with “<i>much more variable</i>”.</p>	
143-147	<p>EFPIA / Pfizer:</p> <p>It is suggested that the paragraph constituted by lines 143-147 be clarified to indicate that the standardisation relates to inclusion of patients of different inspiratory capacities in clinical studies. High flow-rate dependence of a dry powder inhaler (DPI) is intrinsically worrisome, and we are concerned that even with "standardisation of deposition characteristics and inspiratory flow rates", that therapeutic equivalence would not be demonstrated without conducting clinical efficacy studies in the appropriate patient population. Furthermore, it is not clear how deposition characteristics and inspiratory flow rates can actually be standardised in clinical practice. Does "assessment of equivalence across a range of inspiratory capacities (pressure drops / flow rates)" actually refer to in vitro testing?</p> <p>A rewording is thus proposed to clarify the statement.</p> <p>Proposed change: “Therefore, equivalence should be assessed <i>in patients with</i> across a range of inspiratory capacities (pressure drops/flow rates) which represent the patient population covered by the authorisation for the reference product”</p> <p>Innovata Biomed Limited:</p> <p>IBL have experience of trying to match a reference product where three dosage strengths appear to be non-linear with respect to their pharmaceutical performance. This may not be observed in a clinical setting where less sensitive end points and traditional study designs are employed. The current wording would suggest that follow-on/generic products could be penalized by a requirement to match a non-linear reference product. More sensitive clinical study designs (e.g.</p>	<p>EWP comment: <i>The comments have been taken into account. The wording has been changed. However, it should be noted that this section does not only refer to clinical studies but also to in vitro data.</i></p>

	<p>pharmacokinetic/pharmacodynamic designs) are more likely to differentiate between non-linear products but may also demonstrate a non-linear response for a product where equivalence may be expected across a range of (for example) three strengths.</p> <p>IPAC-RS: The paragraph in lines 143-147 should be clarified to indicate that the standardisation relates to inclusion of patients of different inspiratory capacities in clinical studies.</p> <p>Proposed change: <i>“Therefore, equivalence should be assessed in patients with a range of inspiratory capacities (pressure drops/flow rates) which represent the patient population covered by the authorisation for the reference product.”</i></p>	
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4.1.3 Solutions and suspensions for nebulisation		
Line no. ¹⁰ + paragraph no.	Comment and Rationale	Outcome
148 (header)	<p>EFPIA: Header is not quite correct. This section would need 2 subsections to correctly differentiate between the different types of products. It is also suggested a separate section for pump activated liquid reservoir metered dose inhalers instead of inclusion in 4.1.3.</p> <p>Proposed change: 4.1.3 Solutions and suspensions for inhalation. 4.1.3.1 Nebulisers (lines 149-175). 4.1.3.2 Non-pressurised metered dose inhaler (lines 176-180).</p>	<p>EWP comment: <i>We see this point; however for reasons of clarity we would like to keep the current superficial wording. A further subdivision would not be helpful with regard to the ongoing technical development.</i></p>
150	<p>EFPIA: There are now also vibrating mesh nebulisers and there will possibly be other technologies in the future. A suggested rewording is thus proposed.</p>	<p>EWP comment: <i>Partly agreed. The first sentence has been addressed.</i></p>

¹⁰ Where applicable

	<p>As ultrasonic nebulisers are not suitable for nebulisation, a specific statement should be added.</p> <p>Proposed change: “..via a nebuliser, either a jet nebuliser or an ultrasonic nebuliser, is a treatment option for patients with asthma and COPD. <u>Currently jet, ultrasonic and vibrating mesh types of nebulisers are available. Ultrasonic nebulisers are not suitable for nebulisation.</u>”</p>	
176-180	<p>EFPIA:</p> <p>As mentioned above, it would be useful to create a specific subsection for non-pressurised metered dose inhalers.</p> <p>Non-pressurised metered dose inhalers should not be listed in chapter 4.1.3.”Solutions and suspensions for nebulisation”, as they are different; for example, they meter the dose.</p> <p>It is true for all inhalation forms that the patient has to inhale a specific volume of the aerosol to get the delivered dose. This is not specific for non-pressurised metered dose inhalers.</p> <p>In addition, the sentence would need to be amended as proposed to explicitly state that a clinical study is required.</p> <p>Proposed change: “In non-pressurised, pump activated liquid reservoir metered dose inhalers the speed of plume is decreased, <u>and therefore, the inhalation manoeuvre takes longer than in pMDIs (without spacer) and Powder inhalers.</u> In order to get a sufficient amount of active substance the patient has to inhale a specific volume of the aerosol. In <u>all</u> patients, <u>especially those</u> with a limited inhalational capacity (for example, children) it has to be shown <u>in a clinical study</u> that the volume required to produce a clinical effect does not exceed the inhalational capacity of the patient.”</p> <p>IPAC-RS:</p> <p>Non-pressurised metered dose inhalers should not be listed in section 4.1.3.”Solutions and suspensions for nebulisation”, as they are different; for example, they meter the dose.</p> <p>It is true for all inhalation forms that the patient has to inhale a specific volume of the aerosol to get the delivered dose. This is not specific for</p>	<p>EWP comment:</p> <p><i>Thanks for these comments. The raised aspects have been taken over in a modified version.</i></p>

	<p>non-pressurised metered dose inhalers.</p> <p>Proposed change: Create a chapter of its own for non-pressurised metered dose inhalers.</p> <p>Change to: <i>“In non-pressurised metered dose inhalers the speed of plume is decreased, and therefore, the inhalation manoeuvre takes longer than in pMDIs (without spacer) and powder inhalers. In all patients, especially those with a limited inhalational capacity (for example, children) it has to be shown that the target dose per actuation or the dose required to produce a clinical effect can be inhaled in one breath.”</i></p>	
4.1.4 Investigation of additional strengths		
Line no.¹¹ + paragraph no.	Comment and Rationale	Outcome
182	<p>IPAC-RS:</p> <p>The guideline states that <i>“Dose linearity in respect of pulmonary deposition should be investigated in vitro ...”</i>. The terminology of <i>“pulmonary deposition”</i> refers in vivo imaging and PK studies in the Section 4.3.1. In order to avoid confusion, a consistent wording (e.g. individual stage drug deposition) should be used.</p> <p>Proposed change: Ensure consistent terminology among the texts. Change <i>“...pulmonary deposition...”</i> to <i>“...each individual stage or group of stages drug deposition...”</i></p> <p>TEVA:</p>	<p>EWP comment:</p> <p><i>This aspect has been amended. The aspect has been addressed in the final version of the guideline as follows: “Dose linearity should be investigated in vitro for both the test and the reference product across all proposed strengths.”</i></p>

¹¹ Where applicable

	<p>It states that “Dose linearity in respect of pulmonary deposition should be investigated <i>in vitro</i> ...” The terminology of “pulmonary deposition” refers to <i>in vivo</i> imaging and PK studies in the Section 4.3.1. In order to avoid the confusion, consistent wording (e.g. individual stage drug deposition) should be used.</p> <p><u>Proposed change:</u> Ensure consistent terminology among the texts. Change “...pulmonary deposition...” to “...each individual stage or group of stages drug deposition...”</p>	
182-183	<p><u>EFPIA:</u></p> <p>It would be useful to clarify what is meant by "Dose linearity in respect of pulmonary deposition..."</p> <p>Provide the parameters to be measured to demonstrate "dose linearity in respect of pulmonary deposition". Is this a comparison of the emitted dose and fine particle fraction as a function of dose strength of the new product vs. the reference product? Provide information for the expected / accepted variability (perhaps the same criteria as suggested in lines 218 and 229-235).</p>	<p><u>EWP comment:</u></p> <p><i>Thanks for this comment. Limits or a reference to limits have been defined. Furthermore, the wording has been modified.</i></p>

182 –	<p>EGA: The use of the word “dose” is not clear in this context. We suggest using the term “fine particle dose ($\leq 5\mu\text{m}$)”.</p> <p>Proposed change: “Fine particle dose ($\leq 5\mu\text{m}$) Dose linearity in respect of pulmonary deposition should be investigated <i>in vitro</i> for both the test and the reference product across all proposed strengths.”</p>	<p>EWP comment: <i>Dose linearity has to be shown in all stages/justified groups. A measurement of FPD only would not be adequate to assess dose linearity comprehensively.</i></p>
184-187	<p>EFPIA: It should be clarified what “at more than one dose level” means, since if what this means is to use different puffs this does not save really clinical work. Dose proportionality should be shown and the appropriate strength used in clinical studies. Using multiple doses of a lower strength does not reflect actual patient use.</p> <p>IPAC-RS: Using multiple doses of a lower strength does not reflect actual patient use.</p> <p>Proposed change: Dose proportionality should be shown at the strength used in clinical studies?</p>	<p>EWP comment: <i>Thanks for these comments. The raised aspects have been clarified in the final version of the guideline.</i> <i>The aim is to show therapeutic equivalence in a sensitive way. It has to be distinguished between using multiple doses of one strength and the necessity to investigate several strengths. The recommendation of using more than one dose of one strength is only for reasons of sensitivity.</i></p>
184 – 190 -	<p>EGA: For therapeutic equivalence trials an enhancement of study sensitivity by applying more than one dose levels of the lowest strength is recommended. For some substances, however (e.g., Formoterol/Foradil), a single dose of the lowest available strength is already on the plateau phase of the dose response curve, thus the requested enhanced sensibility in such pharmacodynamic trials is not achievable. Another option would be to demonstrate dose linearity through PK studies. Today, the available analytical methods might not be sensitive enough. In addition, the variability of PK data may be too high to show dose linearity. In such cases we believe it should be sufficient to test one dose level, typically the highest dose, for a given strength in the PK study, and to</p>	<p>EWP comment: <i>All these points have been discussed.</i> <i>The first clinical step would be conducting a pulmonary deposition study (e.g. PK). Here we agree, not all active substances are detectable in clinical relevant dosages with analytical methods. However the analytical methods are further developed (e.g. formoterol is now detectable in clinically relevant doses of 6 μg).</i> <i>If this investigation was not successful, clinical studies would be needed.</i> <i>Foradil is available in one strength, but there are other Formoterol powder formulations, which are marketed in several strengths. So – it is the task of the company to look for an adequate reference product. In special situations a national or European advice should always be sought.</i> <i>To the issue of development of several strengths: the EWP strongly</i></p>

	<p>show dose linearity for other strengths along with comparability to the reference product by in-vitro data.</p> <p>Proposed change: The EGA would welcome clarification of the requirements and an indication of possible alternative approaches for substances where dose sensitivity cannot be demonstrated in therapeutic equivalence studies for the lowest marketed strength.</p>	<p><i>believes that this topic has been adequately described in the final version of the updated guideline.</i></p>
186-187	<p>Siegfried Pharma Development GmbH:</p> <p>“It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.” This statement appears to be too general with regard to the issue of “assay sensitivity” and its practical implications and hence, would need further clarification.</p> <p>In case of e.g. highly potent inhaled corticosteroids (ICS) or long-action β-adrenoceptor agonists (LABA) or combinations thereof, a head-to-head TEST/REFERENCE comparison with the lowest dose strength at the lowest clinically recommended dose level would provide the largest discriminative power / assay sensitivity for the comparative efficacy-assessment of the <i>in vivo</i> performance of the TEST product. It is therefore possible that the additional investigation at a higher dose-level would not provide any added value to the overall sensitivity of the study. This holds in particularly true for drug classes (e.g. potent ICS and LABAs) for which difficulties to demonstrate average dose-dependency has been demonstrated in clinical studies.</p> <p>Proposed change: We propose the sentence to be replaced with the following: “In case of e.g. highly potent inhaled corticosteroids (ICS) or long-action β-adrenoceptor agonist (LABA) or combinations thereof, a head-to-head TEST/REFERENCE comparison with the lowest dose strength at the lowest clinically recommended dose level may provide the largest discriminative power / assay sensitivity for the comparative efficacy – assessment of the <i>in vivo</i> performance of the TEST.</p>	<p>EWP comment:</p> <p><i>In the past there were a lot of insensitive studies using an inappropriate study population so that possible differences between test and reference product could not be detected. Therefore, it is needed to investigate more than one dose for reasons of sensitivity.</i></p>
188-190	<p>EFPIA:</p> <p>If linearity or dose proportionality cannot be demonstrated therapeutic equivalence should be established for all strengths.</p>	<p>EWP comment:</p> <p><i>Agreed. The wording has been modified as follows: “If linearity across all proposed product strengths is demonstrated with the test product but</i></p>

		<i>not with the reference product, the two products cannot be deemed to be therapeutically equivalent. Therefore either the test product must be modified such that it matches the reference product in terms of non-linearity (and may then be considered to be therapeutically equivalent) or therapeutic equivalence of the test product to the reference product will have to be established with more than one product strength and possibly with all product strengths (depending on which product strengths of the test product are not matched in respect of linearity with the reference product).“</i>
188-190	<p><u>Innovata Biomed Limited:</u></p> <p>IBL disagree that follow on products should be adapted to a non-linear reference product if a linear product range is more therapeutically appropriate. We believe a linear product range provides distinct clinical advantages in moving the patient through different dosage steps in the management of asthma or COPD.</p>	<p><u>EWP comment:</u></p> <p><i>The EWP agrees that it is worth considering what is therapeutically appropriate but likes to draw the attention to the fact that the guideline is addressing requirements for hybrid applications. The shortened study program is justified with the abridging to the reference product. All the experiences with the reference product that the “hybrid” like to share are only applicable in the case linearity of both products are the same. If the highest strength of the “hybrid” although proportional to its lower strengths was much higher dosed than the corresponding strength of the reference it would raise safety concerns.</i></p> <p><i>We discuss about hybrid inhaled products. Therefore, equivalence has to be shown to an appropriate reference product. The issue: Linearity or non-linearity of the reference product can not be solved by the hybrid medicinal test product.</i></p>

4.2.1 New active substance		
Line no. ¹² + paragraph no.	Comment and Rationale	Outcome
197-199	<p><u>Innovata Biomed Limited:</u></p> <p>IBL believe this section should be expanded upon to reflect the different approaches in new drug development, line extensions, and variations</p>	<p><u>EWP comment:</u></p> <p><i>This guideline does definitively not cover new active substances applications. A clarifying amendment has been included. In case of new</i></p>

¹² Where applicable

	and follow on products/generics. In addition, this section could be expanded upon to discuss products which are not new active substances but are being developed for delivery by inhalation for the first time.	<i>active substances appropriate guidelines exist.</i>
4.2.2 Known active substance		
Line no.¹³ + paragraph no.	Comment and Rationale	Outcome
200-238	<p>EFPIA: <i>In vitro</i> comparability criteria should be more clearly defined. In practice demonstration of <i>in vitro</i> comparability is not as well defined as <i>in vivo</i> comparability.</p> <p>Proposed change: The guideline should be revised to require <i>in vivo</i> clinical testing to demonstrate therapeutic equivalence between a medicinal product and a reference medicinal product, as outline above in the major comments.</p> <p>IPAC-RS: In practice criteria for demonstration of <i>in vitro</i> comparability is not as well defined as <i>in vivo</i> comparability.</p> <p>Proposed change: <i>In vitro</i> comparability criteria should be more clearly defined.</p> <p>Schering Plough: The guidelines allows the possibility of approving new inhaler devices based on <i>in-vitro</i> data only, even if there are differences in fine particle characteristics and differences in excipients. We do not support this.</p>	<p>EWP comment: <i>In contrast to the former guideline, we tried to be more precise with respect to <i>in vitro</i> comparability. From our point of view all aspects have been adequately covered, so that an application based on <i>in vitro</i> data could be possible in certain circumstances. However, based on <i>in vitro</i> data only, an approval for an OiP hybrid product is rarely difficult.</i></p>
205	<p>EFPIA / IPAC-RS: Hydrates or, generally, solvates may also influence pharmaceutical quality and performance of powders and suspensions and should be</p>	<p>EWP comment: <i>Agreed. An amendment has been done.</i></p>

¹³ Where applicable

	<p>mentioned explicitly due to their importance for pharmaceutical and clinical development.</p> <p>Proposed change: “(i.e. same salt, ester, <u>hydrate or solvate</u>, etc.)”.</p>	
206	<p>EFPIA:</p> <p>The term “Pharmaceutical Dosage Form” is a very broad description. Does the dosage form refer to a broad categorization, such as to be used in a MDI, or in a DPI, or in a nebuliser? Or is this more specific, such as to be used in a reservoir DPI or in a pre-metered DPI? It could be amended to reflect the common terminology in Europe (i.e., pharmaceutical form).</p> <p>The guideline highlights that different inhaler classes or types have different properties. To be consistent, the list of criteria should not only include the identical pharmaceutical dosage form (understood to be defined as in EP Monograph 671 <i>Preparations for Inhalation</i>), but also the aspect that test and reference products are from the same inhaler type (which is also indirectly addressed in line 216).</p> <p>Proposed change:</p> <p>“The pharmaceutical dosage form <u>delivery system design</u> is identical” or “The pharmaceutical dosage form is identical” or, “<u>The test product should use the same type of inhalation device.</u>”</p> <p>EGA:</p> <p>The expression “pharmaceutical dosage form” should be more detailed. The term “identical” should be replaced by “similar”. Pressurised metered dose inhalers (PMDIs) are similar devices. However, in addition to propellant and active substances, additional ingredients may vary.</p> <p>Proposed change:</p> <p>For clarification it would be helpful to refer in line 206 to the pharmaceutical dosage forms given in line 30 – 36:</p> <ul style="list-style-type: none"> • pressurised metered dose inhalers • pressurised metered dose inhalers with spacer devices and 	<p>EWP comment:</p> <p><i>Thanks for these comments. A clarification has been implemented.</i></p>

	<p>holding chambers</p> <ul style="list-style-type: none"> • breath-operated inhalers • non-pressurised, pump activated, liquid reservoir metered dose inhalers • dry powder inhalers using a reservoir and metering mechanism • dry powder inhalers using a pre-dispensed dose • solutions and suspensions for nebulisation <p>or to additionally include these dosage forms in line 206. A suggested rewording is: “The pharmaceutical form <u>(see section 2. SCOPE)</u> is <u>identical similar</u>”</p> <p>EPAG: Clinical Requirements Section Bullet No. 1:’ ... inhalation device of the test product is <u>pharmaceutically identical</u> to that of the reference product...’</p> <p>Proposed change: We have difficulty in understanding the terminology, ‘pharmaceutically identical’ and believe you are referring to the ability of paediatrics to operate the device. We suggest a change in text to ’ ... inhalation device of the test product <i>operates in a similar</i> way to that of the reference product. If this is not what is being referred to, then please clarify further what it is that is being referred to.</p> <p>Innovata Biomed Limited: Innovata Biomed believes this sentence is ambiguous and requires further clarification. In interpreting this, IBL considers that a reservoir DPI is identical to a unit dose DPI as they are both dry powders for inhalation in line with the Ph Eur Standard Terms definition.</p> <p>IPAC-RS: The guideline highlights that different inhaler classes or types have different properties. To be consistent, the list of criteria should not only include the identical pharmaceutical dosage form (defined as in EP Monograph 671 <i>Preparations for Inhalation</i>), but also the aspect that test and reference products are from the same inhaler type (which is also indirectly addressed in line 216.</p>	
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	<p>The term “<i>pharmaceutical dosage form</i>” as used in the guideline is vague. It should be clarified and/or amended to reflect the common terminology in Europe.</p> <p>Proposed change: Consider changing line 206 to: ‘The pharmaceutical dosage form <u>delivery system design</u> is identical’.</p> <p>Alternatively, provide a definition for the term “<i>pharmaceutical dosage form</i>” and add the following requirement: “<i>The test product should use the same type of inhalation device.</i>”</p> <p>Pfizer:</p> <p>The term “Pharmaceutical Dosage Form” should be amended to reflect the common terminology in Europe (i.e., pharmaceutical form).</p> <p>Proposed change: Remove “dosage”</p>	
207 (as well as 205-218)	<p>EFPIA:</p> <p>To avoid unclear interpretation, the sentence would need clarification: Is then any attempt to establish <i>in-vitro</i> and/or <i>in-vivo</i> equivalence among a solution in pMDI and a suspension in pMDI prohibited? Same for mDPI and solution in pMDI? Is it on the other hand allowable, if the pMDI contains a suspension?</p> <p>Differences in crystalline structure or polymorphic form may also influence other important pharmaceutical properties. It is recommend to add the following points:</p> <ul style="list-style-type: none"> - The stability behaviour of the test product is comparable to that of the reference product. Differences in stability, e.g. during in-use or at elevated humidity, may be indicative of differences in pharmaceutical performance. - For dry powder inhalers, exhaling into the inhaler should be avoided for the test product at least in the same way as for the reference product. <p>Proposed change:</p> <p>“...any differences in crystalline structure and/or polymorphic form should not influence the solubility <u>in vivo, chemical and physical stability of the active substance, the performance of the product or the aerosol particle behaviour</u>”.</p>	<p>EWP comment:</p> <p><i>Agreed. The wording proposed by EFPIA / IPAC-RS has been taken over. Now this issue should be clarified.</i></p>

	<p>EGA: Clarification as to the exact definition of solubility is requested. Is it the solubility of the active substance in the formulation or in the human respiratory tract? A more detailed description of this requirement would be helpful.</p>	
212	<p>EGA: Concerning the inhalation behaviour of the patient, the EGA recommends that non-significant differences, especially if advantageous, should be considered acceptable during the review by the authority.</p> <p>Proposed change: “Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g., delivered dose uniformity, etc), aerosol particle behaviour (e.g., hygroscopic effect, plume dynamic and geometry) and/or the inhalation behaviour of the patient (e.g., particle size distribution affecting mouth/throat feel or “cold Freon” effect). <u>Differences in the inhalation behaviour of the patient, however, may be acceptable if the differences are not clinically significant or shown to be advantageous to the patients.</u>”</p> <p>IPAC-RS: Differences in crystalline structure or polymorphic form may also influence other important pharmaceutical properties.</p> <p>Proposed change: Change to read “...<i>should not influence the solubility in vivo, chemical and physical stability of the active substance, the performance of the product or the aerosol particle behaviour</i>”.</p>	<p>EWP comment: <i>We appreciate your point of view. But how should the described advantage be verifiable in vitro? Therefore, we don't like to address the proposed sentence in the guideline to avoid any confusion.</i></p>
213-214	<p>IPAC-RS / Schering Plough: Section 4.2 states: “<i>Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product.</i>” This statement is too vague for such an important point as safety. As written, the statement could be interpreted to mean that the sponsor need only</p>	<p>EWP comment: <i>It should be distinguished between new excipients (see section 10 of the final guideline) and differences between test and reference product with regard to the excipients. However, adequate data are always expected, and consequently we should avoid a redundant wording.</i></p>

	<p>assert that it is not anticipated that the proposed qualitative and/or quantitative change in excipients would change the safety profile of the product and that no data of any kind is required to substantiate this assertion. In contrast, section 4.7 addresses safety concerns of new excipients or new "mixes of excipients appropriately".</p> <p>Proposed change: We suggest amending the statement to: "<i>Adequate data should be provided to substantiate that any qualitative or quantitative difference in excipients does not change the safety profile of the product (refer to section 4.7)</i>"</p>	
215	<p>EGA:</p> <p>"The inhaled volume needed to get sufficient amount of active substance" is not decisive for metered dose inhalers (MDIs). It is the spray duration and the time to fully formed spray (plume dynamic), which should be discussed for MDIs.</p> <p>Proposed change: Line 215 should be deleted for MDIs. Plume dynamic is already mentioned in line 211.</p> <p><u>"The inhaled volume needed to get sufficient amount of active substance should be similar"</u></p>	<p>EWP comment:</p> <p><i>An amendment has been implemented. In the final version of the guideline this topic is addressed as follows: 'The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%).' However any deviation of this addressed criterion should be justified.</i></p>
216	<p>Orion Pharma:</p> <p>It should be considered further if the requirement: "The instructions for use of the inhalation device are the same" is relevant on this mandatory list of demonstrating <i>in vitro</i> equivalence to a reference product when the actual similarity requirements of the product performance are established on lines 218-235. Following the given approach on 4.2.2 it should also be possible for a product to demonstrate similar <i>in vitro</i> performance to a reference product using different inhalation devices which have different operating principles and therefore also different instructions (when pharmaceutical dose form is identical as stated on line 206).</p> <p>Proposed change: We propose to leave out line 216.</p> <p>EFPIA:</p> <p>This statement could imply the devices need to be identical. Instructions</p>	<p>EWP comment:</p> <p><i>It is not agreed to delete the line (see comments from ORION PHARMA and PARI Pharma GmbH.) However the wording has been slightly modified. We think the topic is clearly addressed now. Please compare the wording used in the final guideline: "Handling of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar."</i></p>

	<p>for use encompass many factors ranging from the expected breathing manoeuvre to how to clean and store the product. It is not expected that all elements of instructions for use need to be identical to ensure therapeutic equivalence.</p> <p>Such a requirement is hard to meet if the comparison is attempted between pMDIs and DPIs, and even between two different DPIs.</p> <p>The guidance should describe the criteria necessary to demonstrate sameness (interchangeability for patient) although if the product is pharmaceutically equivalent there is no reason to expect the device to be identical.</p> <p>It is proposed that the expectation be recognised as “the method of operation for the devices is the same”.</p> <p>Please, remove this criterion or specify which parts have to be “the same”.</p> <p><u>Proposed change:</u> “The instructions for use of the inhalation device are the same <u>should be similar</u>”</p> <p>or</p> <p><u>“the class of inhaler should be the same and it should be comparable in ease of use”.</u></p> <p>or</p> <p><u>“The handling steps should be the same”.</u></p> <p><u>EGA:</u></p> <p>The instructions for use of generic MDIs/DPIs often differ from those of originator products due to patent reasons for the device. Proving that the instructions of use are the same should be limited to the sections relevant for the inhalation manoeuvre. Details such as lever movements, opening directions of caps, dose counter details, etc should be of subordinate relevance. This also applies for storage orientation and priming actuations.</p> <p><u>Proposed change:</u> “The instructions for use <u>concerning the inhalation from</u> of the inhalation device are the same alike in all relevant parts which are relevant for the inhalation manoeuvre (e.g. lever movements, opening directions of caps, dose counter details, storage orientation,</p>	
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	<p>priming actuations).”</p> <p><u>Innovata Biomed Limited:</u></p> <p>We suggest that this criterion should be limited only to those instructions that relate to the patient inspiratory manoeuvre such as breath hold time, inhalation technique. Devices differ and not all instructions for use for different inhaler devices will be the same. The guidance needs to be more precise as to which aspect of the user instructions must be the same.</p> <p><u>IPAC-RS:</u></p> <p>The requirement that “<i>The instructions for use of the inhaler device are the same</i>” could imply that the devices need to be identical, which is not necessary if products are therapeutically equivalent. Moreover, instructions for use encompass many factors ranging from the breathing manoeuvre to cleaning and storage of the product. Not all elements of the instructions for use need to be identical to ensure therapeutic equivalence.</p> <p><u>Proposed change:</u> The requirement should be clarified. Alternatively, change it to read: “<i>The target delivered dose is the same</i>” and reference the <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u>, which allows not more than 15 % deviation from the target.</p> <p><u>Pari Pharma GmbH:</u></p> <p>“<i>The instructions for use of the inhalation device are the same</i>”</p> <p>This requirement should be taken out of the list, because if two drug products have the same qualitative and quantitative composition and only use two different e.g. jet nebulisers with similar aerosol characteristics, still the instructions of use of the device will never be the same. Since in line 203 it is stated, that <u>all</u> criteria need to be fulfilled, it would mean bridging in such a case on <i>in-vitro</i> data only would be not possible at all.</p> <p><u>Proposed change:</u> Delete this requirement or at least it needs to be further defined what aspects of instructions of use of device need to be</p>	
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	<p>the same.</p> <p><u>Pfizer:</u></p> <ul style="list-style-type: none"> - This line requires that the instructions for use of the inhalation device are the same. This statement could imply the devices need to be identical. If the product is pharmaceutically equivalent there is no reason to expect the device to be identical. - Comment that “The instructions for use of the inhaler device are the same”. Instructions for use encompass many factors ranging from the expected breathing manoeuvre to how to clean and store the product. It is not expected that all elements of instructions for use need to be identical to ensure therapeutic equivalence. <p><u>Proposed change:</u></p> <ul style="list-style-type: none"> - ‘The instructions for use of the inhalation device should be similar’ or ‘the class of inhaler should be the same and it should be comparable in ease of use’. - It is proposed that the expectation be recognised as “the method of operation for the devices is the same”. 	
217	<p><u>EGA:</u></p> <p>This requirement is not relevant for MDIs (see also Guideline on the pharmaceutical quality of inhalation and nasal products, EMEA/CHMP/QWP/49313/2005, item e) on page 6/27).</p> <p><u>Proposed change:</u> Addition of the wording “only for DPIs”</p> <p><u>IPAC-RS:</u></p> <p>The airflow resistance must fall within the range of the innovator drug across airflow rates of the range for the intended patient population(s).</p> <p><u>Proposed change:</u> Include the reference to intended patient population(s).</p>	<p><u>EWP comment:</u></p> <p><i>The EWP completely agrees with these comments. However these points should be clear for all experts. Inclusion of all specifications etc. would be beyond of the scope of this guideline. In addition, it is only discussed about in-vitro investigations in this section.</i></p>
218	<p><u>ANDI-VENTIS:</u></p> <p>For some multi-dose DPIs already available in the Member States (MSs), the labelled claim is not consistent among MSs, e.g. these products are on the market with the label referring to the delivered dose</p>	<p><u>EWP comment:</u></p> <p><i>Thanks for these comments. The raised aspect has been modified as follows:</i></p>

<p>in some MSs and to the metered dose in others. In this situation, the requirement of +/- 15% would yield different limits of <i>in vitro</i> equivalence in different MSs.</p> <p>Proposed change: The labelled claim should refer to the delivered dose.</p> <p>EFPIA: <u>Critical</u></p> <p>The requirement – “The delivered dose is the same (within \pm 15% of labelled claim)” – is open to interpretation and could imply the following:</p> <ul style="list-style-type: none"> • All individual delivered dose results are within \pm 15% of labelled claim. • The mean delivered for the test product is within \pm 15% of labelled claim. • The difference in the mean delivered dose between the test product and reference product is within \pm 15% of labelled claim <p>This specification needs to be qualified further.</p> <p>In addition, while with new products the label claim is the ex actuator or delivered dose, in some older products the label claim may still be the ex valve or metered dose. This should be noted and the criteria for comparison clarified.</p> <p>To avoid any further discussions about the tolerance of 15 %, a rewording is thus proposed in line with the “<i>EMEA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</i>” that allows not more than 15 % deviation from the target the meaning of the sentence remains unchanged.</p> <p>Proposed change: “The target delivered dose is the same (within \pm 15% of labelled claim).</p> <p>IPAC-RS:</p> <p>The requirement “<i>The delivered dose is the same (within \pm 15% of labelled claim)</i>” is open to interpretation and could imply a number of</p>	<p><i>“The target delivered dose should be similar (within +/- 15%).”</i></p> <p><i>With regard to the comment from EFPIA it has to be mentioned that a link to the guideline EMEA/CHMP/QWP/49131/2005corr has been given. Therefore, if there were a need of further clarification the use of this reference guideline would be recommended. The limits should be shortly mentioned, only.</i></p>
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	<p>different protocols, each leading to a different result. In addition, while with new products the label claim is the ex-actuator or delivered dose, in some older products the label claim may still be the ex-valve or metered dose. This should be noted and the criteria for comparison clarified.</p> <p>Proposed change: The requirement should be clarified. Alternatively, change it to read: “<i>The target delivered dose is the same</i>” and reference the <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u>, which allows not more than 15 % deviation from the target.</p>	
219-222	<p>EGA:</p> <p>This requirement is not relevant for MDIs (see also Guideline on the pharmaceutical quality of inhalation and nasal products, EMA/CHMP/QWP/49313/2005, item e) on page 6/27).</p> <p>Proposed change: Addition of the wording “only for DPIs”</p>	<p>EWP comment:</p> <p><i>The EWP completely agrees with this comment. However this point should be clear for all experts. Inclusion of all specifications etc. would be beyond of the scope of this guideline.</i></p>
219-220	<p>IPAC-RS:</p> <p>In general, all inhalers exhibit some degree of flow rate dependence. The sentence on lines 219-220 suggests that there is a flow rate dependence that is negligible.</p> <p>Proposed change: Change to read: “<i>Unless justified otherwise, comparative in vitro data on flow rate dependence should be obtained with a range of flow rates</i>”.</p>	<p>EWP comment:</p> <p><i>This comment seems to be a question of interpretation or wording. However, we have implemented this proposal in the final version of the updated guideline.</i></p>

224-226	<p>EFPIA: The statement: "... safety will also be influenced by the rate and extent of systemic absorption from the gastrointestinal tract..." does not acknowledge that systemic absorption may also occur from the respiratory tract. Absorption from the respiratory tract may be a substantial source of systemic exposure, and may be more important for safety considerations because blood flow from the bronchial tree does not go directly to the liver, and is thus not rapidly subject to first pass metabolism.</p> <p>Proposed change: "In addition, the safety will also be influenced by the rate and extent of systemic absorption from the <u>respiratory tract and the</u> gastrointestinal tract (i.e., the swallowed fraction)."</p>	<p>EWP comment: <i>We do not see any need of modification. The systemic absorption via lung is addressed in the first sentence of this paragraph.</i></p>
224-226	<p>IPAC-RS: Absorption from oropharyngeal mucosa is also relevant.</p> <p>Proposed change: Delete "from the gastrointestinal tract (i.e., swallowed fraction)".</p>	<p>EWP comment: <i>Agreed. The complete way through the gastrointestinal tract starts in the mouth, however in which extent the oropharyngeal mucosa will be relevant is questionable. A small amendment has been implemented.</i></p>
229-235	<p>EFPIA: CMC item "grouping of stages": this is not a standard CMC requirement in the EU. Products for nebulisation: the commercially available nebuliser device has a high impact on the CMC data and therefore equivalence data can only be compared by specifying the type of nebuliser. The proposed difference of "+/- 15 %" is unclear. Does it mean "+/- 15 % of the delivered dose (label claim)" or "+/- 15 % of the amount per stage / per group of stages"? The latter would be unrealistic especially in group stages where the amount of active ingredient is only a few percent of the total dose and, therefore, negligible for the clinical effect. It is thus proposed to reword the statement to keep the flexibility so that analysis can be performed on a case-by-case basis. It would be beneficial to provide some more guidance on how to determine the "pre-established maximum allowable difference" for the</p>	<p>EWP comment: <i>The whole section has been modified.</i></p>

	<p>mean difference between the reference and test products. In <i>in-vitro</i> comparisons, it is important to not only compare the means but the variation of the product results. A variability comparison should be included in the guidance.</p> <p>It is thus recommended that comparisons be based on individual stage APSD profiles not on the proposed 4 stage groupings.</p> <p>Proposed change:</p> <p>1.) State requirements that are in line with standard CMC requirements in the EU.</p> <p>2.) “The maximum allowable <i>in vitro</i> difference should be indicated and justified, e.g. +/- 15% may be justifiable.”</p>	
229-234	<p>IPAC-RS:</p> <p>A statistical comparison based on the 90% confidence interval applied to mean deposition on each stage or each group of stages from a cascade impactor may lead to inappropriate conclusions regarding equivalency. The properties of this or any other proposed statistical method should be understood before it is recommended in a guideline. A methodology for studying performance of a statistical test for comparing cascade impactor data is provided in recent reports from the Product Quality Research Institute.¹⁴ Furthermore, the meaning of the proposed limits (+/- 15 %) is unclear. Does it mean “+/- 15 % of the delivered dose (label claim)” or “+/- 15 % of the amount per stage / per group of stages”? The latter would be unrealistic and clinically irrelevant, especially for groups or stages where the amount of active ingredient is only a few percent of the total dose and is negligible for</p>	<p>EWP comment:</p> <p>1.) <i>We understand the need of the proposed meeting by the industry. However was not possible to manage such one within the tight timeline of this revision process. However, members of the group are open for participating on meetings and on relevant congresses. Hopefully, crucial points can be discussed and clarified. Furthermore, in case of concrete questions to a certain procedure there will be always the possibility to seek for a central or national scientific advice.</i></p> <p>2.) <i>This is a repetition of an issue which has been already raised also by other institutions .However, a justification is always expected for results which are outside of the recommended limits. Mentioned unrealistic and clinically irrelevant differences for groups or stages where the amount of active ingredient is only a few percent of the total dose are not considered as a ‘major concern’, normally.</i></p>

¹⁴ **Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols, Part 1: Background for a Statistical Method.** Adams WP, Christopher D, Lee DS, Morgan B, Pan Z, Singh GJP, Tsong Y, Lyapustina S. AAPS PharmSciTech. 2007; 8(1): Article 4. DOI: 10.1208/pt0801004. Available online at <http://www.aapspharmscitech.org/view.asp?art=pt0801004> (2007)

Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 2 - Evaluation of a Method for Determining Equivalence. Christopher D, Adams WP, Lee DS, Morgan B, Pan Z, Singh GJP, Tsong Y, Lyapustina S. AAPS PharmSciTech. 2007; 8(1): Article 5. DOI: 10.1208/pt0801005. Available online at <http://www.aapspharmscitech.org/view.asp?art=pt0801005> (2007)

Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 3 – Final Report on a Statistical Procedure for Determining Equivalence. D. Christopher, W. Adams, A. Amann, C. Bertha, P. R. Byron, W. Doub, C. Dunbar, W. Hauck, S. Lyapustina, J. P. Mitchell, B. Morgan, S. Nichols, Z. Pan, G. J. P. Singh, T. Tougas, Y. Tsong, R. Wolff, and B. Wyka AAPS PharmSciTech. 2007; 8(4): Article 90. DOI: 10.1208/pt0804090. <http://www.aapspharmscitech.org/view.asp?art=pt0804090> (2007).

	<p>the clinical effect.</p> <p><u>Proposed change:</u></p> <p>1.) This is another topic that would benefit from further discussion and consensus by industry and regulatory experts. We recommend the use of an Interested Parties meeting, led by the EWP, to discuss this topic and others before finalization of the guideline.</p> <p>2.) Consider including comparison of variability's in the guideline.</p> <p>It would also be beneficial for the guideline to provide some more guidance on <u>how</u> to determine the “<i>pre-established maximum allowable difference</i>” for the mean difference between the reference and test products.</p>	
231 -	<p><u>EGA:</u></p> <p>The limits as stated are very tight and could be impractical in certain instances when, for instance, a given stage contains a very small content (e.g., 1µg) which might correspond to the actual detection limit of the analytical method.</p> <p>We would require that limits for the individual stages be removed from this clinical guideline.</p> <p>In addition, the proposed limits of $\pm 15\%$ are too stringent, considering the high variability typically associated with cascade impaction data. Discussion on whether to propose a unique fixed wider range for the limits (e.g., $\pm 25\%$ or $\pm 35\%$) or to remove the limits for them to be set individually on a case by case basis and irrespectively would be more appropriately addressed in quality guidance e.g. under a revision of EMEA/CHMP/QWP/49313/2005.</p>	<p><u>EWP comment:</u></p> <p><i>The proposed limits have also been discussed with an external expert. Furthermore the limits are in line with the quoted guideline EMEA/CHMP/QWP/49313/2005. Each pharmaceutical company should know, the proposed limits in this guideline are a recommendation.</i></p>
231-235	<p><u>EGA:</u></p> <p>In principle different methods of statistical calculations can be considered. These will exercise an influence on the calculated final values of the confidence interval. However, the final acceptance limit stated in the guideline text must be in line with the method of statistical calculation. Experimental prerequisites (e.g., number of batches, cans, total measurements) and appropriate statistical approaches, which could serve as a guide for the in-vitro calculations, should be provided in the</p>	<p><u>EWP comment:</u></p> <p><i>From EWP point of view this proposal would be beyond the scope of this guideline. Statistical topics can be discussed in national or European scientific advices case by case. The inclusion of statistical details would be a very complex area. It is impossible to provide specific guidance as it would change on a case by case basis. This guideline specifies some general rules.</i></p>

	<p>guideline text.</p> <p><u>Proposed change:</u> Inclusion of statistical details and/or literature references appropriate for <i>in-vitro</i> equivalence calculations, which are in line with the required acceptance criterion.</p>	
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231-235	<p>EGA: Proposal for the inclusion of an alternative <i>in-vitro</i> equivalence calculation according to the calculation given in “<i>Human Respiratory Tract Model for Radiological Protection</i>”.</p> <p>Proposed change: Reference to the literature for the alternative calculation: <i>Human Respiratory Tract Model for Radiological Protection</i> (ICRP Publication 66, 1994; Elsevier Science, New York; Ann ICRP 1994; 24; 1-120).</p>	<p>EWP comment: <i>The proposed publication is a book from 1994. In which extent alternative in-vitro equivalence calculations could be accepted is always a question of justification. As mentioned before we discuss about a guideline. A detailed discussion of this issue should be addressed in a scientific advice.</i></p>
232	<p>EGA: Clarification would be welcome as to what the criteria are to conclude a lack of influence for any qualitative and/or quantitative differences in excipients on the performance of the product, aerosol particle behaviour and/or inhalation behaviour of the patient, and the safety profile of the product in order to be qualified for waiver of <i>in vivo</i> studies.</p>	<p>EWP comment: <i>In contrast to the old version of the guideline, we tried to be more precise with respect to in vitro comparability. From our point of view all aspects are adequately covered, so that an application based on in vitro data could be possible.</i> <i>It is the opinion of the EWP that this section is adequately enough in order to justify waivers of in vivo studies.</i></p>
234-235	<p>IPAC-RS: Commercially available nebuliser devices have a high impact on in vitro data and therefore equivalence data can only be compared by specifying the type of the nebuliser.</p> <p>Proposed change: Require that the same type and model of nebulisers be used in comparisons.</p>	<p>EWP comment: <i>Agreed. In section 4.3 is referred to the importance of the different kinds of nebulisation. Furthermore, the recommended nebuliser system should be addressed in the informative texts.</i></p>

4.3.1 Determination of pulmonary deposition		
Line no. ¹⁵ + paragraph no.	Comment and Rationale	Outcome
240-252	<p>Innovata Biomed Limited: Innovata Biomed Limited, whilst interested in different techniques available to demonstrate equivalence believes that the use of volunteers and imaging studies are not the most sensitive technique available. Innovata Biomed Limited believes that less emphasis should be given to this. IBL would query if healthy volunteers are suitable surrogates in imaging studies for patients with asthma and COPD.</p>	<p>EWP comment: <i>The EWP agrees. Imaging studies should be conducted with patients. In the concerned section the wording has been changed. Overall, equivalent pulmonary deposition demonstrated through imaging studies should be regarded as supportive data when used in the assessment of therapeutic equivalence in respect of efficacy.</i></p>
240-267	<p>Schering Plough: Is it accepted that pharmacokinetic studies can be considered deposition studies? In some cases plasma concentrations may reflect largely drug absorbed across the lung, in other cases that it is less clear. While the charcoal block may be able to bind drug in the stomach and beyond, it may not prevent absorption from the mouth and pharynx. We are not convinced it is possible to reliably separate pulmonary and gastrointestinal absorption for all compounds. Kinetic data can be considered in the context of other data but they cannot generally substitute true deposition data.</p>	<p>EWP comment: <i>PK studies can depict a model for assessment of pulmonary deposition. However, the EWP knows that PK studies for pulmonary deposition are not always possible or feasible. Another option to test lung deposition would be imaging studies. Imaging studies alone are not sufficient to claim therapeutic equivalence. If lung deposition can not be assessed the next step (i.e. clinically pharmacodynamic studies) will be necessary. To sum it up, if PK is not possible the agencies will not insist on PK. But the proof of TE via sufficient PK data (for safety and efficacy) will be acceptable.</i></p>
243	<p>EFPIA / IPAC-RS / Pfizer: The term “pharmaceutical quality” is described as a factor potentially impacting pulmonary deposition. However, the term pharmaceutical quality is a broad term considering standards of manufacture (e.g. cGMP) and elements of the performance of a dosage form. It is thus proposed to amend the sentence. Proposed change: Different excipients, different devices or different pharmaceutical quality aerosol performance characteristics of inhalation products containing the same active substance may have an</p>	<p>EWP comment: <i>Many thanks for this hint. The wording has been changed (please compare final version of the guideline).</i></p>

¹⁵ Where applicable

	important influence on pulmonary deposition resulting in a clinically relevant impact on efficacy and safety.	
245-248	<p>EFPIA: Please provide clarification and additional information (for example a literature reference or data) to support the statement that ... "one way to demonstrate equivalence in terms of local availability may be through a comparison of pulmonary deposition." In principle, a failure to show <i>in vitro</i> bioequivalence should not allow <i>in vivo</i> testing of lower sensitivity to establish bioequivalence e.g. lung deposition or pharmacodynamic endpoints.</p>	<p>EWP comment: <i>It is believed by the EWP that the development of a hybrid product should be done according a hierarchical concept. Firstly, in vitro comparability is tested, if this test is not successful, then secondly pulmonary deposition should be compared and if here the results are not successful again, thirdly the influence of these in vitro and in vivo differences has to be investigated in (an) adequate pharmacodynamic study / studies.</i></p>
249	<p>EFPIA: This indicates that pulmonary deposition studies should be double blind. This can be extremely difficult when devices differ in appearance and, are also probably unnecessary considering the objective nature of these studies. Proposed change: Remove requirement for double-blind studies.</p> <p>EGA: It should be reconsidered whether double-blind studies are really mandatory for pharmacokinetic (PK) studies. Classical PK studies for oral applications are in accordance with the respective guidance for bioequivalence (EMA CPMP/EWP/1401/98, 2001) unblinded and it is not comprehensible that a "hard" parameter such as plasma concentrations could be influenced by the investigator and/or subject in the direction of equivalence within the narrow equivalence limits. Furthermore, a double-blind design is unfeasible for substances with very short Tmax: In most cases the mouthpieces of the generic inhalator will differ from the reference product due to reasons of patent, which necessitates a double-dummy approach to allow double-blinding. Present analytical methods are, for many substances, not sensitive enough to perform plasma concentration measurements over the entire time that is necessary to establish an AUC. In consequence, two or more actuations will be necessary for many substances. A double-dummy design will</p>	<p>EWP comment: <i>Pulmonary deposition studies should be double-blinded designed. It is well-accepted that the inhalation manoeuvre is one important aspect of pulmonary deposition. Therefore, any manipulation of the inhalation manoeuvre should be excluded or the procedure should be harmonised. A dummy device can always be produced and disadvantage of the time consuming process (inhalation of two devices) will always be the same. Difficulties due to logistical reasons (e.g. Tmax of Salmeterol / Formoterol is after 5-10 minutes) will also be the same in both groups. Furthermore the main PK parameters are Cmax and AUC. The EWP is convinced that a blinding is feasible. The issue of possible insensitive analytical methods for detection was discussed previously (compare aforementioned comments).</i></p>

	<p>double the amount of actuations (i.e., 4 or even more), as the same number of inhalations has to be performed from the active arm and from the placebo containing device and as the time between two actuations is usually 30 seconds. The time between the first and last actuation in a double dummy design would be about 2 or more minutes, which is not practicable for very rapidly absorbed substances (for example salmeterol, formoterol have a tmax of 5 minutes).</p> <p><u>Proposed change:</u> Please re-consider term “double blind”.</p>	
250	<p><u>EGA:</u></p> <p>The term “clinically relevant doses” should be specified, i.e., whether the maximum single or daily dose should be preferred. However, it has to be taken into consideration that for many substances the current analytical methods are not sensitive enough to quantify drug level for a sufficient period of time after a single inhalation.</p> <p><u>Proposed change:</u> Please clarify term “clinically relevant doses”.</p>	<p><u>EWP comment:</u></p> <p><i>The aspect of possible insensitive analytical methods has been already discussed. The term “clinically relevant doses” should be clear with regard to pulmonary deposition studies (clinical recommended dosages which should be detectable over a relevant time) as well as with regard to pharmacodynamic studies (proof of assay sensitivity; safety aspects should be investigated with the highest recommended dose).</i></p>
251	<p><u>EFPIA:</u></p> <p>Healthy subjects should not be used in deposition studies since we know that patients with lung disease have altered lung deposition compared to healthy subjects.</p>	<p><u>EWP comment:</u> Agreed. An amendment has been implemented in the final version of the guideline.</p>
252	<p><u>IPAC-RS:</u></p> <p>The text of the guideline may need to explain more clearly that PK studies may be useful as a tool in certain circumstances to investigate pulmonary deposition and that care should be taken in interpreting the results.</p> <p>In some cases plasma concentrations may reflect largely drug absorbed across the lung, in other cases that it is less clear. While the charcoal block may be useful in some cases, it may not be able to reliably separate pulmonary and gastrointestinal absorption for all compounds (e.g., due to absorption from the mouth and pharynx). Kinetic data can be considered in the context of other data, e.g., in combination with data on oral absorption, although they may not always substitute true deposition data.</p>	<p><u>EWP comment:</u></p> <p><i>PK studies can depict a model for assessment of pulmonary deposition. However, the EWP knows that PK studies for pulmonary deposition are not always possible or feasible. Another option to test lung deposition would be imaging studies. Imaging studies alone are not sufficient to claim therapeutic equivalence. If lung deposition can not be assessed the next step (i.e. clinically pharmacodynamic studies) will be necessary. To sum it up, if PK is not possible the agencies will not insist on PK. Concerning absorption from the mouth and oropharynx: the patients should rinse their mouth after inhalation.</i></p> <p><i>2.) The implementation of a decision tree for determining which studies are needed under which circumstances was intensively discussed by the EWP. A decision tree does also open the possibilities of confusing,</i></p>

	<p><u>Proposed change:</u></p> <p>1.) This is a third topic that would benefit from further discussion and consensus by industry and regulatory experts. We recommend the use of an Interested Parties meeting, led by the EWP, to discuss this topic and others before finalization of the guideline.</p> <p>2.) It would be extremely helpful if the guideline included a decision tree for determining which studies are needed under which circumstances.</p>	<p><i>because not all pros and cons can be reflected simply in such a decision tree.</i></p> <p><i>Therefore, it was tried to be as concrete as possible/necessary in the final version of the guideline.</i></p>
252, 262-262, 265-267	<p><u>TEVA:</u></p> <p>It is proposed that the demonstration of therapeutic equivalence could be established with pulmonary deposition studies (imaging or PK studies) in healthy volunteers and these type of studies should be carried out <u>prior to</u> carrying out therapeutic equivalence studies”. In the later text, it states that “Equivalent pulmonary deposition in combination with safety data (for example data from a systemic safety PK study) might be considered as sufficient demonstrating of therapeutic equivalence.” This text implies that pulmonary deposition with imaging studies only is not sufficient for demonstration of therapeutic equivalence.</p> <p>There is a need for clarification in the following areas:</p> <ul style="list-style-type: none"> ➤ Whether or not clinical studies are still required if comparable pulmonary deposition is demonstrated? ➤ Whether or not both Imaging and PK studies are required or only one of them is required or one imaging study and a PK study without charcoal? <p>It should also be noted that there are no validated methods and surrogate for imaging studies. Further guidance would be necessary to avoid potential interpretation differences among the Member States.</p> <p><u>Proposed change:</u></p>	<p><u>EWP comment:</u></p> <p><i>This comment is in line with some other statements.</i></p> <p><i>1.) This wording opens space for interpretation. However, equivalent lung deposition, which can be shown via PK studies as well as imaging studies, does not simultaneously imply equivalent safety. Additional investigations will be necessary. Furthermore, the final decision depends on the study. It is not possible to say ‘is considered’ (instead of ‘might be considered’), because there are a lot of gaps and possibilities for major objections. TE has to be shown with regard to efficacy and safety and then there will be no basis for further requirements.</i></p> <p><i>However, it has to be pointed out that the statistical criteria will be slightly modified. The section has been modified.</i></p> <p><i>2.) A decision tree has not been implemented for several reasons (see aforementioned general comment.).</i></p>

	<p>1.) It should be made clear that no further clinical studies are required if equivalence criteria (see below), as determined by pulmonary deposition (including safety data from the PK study) is demonstrated between the test and the reference product.</p> <p>Two inhaled products are considered to be equivalent in pulmonary deposition if the following criteria are met:</p> <p>Imaging studies: 95%CI, 0.8-1.25 (% deposition in the whole lung, central, intermediate and peripheral lung zone, oropharynx, mouthpiece, actuator and exhalation filter).</p> <p>PK studies: (a) with charcoal: 95%CI, 0.8-1.25 for C_{max}, T_{max} and AUC and/or (b) without charcoal (systemic exposure-safety): 90%CI 0.8-1.25</p> <p>Equivalent pulmonary deposition can be demonstrated by either imaging studies and PK systemic studies or PK studies with and without charcoal.</p> <p>2.) A decision tree could be referenced.</p>	
260	<p>EGA:</p> <p>The term “plasma concentrations” should be modified into “plasma/urinary concentrations” for purposes of consistency, in accordance with line no. 254.</p> <p>Proposed change: “some cases plasma/<u>urinary</u> concentrations”...</p>	<p>EWP comment:</p> <p><i>Agreed. The word 'urinary' has been added in the final version of the guideline.</i></p>
260	<p>EGA:</p> <p>Concerning the term “clinical doses”, please see comment concerning line no. 250 “clinically relevant doses”.</p> <p>If plasma concentrations are not sufficiently measurable in classical bioequivalence studies, the number of tablets can be increased. The same is, in our opinion, applicable to OIP PK studies, i.e. the number of actuations is to be increased. Any possible upper limit should be specified as well.</p> <p>Proposed change: Please clarify term “clinical doses” and specify any possible upper dose/actuation limit.</p>	<p>EWP comment:</p> <p><i>See aforementioned comment. Possible upper dose/actuation limits can only be defined case by case (depends on clinical benefit/risk assessment).</i></p>
262	<p>EFPIA:</p>	<p>EWP comment:</p>

<p>It is mentioned in the draft guideline, there seem to be circumstances in which equivalent pulmonary deposition in combination with safety data might be considered sufficient to demonstrate therapeutic equivalence. In principle, equivalent pulmonary deposition in combination with safety data (for example data from a systemic safety PK study) might be considered as sufficient demonstration of therapeutic equivalence. Please indicate the circumstances in which equivalent pulmonary deposition in combination with safety data would be considered sufficient to demonstrate therapeutic equivalence. Taking into account that the validation of pulmonary deposition studies is still not sufficient to allow this, it could be also considered to keep the existing wording from the previous guideline “Comparative studies of in vitro inhaler performance, in vivo lung deposition and pharmacokinetics have yet to be validated as surrogates of the safety and efficacy of inhaled anti-asthmatic agents”.</p> <p>Proposed change: “Comparative studies of in vitro inhaler performance, in vivo lung deposition and pharmacokinetics have yet to be validated as surrogates of the safety and efficacy of inhaled anti-asthmatic agents”.</p> <p>Pfizer:</p> <p>The circumstances in which equivalent pulmonary deposition in combination with safety data might be considered sufficient to demonstrate therapeutic equivalence are not given.</p> <p>Proposed change: Indicate the circumstances in which equivalent pulmonary deposition in combination with safety data would be considered sufficient to demonstrate therapeutic equivalence.</p> <p>IPAC-RS:</p> <p>The circumstances in which equivalent pulmonary deposition in combination with safety data might be considered sufficient to demonstrate therapeutic equivalence are not given.</p> <p>Proposed change: Indicate the circumstances in which equivalent pulmonary deposition in combination with safety data would be considered sufficient to demonstrate therapeutic equivalence. In</p>	<p><i>This will be a case by case decision. However, we would like to avoid a more fixed statement. The final decision depends on the presented information.</i></p> <p><i>For example, there are not any doubts on safety and efficacy data which based on a complete (e.g. with and without charcoal) pharmacokinetic study and the active substance can be measured systemically in an adequate amount (no limits of detection) and in vitro equivalence has been nearly shown (showing of equivalence in vitro was not possible for limited causes) then the presented data would be sufficient.</i></p> <p><i>Based on these facts, the proposed wording has not been implemented. However, the whole section has been modified (Please compare final version of the guideline). The acceptance criteria have been well described in the final version. (Please compare paragraph in vitro and pulmonary deposition). If requirements have been fulfilled the next step will not be necessary.</i></p>
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	<p>addition, clarify circumstances in which a PK study and in vitro data may be sufficient / acceptable.</p> <p>Siegfried Pharma Development GmbH: It needs to be clarified what is described with the wording “Equivalent pulmonary deposition...” in this sentence because according to previous definitions given in this chapter this may be either an imaging study or an PK study. The definition of equivalence should be clarified. For instance, what would be the criteria for fixed combinations, e.g. ICS/LABAs as the desired deposition might be different for each component due to different mode of actions and possibly of different site of actions. Proposed change: Rephrase the sentence to clarify what is meant with e.g.: “Equivalence in pulmonary deposition, as evidenced by imaging studies.”</p>	
262-263	<p>EGA: The preferred dose for a systemic safety study, i.e. the maximum single or daily dose, is not clear. Clarification as to the reason for having emphasised the ‘might’ (in bold type) would be welcome. Proposed change: Please specify the dose for systemic safety studies.</p> <p>Siegfried Pharma Development GmbH: The term “systemic safety PK study” is here introduced first-time without further explanation. The reader may wonder about the differences between a “pulmonary deposition PK study” and a “systemic safety PK study”. Proposed change: We suggest explaining the term “systemic safety PK study” in the GLOSSARY particularly in its differentiation to the “pulmonary deposition PK study”.</p>	<p>EWP comment: <i>See aforementioned comment. It should be highlighted that the proof of equivalent safety via PK (assessment of the systemic amount after pulmonary and gastrointestinal absorption in a clinical relevant dose; possibility of extrapolation) has to be differentiated from the proof of equivalent safety via classically pharmacodynamic and/or clinical studies (here the highest recommended dose has to be investigated). As requested, a clarification has been implemented.</i></p>
262-264	<p>Pfizer: Equivalent pulmonary deposition in combination with safety data (for example data from a systemic safety PK study might be considered as</p>	<p>EWP comment: <i>A modified wording of the raised issues has been implemented. Please compare.</i></p>

	<p>sufficient demonstration of therapeutic equivalence. Otherwise therapeutic equivalence must be demonstrated by means of appropriate clinical studies.</p> <p>Proposed change: It is proposed that the statement on “will almost always be required” be clarified – for example where in vitro equivalence and equivalent PK deposition is observed then Therapeutic Equivalence studies are not required. Moreover, clarity on where the conditions where a PK study and in vitro data may be acceptable should be provided.</p>	<p><i>However, it should be stated that the development of inhaled products is a step by step process: in vitro -> in vivo pulmonary deposition-> in vivo PD studies. It is tried in the NfG to emphasize in which case / in which circumstances clinical studies are necessary and in which extent.</i></p>
265-267	<p>Innovata Biomed Limited:</p> <p>Innovata Biomed Limited believes that this should reference pharmacokinetic studies rather than deposition studies. Innovata Biomed Limited believes this guideline suggests a Bioequivalence approach is preferred over a traditional therapeutic equivalence approach to demonstrate equivalence for follow on/generic products. A key question that remains is: Are traditional “therapeutic equivalence” studies considered to be the final step in the “stepwise approach” when PK/PD studies have failed to demonstrate bioequivalence? Or, is a failure to demonstrate bioequivalence in a PK/PD study an end to the route of generic hybrid marketing authorisation application according to Directive 2004/27/EC, Article 10(3), leading the company instead into full stand alone placebo controlled studies in line with the Fixed Dose Combination Guideline?</p>	<p>EWP comment:</p> <p><i>It is a part of the recommended stepwise approach that pharmacodynamic studies as described in the updated guideline are the final step to confirm therapeutic equivalence when lung deposition studies failed the demonstrate equivalence.</i></p>
266	<p>EFPIA:</p> <p>“Prior to” is not adequate and could be misinterpreted. A revision is thus proposed.</p> <p>Proposed change: “Pulmonary deposition (whenever possible) and <i>in vitro</i> characterisation of the active drug, comparing the new product with a reference product, should be investigated prior <u>in addition to</u> carrying out therapeutic equivalence studies”.</p>	<p>EWP comment:</p> <p><i>Please note ‘should’ and prior. Complete TE studies would only be necessary if TE was not shown by in vitro and pulmonary deposition studies.</i></p>

4.3.1.1 Imaging studies		
Line no. ¹⁶ + paragraph no.	Comment and Rationale	Outcome
269-276	<p>EFPIA / Pfizer:</p> <p>We are not aware of a validated imaging method to use to establish bioequivalence of inhaled products. However, using a combination of <i>in vitro</i> data and pulmonary deposition data would make a stronger case regarding the equivalence of two inhalers as it allows for the variability introduced when people (rather than impactors) are used to sample the aerosol cloud. However there are a number of technical details that need to be attended to if the data from a scintigraphic deposition study are to be considered meaningful. The deposition studies must therefore be conducted in line with scientific best practice (Snell and Ganderton, 1999)¹⁷. Of particular note is the need to ensure that the time to acquire the images is controlled and relevant to the radiopharmaceutical used to radiolabel the aerosol and the methodology used to correct for the attenuation (scatter and absorption) of the gamma rays by the body.</p> <p>The draft guideline mentions that both 2D and 3D imaging techniques may be used. When scintigraphic studies are conducted correctly, planar (2D) imaging will provide accurate data regarding the amount of drug deposited in the whole lung, along with a semi-quantitative assessment of how much drug has been deposited in the different lung zones. 3D imaging modalities such as SPECT and PET can also provide accurate data regarding whole lung deposition and are inherently better at discriminating between large and small airways. However, the images need to be analysed and the methods for generating deposition data for different airways are still being developed and subject to validation.</p>	<p>EWP comment:</p> <p><i>The EWP has strongly considered all the raised argumentations to the controversial topic. The requirement:</i></p> <p><i>“3D dimensional scintigraphic methods „has been deleted.</i></p> <p><i>For evaluation of lung deposition, the possibility of radiolabeling studies has been shortly explained in this guideline. Also the validity/ranking of radiolabeling studies has been discussed.</i></p> <p><i>Imaging studies do not investigate any safety aspect. Therefore, further investigations would be necessary in each case.</i></p> <p><i>The requested 90%CI has been included .The fulfilling of the criteria of highly variable drugs is a case by case decision within a certain approval procedure.</i></p> <p><i>All in all, this section has been completely modified. All other aspects which are not addressed in the final version of the guideline can be discussed during a scientific advice / pre-submission meeting before start of the procedure or within the special approval procedure.</i></p>

¹⁶ Where applicable

¹⁷ Snell, NJC and Ganderton, D; Report: Assessing Lung Deposition of Inhaled Medications – Consensus statement from a workshop of the British Association for Lung Research, held at the Institute of Biology, London UK (Apr 1998); Respiratory Medicine (1999) 92, 123-133.

¹⁸ Snell, NJC and Ganderton, D; **Report: Assessing Lung Deposition of Inhaled Medications – Consensus statement from a workshop of the British Association for Lung Research, held at the Institute of Biology, London UK (Apr 1998); Respiratory Medicine (1999) 92, 123-133.**

	<p>Coupled to the observation, is the fact that the 3D imaging modalities are more technically challenging in terms of radiolabeling the drug in question. Consequently, 2D imaging is likely to remain the modality of choice for companies wishing to assess drug delivery from inhalation devices.</p> <p>In addition, and in line with the major comments raised at the beginning of the document, it is our view that equivalent lung deposition of two drugs can be concluded if the 95 % CI of the radioactivity in all of the several airway areas is within a range of 0.8 to 1.25. However, given the relatively small nature of these studies due to operational practicalities, using a 95% CI with 80-125% acceptance criteria may result in many ‘failed’ studies simply due to within subject variability not allowing CI’s to be that narrow.</p> <p>The draft guideline also indicates that equivalence can be determined if “all of several airway areas” have CIs for the ratios between test and reference that fall within 80-125%. Does this mean that independently each area, i.e., whole lung, central, peripheral, intermediate, etc, has to meet the BE criteria? Please clarify.</p> <p>Finally, the draft guideline requests the radiolabeling should have “no influence on the deposition characteristics”. This in our view would exclude radiolabeled studies to be used.</p> <p><u>Proposed change:</u></p> <p>1.) Acknowledgment of the consensus statement should be factored into the draft guideline, particularly the conclusions 2D vs. 3D.</p> <p>Additionally, the guideline may need to state that provided both inhalers are radiolabeled to the same ‘quality standard’ (i.e. acknowledge that a degree of mismatch between drug and radiolabel is inevitable but state what is acceptable and what is not) then methodology could be used to show equivalence.</p> <p>This is particularly difficult problem to resolve. As a minimum, the radiolabeling validation data should be clearly presented and any mismatches between drug and radiolabel noted and discussed in relation to the objective of the clinical study.</p> <p>2.) Suggest changing to 90% CI and allowing prospective widening of acceptance boundary for highly variable reference drugs.</p>	
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	<p>3.) Proposed rewording: “The influence of the radiolabeling on the deposition characteristics should be evaluated at relevant flow rates and be shown to have negligible It has to be assured that the radio labelling of the inhaled products has no influence on the deposition characteristics”.</p> <p>IPAC-RS:</p> <p>Radioimaging studies may be an important tool for inhaler developments but they cannot widely substitute efficacy data. Using a combination of in vitro data and pulmonary deposition data would make a stronger case regarding the equivalence of two inhalers as it allows for the variability introduced when people (rather than impactors) are used to sample the aerosol cloud. However there are a number of technical details that need to be attended to if the data from a scintigraphic deposition study are to be considered meaningful. The deposition studies must therefore be conducted in line with scientific best practice (Snell and Ganderton, 1999)¹⁸. Of particular note is the need to ensure that the time to acquire the images is controlled and relevant to the radiopharmaceutical used to radiolabel the aerosol and the methodology used to correct for the attenuation (scatter and absorption) of the gamma rays by the body.</p> <p>The draft guideline mentions that both 2D and 3D imaging techniques may be used. When scintigraphic studies are conducted correctly, planar (2D) imaging will provide accurate data regarding the amount of drug deposited in the whole lung, along with a semi-quantitative assessment of how much drug has been deposited in the different lung zones. 3D imaging modalities such as SPECT and PET can also provide accurate data regarding whole lung deposition and are inherently better at discriminating between large and small airways. However, the images need to be analysed and the methods for generating deposition data for different airways are still being developed and subject to validation. Coupled to the observation, is the fact that the 3D imaging modalities are more technically challenging in terms of radiolabeling the drug in question. Consequently, 2D imaging is likely to remain the modality of choice for companies wishing to assess drug delivery from inhalation</p>	
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	<p>devices.</p> <p>Proposed change: Acknowledgment of the consensus statement should be factored into the draft guideline, particularly the conclusions regarding 2D vs. 3D imaging.</p> <p>Additionally, the guideline may need to state that provided both inhalers are radiolabeled to the same 'quality standard' (i.e., acknowledge that a degree of mismatch between drug and radiolabel is inevitable but state what is acceptable and what is not) then methodology could be used to show equivalence.</p> <p>This is particularly difficult problem to resolve. As a minimum, the radiolabeling validation data should be clearly presented and any mismatches between drug and radiolabel noted and discussed in relation to the objective of the clinical study.</p> <p>Pari Pharma GmbH:</p> <p>For imaging studies no standard procedure is available. The sensitivity and precision of the techniques depends very much on the institute that performs the analysis. To distinguish between the different regions of interest with 2D imaging techniques is due to the nature of the technique not a real determination; at most it could be regarded as estimation. 3D imaging techniques might be better in this respect, but have a higher radioactive burden for the patient, which is, particularly with studies in children, not wanted. Since many inhalation drugs are primarily used in the younger population, 2D studies will still remain of value. Thus proving equivalent lung deposition for all of the several airways is not within the scope of the today available techniques. We would hence propose that equivalent lung deposition should be based on total lung deposition, only.</p> <p>Schering Plough:</p> <p>Radioimaging studies may be an important tool for inhaler developments but they can not widely substitute efficacy data. There are a number of methodological limitations including the fact that the radiolabeling process has the potential to alter the product in various ways which may or may not be captured by the in-vitro validation.</p>	
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271-272	<p>Orion Pharma: It is proposed that equivalent lung deposition of two drugs can be concluded if the 95% CI of the radioactivity in all of the several airway areas is within a range of 0.8 to 1.25. It is not clear what “all of the several airway areas” refers to. Does it mean total lung AND central lung AND intermediate lung AND peripheral lung AND oropharynx? And are the confidence intervals for each of these to be within 0.8 to 1.25? Due to the stochastic nature of confidence intervals, it is likely that all confidence intervals would not simultaneously be within the acceptance range even when two batches of the same product were compared, and this requirement (if correctly interpreted) seems overly restrictive. For a comment on the 95% confidence interval, please see the comment given in the next row. Proposed change: Please state the requirement explicitly. Instead of a 95% confidence interval, a 90% confidence interval should be used.</p> <p>EGA: Bearing in mind a perspective of bioequivalence (acceptance range i.e. 80 - 125%), it is believed this should read 90%CI not 95%CI.</p> <p>IPAC-RS: Given the relatively small nature of imaging studies due to operational practicalities, using a 95% CI with 80-125% acceptance criteria may result in many ‘failed’ studies simply due to within-subject variability not allowing CIs to be that narrow. Proposed change: Suggest changing to 90% CI and allowing prospective widening of acceptance boundary for highly variable reference drugs.</p> <p>Pari Pharma GmbH: “Equivalent lung deposition of two drugs can be concluded if the 95 % CI of the radioactivity in all of the several airway areas is within a</p>	<p>EWP comment: <i>The EWP partly agrees. For analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here the 95% CI should lie within the acceptance range of 0.8 to 1.25, unless other justified. One exemption has to be raised. For calculation of the relative potency the CI can be widened (please compare final guideline). The addressed widening of acceptance boundary (compare IPAC-RS comment) should be a case by case decision. Please take into account that a widening of AUC is not possible. It is advised to seek for a scientific advice.</i></p>

	<p><i>range of 0.8 to 1.25.”</i></p> <p>Delivery efficiency in inhalation therapy is depending on many factors such breathing pattern, airways dimensions, disease condition, age of the patient, the device used, and the device handling. The defined statistical criteria to prove equivalent lung deposition are from our experience unrealistic for a therapy with a known higher variability in drug delivery accuracy. We would propose to set a statistical criterion that also is defined in the current bioavailability guideline (EWP/QWP/1401/98) for products of higher variability of 90% CI of 0.75-1.33.</p> <p><u>Proposed change:</u> Equivalent lung deposition of two drugs can be concluded if the 90% CI of the radioactivity in the total lung is within a range of 0.75 to 1.33.</p> <p><u>Pfizer:</u></p> <p>Equivalent lung deposition of two drugs can be concluded if the 95 % CI of the radioactivity in all of the several airway areas is within a range of 0.8 to 1.25.</p> <p>Given the relatively small nature of these studies due to operational practicalities, using a 95% CI with 80-125% acceptance criteria may result in many ‘failed’ studies simply due to within subject variability not allowing CI’s to be that narrow.</p> <p><u>Proposed change:</u> Suggest changing to 90% CI and allowing prospective widening of acceptance boundary for highly variable reference drugs.</p> <p><u>Siegfried Pharma Development GmbH:</u></p> <p>The statement “... the acceptance criterion of 95% CI should be within a range of 0.8 to 1.25” is not in line with the BE requirements for oral products as detailed in CPMP/EWP/QWP/1401/98.</p> <p>Please refer also to section 4.3.1.2.and also 4.3.2.2.</p> <p><u>Proposed change:</u> We propose to replace “95%” by “90%” for the confidence interval.</p>	
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4.3.1.2 Pharmacokinetic studies		
Line no. ¹⁹ + paragraph no.	Comment and Rationale	Outcome
278-282	<p>EGA: For some substances like fluticasone propionate gastrointestinal absorption is negligible (<1%) and the systemic activity results mainly from pulmonary absorption. In these cases one pharmacokinetic study assessing pulmonary deposition should be sufficient.</p> <p>Proposed change: “a pharmacokinetic study to investigate systemic safety has to measure total systemic exposure and therefore must not exclude that amount of the active moiety absorbed through the gastrointestinal tract. <u>However, for substances with negligible gastrointestinal absorption, the PK study designed only to assess the pulmonary deposition study is sufficient.</u>”</p>	<p>EWP comment: <i>Many thanks for this comment. The proposed sentence has been added in the relevant paragraph.</i></p>
278-285	<p>EFPIA/ IPAC-RS / Pfizer: It is unclear whether the bioequivalence criteria are to be applied to the formulations in the presence of charcoal (which gives an estimate of lung dose) or in the absence of charcoal (which may relate to systemic effects) or both. It should be mentioned whether the method using charcoal blockade needs to be validated. Does the charcoal completely block GI absorption? Is the particular charcoal-dosing schedule (amount, time, etc.) used in the investigation able to adequately block the GI absorption? Proposed change: Additional clarity should be provided. It is unclear to the reader if the first sentence should be two separate points, i.e. pulmonary deposition vs. PK. Therefore, indicate whether the bioequivalence criteria are to be applied</p>	<p>EWP comment: <i>All the raised aspects have been considered by the EWP. The section has been comprehensively amended and modified. Please compare the final version of the guideline.</i> <i>With regard to the charcoal aspect, the use of charcoal is only given as an example to investigate the lung deposition. Of course, if charcoal is used the method will have to be validated (as well as all other used methods should be validated).</i> <i>Therapeutic equivalence should be investigated with regard to efficacy and safety. Statistical criteria for equivalence with regard to efficacy and safety are described in the final version of the guideline. Please compare.</i> <i>All in all, the statistical issues are re-considered. Slight amendments are implemented.</i></p>

¹⁹ Where applicable

	to the formulations in the presence of charcoal (which gives an estimate of lung dose) or in the absence of charcoal (which may relate to systemic effects) or both.	
282-285	<p>EFPIA:</p> <p>The guideline makes reference that bioequivalence be compared using Cmax, AUC and Tmax.</p> <p>Please provide additional data to support the premise that the mentioned PK parameters correlate with clinical efficacy for orally inhaled medicinal products.</p> <p>In addition, the inclusion of Tmax could mean that small clinically irrelevant differences (in Tmax), particularly for an anti-inflammatory drug, may result in a conclusion of lack of equivalence. In contrast the Guideline on Bioavailability and Bioequivalence requires Tmax is only required to be evaluated “if there is a clinically relevant claim for rapid release or actions or signs related to adverse events”. A similar position should be reflected in this guidance.</p> <p>The draft guideline states “Equivalent pulmonary deposition of two inhaled products may be concluded if the 95 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25”.</p> <p>Proposed change:</p> <p>1.) Revised the guideline to reflect that “<u>Tmax should only be evaluated if there is a clinically relevant claim for rapid release or actions or signs related to adverse events</u>”.</p> <p>2.) PK acceptance boundary should be based on 90% confidence interval to be consistent with other regulatory guidance’s, e.g. http://www.emea.europa.eu/pdfs/human/ewp/4032606en.pdf</p> <p>Similarly, consideration should be made for reference drugs/products with highly variable pharmacokinetics – the acceptance boundaries could be widened prospectively for drugs with high within subject variability.</p> <p>Finally, provide scientific justification for the bioequivalence criteria as</p>	<p>EWP comment:</p> <p><i>The proposed hints have been taken into account. The EWP decided to modify the wording (please compare final version of the guideline).</i></p> <p><i>For analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here it is expected that the 95% CI lies within the acceptance range of 0.8 to 1.25, unless other justified. One exemption has to be raised. For calculation of the relative potency the CI can be widened (please compare final guideline).</i></p> <p><i>With regard to PK studies, a widening of acceptance boundary (e.g. for Cmax) should be a case by case decision. However, a widening of AUC is not possible. In these cases, it is advised to seek for a scientific advice.</i></p>

	<p>applied to safety end points, or allow for sponsors to justify criteria to be applied for individual products, based on therapeutic index of drug.</p> <p>IPAC-RS: The guideline recommends that bioequivalence be compared using C_{max}, AUC and T_{max}. The inclusion of T_{max} could mean that small clinically irrelevant differences (in T_{max}), particularly for an anti-inflammatory drug, may result in a conclusion of lack of equivalence. In contrast, in the <u>CPMP/QWP/EWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence</u> (http://www.emea.europa.eu/pdfs/human/ewp/140198en.pdf), T_{max} is only required to be evaluated “<i>if there is a clinically relevant claim for rapid release or actions or signs related to adverse events</i>”. A similar position should be reflected in this guideline. Proposed change: Revise the guideline to reflect that T_{max} should only be evaluated “<i>if there is a clinically relevant claim for rapid release or actions or signs related to adverse events</i>”.</p> <p>Pfizer: The guideline makes reference that bioequivalence be compared using C_{max}, AUC and T_{max}. The inclusion of T_{max} could mean that small clinically irrelevant differences (in T_{max}), particularly for an anti-inflammatory drug, may result in a conclusion of lack of equivalence. In contrast the Guideline on Bioavailability and Bioequivalence requires T_{max} is only required to be evaluated “if there is a clinically relevant claim for rapid release or actions or signs related to adverse events”. A similar position should be reflected in this guidance. Proposed change: Revise the guideline to reflect that T_{max} should only be evaluated “if there is a clinically relevant claim for rapid release or actions or signs related to adverse events”.</p>	
282-285	<p>EGA: According to the beginning of the sentence “In accordance with the standard accepted methods of assessment of bioequivalence”, standard methods according to the respective guidance for bioequivalence</p>	<p>EWP comment: <i>We share the view with regard to T_{max}. An amendment has been implemented (please compare). The statistical criteria are re-considered. Slight amendments have been</i></p>

	<p>(EMA CPMP/EWP/1401/98, 2001) should be applied for the pulmonary deposition, which imply the calculation of the 90% confidence intervals for ratios (test/reference) of means of the primary endpoints AUC and C_{max}. According to standard procedures, T_{max} should not be included in the 90% CI calculation because of its variability and clinical importance. It should be analysed by hypothesis testing based on non-parametric analysis as secondary endpoint. The criteria for demonstration of bioequivalence in the systemic safety study should be specified as well. They should be the same as for the pulmonary deposition study (which is in accordance with the criteria specified in section 4.3.2.2 line 340-435).</p> <p>Proposed change: In accordance with the standard accepted methods of assessment of bioequivalence C_{max}, the time to C_{max} (T_{max}) and the area under the curve (AUC) should be compared. Equivalent pulmonary deposition of two inhaled products may be concluded if the 90 95% confidence interval for <u>both each</u> parameters lies within the acceptance range of 0.8 to 1.25. <u>The same applies to systemic safety studies.</u></p>	<p><i>implemented.</i></p>
283-285	<p>Pari Pharma GmbH:</p> <p><i>“In accordance with the standard accepted methods of assessment of bioequivalence C_{max}, the time to C_{max} (T_{max}) and the area under the curve (AUC) should be compared. Equivalent pulmonary deposition of two inhaled products may be concluded if the 95 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25.”</i></p> <p>It is unclear if the defined acceptance criteria are supposed to be applied only if the PK study is meant to act as a <u>substitute for an imaging study</u> to show equivalent lung deposition (using for example charcoal to eliminate gastrointestinal adsorption). We hence would propose to change the order of the sentences in this paragraph (see text proposal right column).</p> <p>The draft guideline states it would be in compliance with standard accepted methods of bioequivalence. The guideline EWP/QWP/1401/98 however demands a 90% CI not a 95% CI for C_{max}, T_{max} and AUC.</p>	<p>EWP comment:</p> <p><i>This paragraph/section has been completely modified. Please compare final version of the guideline.</i></p> <p><i>For analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here the 95% CI should lie within the acceptance range of 0.8 to 1.25, unless other justified. One exemption has to be raised. For calculation of the relative potency the CI can be widened (please compare final guideline). All in all, the use of other margins should always be justified.</i></p>

	<p>Still a range of 0.8 to 1.25 even for a 90% CI is unrealistic for inhalation therapies with an intrinsic variability in delivery efficiency. We again would propose to have a 90% CI with 0.75 to 1.33 in compliance with the current bioavailability guideline (EWP/QWP/1401/98) for products of higher variability.</p> <p>Further the guideline should also consider that in cases of locally acting products (e.g. inhaled antibiotics) a PK study could have the objective to have lower systemic plasma drug levels as the reference product. In such cases to have a lower limit for C_{max} and AUC does not make sense. We hence would propose to have for systemic PK studies or studies with locally acting drugs no limits defined.</p> <p>Proposed change: A pharmacokinetic study designed to assess pulmonary deposition, has to be able to exclude absorption of the active moiety from the gastrointestinal tract (for example by using charcoal blockade); In accordance with the standard accepted methods of assessment of bioequivalence C_{max}, the time to C_{max} (T_{max}) and the area under the curve (AUC) should be compared. Equivalent pulmonary deposition of two inhaled products may be concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 0.75 to 1.33.</p> <p>A pharmacokinetic study to investigate systemic safety has to measure total systemic exposure and therefore must not exclude that amount of the active moiety absorbed through the gastrointestinal tract. For such studies or for PK studies evaluating the systemic safety of locally acting compounds, the acceptance limits for C_{max}, t_{max} and AUC have to be prospectively defined and justified.</p> <p>Pfizer:</p> <p>Equivalent pulmonary deposition of two inhaled products may be concluded if the 95 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25.</p> <p>Proposed change: PK acceptance boundary should be based on 90% confidence interval to be consistent with other regulatory guidance's, e.g. http://www.emea.europa.eu/pdfs/human/ewp/4032606en.pdf</p> <p>Similarly, consideration should be made for reference drugs/products</p>	
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	<p>with highly variable pharmacokinetics – the acceptance boundaries could be widened prospectively for drugs with high within subject variability.</p> <p>Finally, as noted above, provide scientific justification for the bioequivalence criteria as applied to safety end points, or allow for sponsors to justify criteria to be applied for individual products, based on therapeutic index of drug.</p> <p>Orion Pharma:</p> <p>It is proposed that equivalent pulmonary deposition of two inhaled products may be concluded if the 95% confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25. For assessment of equivalent bioavailability, the 90% confidence interval is conventionally used (CPMP/EWP/QWP/1401/98). There is a valid rationale behind the use of the 90% confidence interval in this context and its use is well harmonised. Therefore, it seems odd to introduce a 95% confidence interval requirement in this context.</p> <p>Proposed change: Instead of a 95% confidence interval, a 90% confidence interval should be used.</p> <p>IPAC-RS:</p> <p>The 95% confidence interval and 0.8-1.25 acceptance range recommended for PK (lines 284-285) and PD efficacy studies (lines 338-339) appear inappropriately strict for orally inhaled products.</p> <p>Proposed change: This is a fourth topic that would benefit from further discussion and consensus by industry and regulatory experts. We recommend the use of an Interested Parties meeting, led by the EWP, to discuss this topic and others before finalization of the guideline.</p> <p>Some preliminary considerations include the following:</p> <p>a) Consider the relevance of EMEA/CHMP/EWP/40326/2006 “Questions & Answers on the Bioavailability and Bioequivalence Guideline (http://www.emea.europa.eu/pdfs/human/ewp/4032606en.pdf) to these products.</p> <p>b) Provide scientific justification for the bioequivalence criteria as</p>	
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	<p>applied to safety end points.</p> <p>TEVA: Current guidelines for bioequivalence of solid dose products use 90% CI (not 95% CI) and use C_{max} and AUC_{0-t} and AUC_{0-∞} (not t_{max}). Since absorption from an inhaled drug is inherently more variable than from an oral drug because of differences in inhaler technique between patients / subjects, why are the equivalence criteria being set higher. Proposed change: See comments for lines 338-341 below.</p>	
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4.3.2.1 General considerations in the investigation of therapeutic equivalence		
Line no. ²⁰ + paragraph no.	Comment and Rationale	Outcome
288 - 293	<p>EFPIA / Pfizer: This statement is contradictory, as it seems to make an implied differentiation between a clinical study being ‘required’ and being ‘mandatory’. This could allow regulators to ‘require’ a clinical study even if the <i>in vitro</i> criteria are fully met. Clarity should be provided on when a clinical study is ‘required’ if not deemed ‘mandatory’ or this contradiction removed as suggested in ‘proposed change’</p> <p>Proposed change by EFPIA: “Therapeutic equivalence demonstrated by means of appropriate clinical studies using well-validated study designs and comparing the test product with the reference <u>compound product</u>, will almost always be required <u>unless</u> and becomes mandatory when equivalence is not shown <u>in vitro according to the criteria provided in section 4.2.2 and/or through investigation of pulmonary deposition as discussed in section 4.3.1.</u>and is not shown through investigation of pulmonary deposition”.</p>	<p>EWP comment: <i>A modified wording has been implemented (with references to the corresponding sections). Please compare. However, the development of inhaled products should be a step by step process: in vitro -> in vivo pulmonary deposition-> in vivo PD/clinical studies. It is tried to emphasize in which case/ in which circumstances clinical studies are necessary and in which extent. From EWP point of view these aspects have been adequately reflected in the final version of the guideline (please check).</i></p>

²⁰ Where applicable

	<p><u>Proposed change by Pfizer:</u> Clinical studies....will always be required UNLESS equivalence is shown <i>in vitro</i> according to the criteria provided in section 4.2.2 and/or through investigation of pulmonary deposition as discussed in section 4.3.1.</p>	
290-293	<p><u>IPAC-RS:</u> This statement is contradictory as it seems to make an implied differentiation between a clinical study being ‘required’ and being ‘mandatory’. This could allow regulators to ‘require’ a clinical study even if the <i>in vitro</i> criteria are fully met. Clarity should be provided. <u>Proposed change:</u> This is the fifth topic that would benefit from further discussion and consensus by industry and regulatory experts. We recommend the use of an Interested Parties meeting, led by the EWP, to discuss this topic and others before finalization of the guideline. The guideline should clarify the intent of the statement. A decision tree could be helpful to clarify the path for establishing therapeutic equivalence.</p>	<p><u>EWP comment:</u> <i>This aspect has been addressed in a modified version in the updated guideline. However, it should be kept in mind that the development of inhaled products should be a step by step process: in vitro -> in vivo pulmonary deposition-> in vivo PD studies. It is tried to emphasize in which case / in which circumstances clinical studies are necessary and in which extent. The wording: ‘almost always be required’ should only depict an assumption. However, this wording has been removed. The wording ‘becomes mandatory’ emphasizes the necessity of comprehensive PD studies if step 1 and step 2 were not successful.</i></p>
290-293	<p><u>TEVA:</u> It should be made clear whether or not clinical studies are only required when equivalence via both <i>in-vitro</i> (see Section 4.2.2) and pulmonary deposition (Section 4.3.1: Imaging or PK studies) studies are not demonstrated. <u>Proposed change:</u> See comments above for Section 4.3.1 Change to “<i>Therapeutic equivalence ... will always be required unless equivalence is shown in vitro (section 4.2.2) and through investigation of pulmonary deposition (section 4.3.1).</i>” A decision tree could be referenced to establish therapeutic equivalence.</p>	<p><u>EWP comment:</u> <i>The implementation of a decision tree was discussed. However an excessive revision of the published draft of the revised guideline was preferred.</i></p>
294-297	<p><u>EFPIA:</u> This recommendation makes sense in principle, but should also express that it is not a prohibition per se for other imaginable comparisons between test and reference products belonging to a different type of device.</p>	<p><u>EWP comment:</u> <i>We agree, however it is only a recommendation. We have added some recommendation/hints to the favoured design of bronchodilating studies in the final version of the guideline.</i></p>

	If one DPI is compared to another for therapeutic equivalence, there is no mention of how blinding is supposed to be done.	
298-300	<p>EGA: For reasons of consistency, a reference to section 4.1.2 should be added, where DPIs with high flow rate dependency are exempted from the general possibility of extrapolation to other patient populations (i.e., between asthma and COPD).</p> <p>Proposed change: Please add after first sentence “(except for DPIs with high flow rate dependency, see 4.1.2)”</p>	<p>EWP comment: <i>Please compare aforementioned comment. The EWP completely agrees with this comment. However this point should be clear for all experts. Inclusion of all specifications etc. would be beyond of the scope of this guideline.</i></p>
298-306	<p>EFPIA: The clinical conditions of asthma and COPD can have marked differences in lung pathology (including airway geometry) and pathobiology. Equal responsiveness to any given drug is not always observed. Therefore, the use of <i>in vitro</i> data would need to be discussed/considered on a case-by-case basis.</p>	<p>EWP comment: <i>It should be emphasized that it is unequal more difficult to develop ‘hybrid products’ (EC/2001/83: 10(3)) than a usual ‘generic product’ (EC 2001/83: 10(1)) which is investigated via classical BE-study. But it is not a new development! Hence, we do not think that all indications and all severity stages of an obstructive disease should always be investigated if equivalence has been shown either via in vitro or via in vivo investigations.</i></p>
304	<p>EGA: This requirement is not relevant for MDIs (see also Guideline on the pharmaceutical quality of inhalation and nasal products, EMEA/CHMP/QWP/49313/2005, item e) on page 6/27) as flow rate and pressure drop range are considered as DPI characteristics.</p> <p>Proposed change: Addition of the wording “only for DPIs”</p>	<p>EWP comment: <i>If only one flow rate is clinically relevant then, of course, only this flow rate will have to be tested. All in all, the EWP completely agrees with this comment. However this point should be clear for all experts. Inclusion of all specifications etc. would be beyond of the scope of this guideline.</i></p>

4.3.2.2 Requirements for clinical studies in patients with asthma		
Line no. ²¹ + paragraph no.	Comment and Rationale	Outcome
307-345	EFPIA:	EWP comment:

²¹ Where applicable

	<p>As already mentioned above in our major comments, several points are also valid for COPD. Please clarify.</p> <p>IPAC-RS: Section 4.3.2.2 should be revised. Many of the considerations presented in this section are also valid for COPD. Proposed change: Point out the applicability of considerations to COPD.</p>	<p><i>We agree, but as we mentioned before it is more difficult showing TE in vivo in COPD patients than in asthmatic patients. Therefore for the case, that in vivo studies are necessary, we do more focus on asthma.</i></p> <p><i>There was a general consensus that it is unlike more difficult to conduct a sensitive pharmacodynamic study for a 'hybrid' product in COPD patients than in asthmatic patients. Therefore for currently marketed, inhaled products that are indicated both on asthma and COPD the usual way would be to conduct the pharmacodynamic study in asthmatic patients. For the whole marketing authorisation TE should only be demonstrated in one of the claimed patient population. Most of the considerations which are reflected in this section deal with asthma. Therefore we do not see a need of a general amendment. (See also comment before (EFPIA)).</i></p>
308-311	<p>EFPIA: It seems the term therapeutic equivalence is used in some instances for "efficacy" while it is defined on line 288 as "equivalent efficacy and safety". In addition, from line 331 and onwards, both safety and efficacy are again discussed. Proposed change: It is suggested to create one subsection for efficacy and one for safety under section 4.3.2.1 (General considerations in the investigation of therapeutic equivalence).</p>	<p>EWP comment: <i>Agreed. This aspect has been reconsidered. The section has been amended and a clarification has been implemented.</i></p>
314	<p>EGA: (In accordance with GINA report (2007), the request for an 200 ml improvement in FEV₁ (in connection with a $\geq 12\%$ improvement) should be specified of an improvement of <u>at least</u> 200 ml. Proposed change: ...” or $\geq 12\%$ and a ≥ 200 ml improvement of FEV₁”</p>	<p>EWP comment: <i>The proposed criterion is well accepted in Europe. As proposed, we added ≥ 200 ml. Issue should be resolved.</i></p>
317-8 +	<p>Orion Pharma: It is proposed that “The study carried out must be sensitive enough ... and to be able to pick up differences which might exist between the two products.” We feel that the primary focus should be on the ability of the study to detect differences that are clinically relevant, not just any difference. Proposed change: Please add “clinically relevant” before the word</p>	<p>EWP comment: <i>Agreed. The wording “clinically relevant” has been implemented.</i></p>

	“differences” on line 318.	
317-322	<p>EGA:</p> <p>We would like to re-emphasise the difficulty of carrying out PD studies, both in recruiting for and running such studies, such that the sensitivity targeted here becomes impractical. Literature examples quoted by regulators to date (in terms of their wide equivalence limits) support this assertion.</p>	<p>EWP comment:</p> <p><i>This statement based on the experiences of the European assessors. Several studies were conducted in this way in the past and it has to be concluded: ‘IT WORKS.’ The main question is the method of patient’s recruiting, however we discuss about frequent and chronic diseases. To sum it up, it should be feasible.</i></p>
317-322	<p>EGA:</p> <p>Demonstration of therapeutic equivalence on the y-axis could also be acceptable providing that the assay sensitivity is demonstrated indisputably. Clarification is sought as to which conditions would allow for a demonstration of therapeutic equivalence on the y-axis would also be acceptable.</p> <p>Would a study of a dose at the middle part of the dose response curve be adequate?</p> <ul style="list-style-type: none"> • If yes, what are the criteria for demonstrating therapeutic equivalence with this approach? <p>If no, what is needed to show that assay sensitivity is demonstrated indisputably?</p> <p>For compounds where the lowest single dose is already on the flat part of the dose-response curve (and the application of a further higher dose is of no value) as well as for the application of two doses. In the latter case, is it sufficient if the patients demonstrate a dose response for the reference product during screening and what are the criteria (i.e., increases) for the demonstration of a dose response when doubling the dose?</p>	<p>EWP comment:</p> <p><i>The EWP thinks that a complete explanation of this topic would be beyond the scope of this guideline. However, this section was intensively updated and modified. Remaining specific questions should be solved in drug-related scientific advices.</i></p>

317-322	<p>EGA:</p> <p>In our opinion demonstration of therapeutic equivalence on the y-axis is an appropriate approach if the higher of the two doses to be used is expected to be on the plateau part of the dose-response curve, which means, in consequence, that the regression lines of test and reference will cross or converge at the higher dose.</p> <p>In such a case, dose potency calculation according to Finney hardly makes any sense as one of the three assumptions of the Finney assay requests no departure from parallelism. We expect that at least the second (higher) dose of many reference products will be on the plateau part even if the lowest available strengths and doses and populations with high sensitivity are used.</p> <p>A clear distinction between (therapeutic) equivalence and non-inferiority (i.e., as “at least as good/not worse than”) is necessary. In many cases, such as the demonstration of equivalence on the y axis by quantitative efficacy parameters (i.e., spirometric parameters as FEV1, etc), non-inferiority is common and accepted by authorities. It should be clarified whether therapeutic equivalence indisputably implies a two-sided question or whether actually non-inferiority is meant.</p> <p>In contrast to oral preparations for OIPs, a demonstration of the safety profile is additionally required. Therefore, any safety concerns in respect to non-inferior efficacy can be ruled out anyway. In addition, increases in spirometric parameters are not unlimited, but confined by the lung capacity.</p>	<p>EWP comment:</p> <p><i>This section was comprehensively updated in the final version of the guideline. The statistical issue is more explained in this final guideline. Remaining specific questions should be solved in drug-related scientific advices.</i></p> <p><i>With regard to the specific question: TE should be a two-sided approach in accordance to the BE. The definition of TE will be not fulfilled with this non-inferiority-proceeding. (See also definition section in the appendix of the final guideline). Efficacy and safety should always be considered jointly. In case of improved efficacy and/or reduced safety we see open issues with the recommended doses. Normally, if efficacy was improved a dose-reduction would be needed. The informative texts of the test product can't be adapted for those of the reference product. Therapeutic equivalence would not be given.</i></p>
318-20/22	<p>Orion Pharma:</p> <p>Relative potency is given as the recommended approach. Considering the fundamental implications this recommendation has in terms of the whole philosophy of demonstration of “therapeutic equivalence” (as discussed above under General comments), it is not at all acceptable to “slip” such a major recommendation with profound influences in just a single sentence!</p> <p>Proposed change: The whole section needs to be rewritten, with due respect to the fundamental nature of the proposed change of approach. Elaboration of the various biological assay approaches (e.g. parallel-line or slope-ratio) to relative potency should be provided. It should be</p>	<p>EWP comment:</p> <p><i>As requested, this section (this topic) has been re-written / modified / clarified. In addition, the requirements have been also clearly addressed. Furthermore the wording “relative potency” has been defined in the glossary.</i></p> <p><i>However not all relevant aspects can be covered by this guideline. Some requested clarification would be beyond the scope of this guideline (compare EFPIA comment). For example, sample size calculation depends on the actual study design and can therefore not be covered by a guideline. Special questions (e.g. special study designs) should be discussed in a frame of a national or European SA case by case.</i></p>

<p>clearly stated what type of study designs for the bioassay are acceptable. For example, is a parallel-line bioassay using cumulative doses acceptable?</p> <p>EFPIA: Although the advantages of using the relative dose-potency to declare therapeutic equivalence could be recognised, it is considered that the chosen limits are too strict, making it almost impossible to declare equivalence using a reasonable sample size. Even if widening the limits allowed, this method could only be applied in situations where a dose-sensitive efficacy parameter exists. In other situations, choosing an appropriate interval on the y-axis as the equivalence margin should be considered a sufficient method, but the chosen interval must take the expected size of the difference between dose-levels tested into consideration. It is unclear what is meant by ‘relative potency comparison’ and ‘demonstration of therapeutic equivalence on the y axis’. There is also no indication of the subject numbers likely to be required for crossover or parallel group designs. Proposed change: Clarify exactly what study designs are being proposed or remove this wording.</p> <p>Siegfried Pharma Development GmbH: Please clarify the term “relative potency” and the context of assay sensitivity and different dose strength (x-axis).</p> <p>TEVA: It is not clear which method should be used to determine the relative potency from the statement "Demonstration of therapeutic equivalence on the y-axis". It leaves space for interpretation which may lead to different directions. This may be referring to the Finney bioassay, which is a well established method and has been used in the literature for SABAs in bronchoprotection studies. Proposed change: “Demonstration of therapeutic equivalence on the y-</p>	<p><i>Therefore, if there is a need for further clarification, a national or central scientific advice should be sought.</i></p>
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	axis (e.g. Finney bioassay) could also be acceptable ...”	
321	<p>Orion Pharma: Empirical research rarely can demonstrate anything “indisputably”, and inference is always inherently subjective. Proposed change: Delete the word “indisputably” from line 321.</p>	<p>EWP comment: <i>The section has been modified.</i></p>
321-328	<p>EGA: For therapeutic equivalence trials assay sensitivity is requested by applying at least two dose levels on the steep segment of the dose-response curve. However, for some substances (for example Formoterol / Foradil, see also general comments and line 184) the lowest available dose is already on the plateau segment of the dose-response curve, thus the requested enhanced sensibility is not realizable. Proposed change: Please specify requirements / alternatives for substances, where dose sensitivity cannot be demonstrated by using at least two doses on the steep segment of the dose-response curve.</p>	<p>EWP comment: <i>Please compare aforementioned comment. It is always a question of an appropriate reference product.</i></p>
323-8	<p>Orion Pharma: Recommendations to enhance assay sensitivity of studies aiming to demonstrate “therapeutic equivalence on the y-axis” are given. As such, these recommendations are better suited for biological assays aiming to measure relative potency (“equivalence on the x-axis”). In principle at least, if two products both produce the maximum response after e.g. a single actuation, it is no longer a question of sensitivity – by definition, there is no difference in response between the products! The essential question then is whether there are relevant patient groups and/or conditions of use where the equivalence in response would not hold. (And certainly, simultaneous confirmation of non-inferior safety is needed.) The advice given here does not address the proper issue. Furthermore, it should be noted that the GINA Guidelines 2006 are not primarily intended to serve as definite guidance for determining eligibility in clinical trials, but rather as guidance to practicing physicians for categorising patients for purposes of treatment decisions.</p>	<p>EWP comment: <i>It is agreed that reference to the ICH Topic E10 should be made. A corresponding wording is implemented in the guideline. Nevertheless it has to be kept in mind that the ICH guideline covers non-inferiority and superiority trials but not equivalence trials so that the recommendations of the ICH guideline can not be transferred one-to-one.</i></p>

	<p>In addition, the GINA guidelines are likely to change frequently. Therefore, this is not a proper reference for patient eligibility requirements in a therapeutic equivalence study.</p> <p>Proposed change: Issues related to assay sensitivity in equivalence trials are comprehensively discussed in <i>ICH Topic E 10, Choice of control group in clinical trials</i> (CPMP/ICH/364/96). An excerpt should be provided here and reference made to that guideline for more details. If any of the recommendations made here are retained in this context, reference to the GINA 2006 guideline should be deleted and the essential characteristics of the patients to be enrolled should be listed.</p>	
325-326	<p>Siegfried Pharma Development GmbH:</p> <p>Testing of 2 different strengths of reference and test product is one option of showing assay sensitivity but appears to be not always feasible (e.g. rather flat dose-response curve of steroids; more than 90% of the maximum therapeutic effects of potent ICS products are already achieved at dose-levels that are only about 50% of the currently maximum recommended daily doses) or the only way of proving sensitivity. Please refer also to 4.3.2.3.2.</p> <p>Proposed change: Would it be possible to include alternatives here into the guideline e.g. use of low-dose comparator ICS that may be below the lowest currently recommended/approved daily dose.</p>	<p>EWP comment:</p> <p><i>Alternatives can not be addressed due to the aim of the study (assessment of therapeutic equivalence) and for sensitivity reasons.</i></p>
326	<p>EFPIA / Pfizer:</p> <p>The draft guideline states “In general and unless otherwise justified.....require testing more than one dose of both the test and reference product”.</p> <p>Proposed change: State in the guideline that it is acceptable to use only 1 dose of reference product if critical <i>in vitro</i> criteria described in section 4.2.2 are confirmed, and if dose linearity demonstrated. Testing of more than one doses should only be required if these criteria are not met.</p>	<p>EWP comment:</p> <p><i>As mentioned before the equivalence testing approach should be done according a hierarchical concept. If TE is confirmed by fulfilling of all in vitro criteria which are adequately described in the guideline (final version: section: 5.2), no further investigation will be necessary. If not, for reasons of assay sensitivity more than one dose should normally be examined in all PD/clinical studies. The proposed issue has been not implemented.</i></p>
331-333	<p>EFPIA:</p> <p>This seems to suggest that “bioequivalence” of safety data, including AEs, needs to be demonstrated.</p>	<p>EWP comment:</p> <p><i>The EWP do not agree with the proposed deletion of the sentence. It is a matter of normal and well accepted descriptive analysis.</i></p>

	<p>How is this done statistically? It is suggested to delete the sentence as this is fully covered by lines 340-345, where the requirements are more clearly expressed.</p> <p>Proposed change: “Therapeutic equivalence in respect of safety should be demonstrated by investigation of bioequivalence based on pharmacokinetic data, relevant cardiovascular, biochemical and physiological parameters, and monitoring of adverse events.”</p>	
337/338-9	<p>ANDI-VENTIS:</p> <p>The specified equivalence interval (80 – 125%) is applicable to all classes of inhaled drugs for asthma, i.e. inhaled corticosteroids (ICS), short-acting β_2-agonists (SABA), long-acting β_2-agonists (LABA), and combinations. The recommendations in the new CHMP guideline on OIP are similar to those in the guidelines issued by Health Canada²². The Canadian guidelines recommend as well the “relative potency” approach, i.e. two dose levels of the two study drugs, and define exactly the same CI interval for equivalence, i.e. 80 - 125%, but <u>they refer specifically to SABA</u> and not to all classes of inhaled drugs as the CHMP guideline does. The second difference between the Canadian and CHMP guideline is the definition of CI. While the limits are the same, i.e. 80 - 125%, the Canadian guideline considers <u>90% CI</u>, while the CHMP guideline states it must be <u>95% CI</u>. No study have been published yet (8 years from the publication of the Canadian guidelines) in which LABAs were studied with the relative potency approach. <i>The scientific basis for applying the equivalence limits of 80 – 125% to all classes of inhalation drugs has not been justified by the EMEA guideline.</i></p> <p>Proposed change: The statements relevant to the use of 95% CI 80-125% for all class of inhaled drugs and for both efficacy and tolerability need to be justified for each specific class of products. Alternatively, allow flexibility to justify different criteria being applied.</p>	<p>EWP comment:</p> <p><i>The EWP partly agrees. For analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here the 95% CI should lie within the acceptance range of 0.8 to 1.25, unless other justified. One exemption exists. The CI can be widened for calculation of the relative potency (please compare final guideline).</i></p>


²² Health Canada. Guidance to establish equivalence or relative potency of safety and efficacy of a second entry short-acting beta2-agonist metered dose inhaler. February 1999

	<p>Orion Pharma:</p> <p>Relative potency measures bioavailability of the active substance/moiety at the site(s) of intended pharmacological action, and is therefore one way of investigating bioequivalence (“equivalence on the dose scale”). Consequently, the general principles in the bioavailability/bioequivalence guideline (CPMP/EWP/QWP1401/98) should be applied as appropriate, and therefore the 90% confidence interval should logically be used instead of the 95% confidence interval. Due consideration should be also given to the fact that the variance of the pharmacodynamic measures in a biological assay is considerably larger than that in a conventional bioequivalence study based on pharmacokinetic measures calculated from the plasma concentrations over time. Therefore, a very large sample size (up to hundreds of patients) may be required to meet the acceptance range of 0.8 to 1.25 for relative potency. In the literature, justification has been provided for an equivalence range of 0.67 to 1.5 – and even 0.5 to 2.0. One potential compromise could be requiring the point estimate to be within the conventional 0.8 to 1.25 and allowing a wider range for the confidence interval.</p> <p>Proposed change: Instead of a 95% confidence interval, a 90% confidence interval should be used. The acceptance range for the confidence interval should be wider, or at least a wider acceptance range should be allowed in justified cases.</p> <p>EGA:</p> <p>Bearing mind a perspective of bioequivalence (acceptance range, i.e., 80-125%), it is believed that these should read 90%CI not 95%CI. 90% CI instead of 95% CI should be sufficient for concluding equivalence with the relative potency approach because the comparison is now based on a difference in the x-axis (dose) not the y-axis (efficacy measure). This is equivalent to the use of 90% CI in conventional bioequivalence study, which compares the dose absorbed between products, of orally administered medicinal products.</p>	
338-9;340-1	Orion Pharma:	EWP comment:

<p>As already discussed in the General comments, therapeutic equivalence should be satisfied when non-inferior efficacy and non-inferior safety is jointly demonstrated. Therefore, it is not rational to impose an upper limit for the equivalence range of the measure of bioavailability at the site of the intended action or a lower limit for the measure of systemic availability [which acts as a surrogate for availability at the site(s) of unintended (systemic) action(s)].</p> <p>For example, consider comparing a new product T with innovator R. The emitted dose from both is 100 µg, and the total lung dose is 50 µg. The aerodynamic particle size distribution and other relevant determinants of deposition, however, differ to such an extent that <i>in vivo</i> T deposits 50 µg at the (anatomically unknown) site of action in the airways, whereas R deposits only 25 µg at the site of action. Since the pulmonary and enteral doses are the same, it is likely that there would be no difference in terms of safety. Nevertheless, the product would be rejected based on a relative potency of 0.5, which is below the proposed acceptance range. If this product were then reformulated so that it would deliver only 25 µg to the lungs (and to the site of action), the relative potency estimate would then approach unity. Due to high first-pass metabolism, however, the pharmacokinetic measures of systemic availability would not meet the equivalence criterion – C_{max} and AUC would be “too low” – and again the product would be rejected. So the product T with a benefit–risk profile clearly superior to R would fail to get marketing authorisation.</p> <p>Proposed change: Only an upper limit for the relative potency estimate should be defined. Only an upper limit for bioequivalence in respect of systemic safety should be defined.</p> <p>EGA:</p> <p>For the demonstration of therapeutic equivalence for efficacy the demonstration of non-inferiority should be sufficient.</p> <p>A clear distinction between (therapeutic) equivalence and non-inferiority (i.e., as “equivalent” versus “at least as good/not worse than”) is necessary. In many cases, for example demonstration of equivalence on the y-axis by spirometric parameters (FEV1 etc.) non-inferiority is common and accepted by authorities. Does therapeutic equivalence mean</p>	<p><i>It is not comprehensible why the upper limit should be defined in order to proof non-inferiority.</i></p> <p><i>As it has already aforementioned commented: TE should be a two-sided approach in accordance to the BE.</i></p> <p><i>The definition of TE will be not fulfilled with this non-inferiority-proceeding. Efficacy and safety should always be considered jointly. In case of improved efficacy and/or reduced safety we see open issues with the recommended doses. Normally, if efficacy was improved a dose-reduction would be needed. In this case, the informative texts of the test product can't be adapted for those of the reference product.</i></p>
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	<p>indisputably a two-side question or is non-inferiority implied? As already discussed (please see Section 4.3.2.2. Lines 320 – 321) for demonstration of equivalence on the y-axis, the non-inferiority approach should also be applicable for equivalence demonstration on the x-axis, i.e., the relative dose-potency.</p> <p><u>Roche Products Limited:</u> The requirement for therapeutic efficacy is stated as ‘the 95% confidence interval ... within 80% - 125%. This seems a hybrid of approaches for clinical equivalence (where 95% confidence intervals are accepted as standard – but not necessarily the range 80% - 125%) and bioequivalence (where the 80% - 125% limits are typically used, but not 95% confidence intervals). Both ICH E10 and the Guideline on the choice of the non-inferiority margin go to great efforts to stress that a <i>clinical justification</i> as well as a statistical justification is needed for any margin. But this margin is simply stated, with no justification. This seems to set a bad precedent. <u>Proposed change:</u> Concepts set out in the Guideline on the choice of the non-inferiority margin should be used to specify and justify a margin.</p>	
338-345	<p><u>EFPIA:</u> Criteria for efficacy and safety are 2-sided; however a new formulation with improved efficacy and/or reduced safety signal would be an improved therapy. The existing guideline on Replacement of CFC in metered dose inhalation products (section 4.1.1) to which this draft guideline cross refers, specifically addresses this point and advises a non-inferiority approach is more appropriate. The 80-125% criteria (normally associated with PK) applied to efficacy is considerably more restrictive than applying a rule of half the accepted minimum efficacious effect. These criteria will require higher study numbers and will be a more significant hurdle, particularly for anti-inflammatory drugs. <u>Efficacy:</u> If the relative potency approach is used the 95% confidence interval for the primary endpoint must be contained entirely within 80 – 125 %. It is to be noticed that this is inconsistent with line 284 (95% vs.</p>	<p><u>EWP comment:</u> <i>As mentioned previously, the CFC Directive will expire soon. Furthermore, the definition of TE has been given at the end of the final guideline (compare definitions). It has to be emphasized that TE should be a two-sided approach in accordance to the BE. The acceptance of non-inferiority margins has been not addressed, because a discussion of this topic would be beyond the scope of this guideline. The definition of TE will be not fulfilled with the recommended non-inferiority-proceeding. Efficacy and safety should always be considered jointly. In case of improved efficacy and/or reduced safety we see open issues with the recommended doses. Normally, if efficacy was improved a dose-reduction would be needed. The informative texts of the test product can't be adapted for those of the reference product.</i></p>

<p>90% CI). As noted earlier in our major general comment, the use 90% may be more appropriate.</p> <p><u>Proposed change:</u></p> <p>1.) Accept non-inferiority of safety and efficacy rather than equivalence as discussed in the existing CFC guideline.</p> <p>2.) Suggest guidance state a non-inferiority margin based on applying a rule of half the accepted minimum efficacious effect.</p> <p><u>IPAC-RS:</u></p> <p>Criteria for efficacy and safety are 2-sided; however a new formulation with improved efficacy and/or reduced safety signal would be an improved therapy. The existing guideline on Replacement of CFC in metered dose inhalation products (section 4.1.1) to which this draft guideline cross refers, specifically addresses this point and advises a non-inferiority approach as more appropriate.</p> <p><u>Proposed change:</u> Accept non-inferiority of safety and efficacy rather than equivalence as discussed in the existing CFC guideline.</p> <p><u>Pfizer:</u></p> <p>1.) The 80-125% criteria (normally associated with PK) applied to efficacy is considerably more restrictive than applying a rule of half the accepted minimum efficacious effect. These criteria will require higher study numbers and will be a more significant hurdle, particularly for anti-inflammatory drugs.</p> <p>2.) Efficacy: If the relative potency approach is used the 95% confidence interval for the primary endpoint must be contained entirely within 80 – 125 %.</p> <p>3.) Criteria for efficacy and safety are 2-sided; however a new formulation with improved efficacy and/or reduced safety signal would be an improved therapy. The existing guideline on Replacement of CFC in metered dose inhalation products (section 4.1.1) to which this draft guideline cross refers, specifically addresses this point and advises a non-inferiority approach is more appropriate..</p> <p><u>Proposed change:</u></p> <p>1.) Suggest guidance state a non-inferiority margin based on applying a</p>	<p><i>To clarify the raised statistical issue, for analysis of in vitro data and in vivo data (with regard to pulmonary deposition studies and safety via PK) the 90% CI should be used. 90% CI should lie within the acceptance range of 0.8 to 1.25. However for analysis of in vivo data with regard to efficacy (PD) this criterion should be stronger. Here it is expected that the 95% CI lies within the acceptance range of 0.8 to 1.25, unless otherwise justified. However, in seldom circumstances a widening or a tightening may be necessary, but this case will be a 'case by case' decision.</i></p>
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	<p>rule of half the accepted minimum efficacious effect (see further comment below).</p> <p>2.) Note inconsistency with line 284 (95% vs. 90% CI). As noted earlier, the use 90% may be more appropriate.</p> <p>3.) Accept non-inferiority of safety and efficacy rather than equivalence as discussed in the existing CFC guideline.</p>	
338-340	<p>TEVA:</p> <p>The equivalent limit of 95%CI 0.8-1.25 is considered to be unrealistic for most inhalation products, although it has been recognised that typically, bioequivalence limits are set at 0.8-1.25 for orally administrated products such as tables/capsules. It is well known that the variability of inhalation products is much higher than conventional tablets/capsules and a wider limit should be considered when intra-subject variability exceeds 30%. The therapeutic equivalence limit should also be set based on the characteristic of dose-response curve, the study type, as well as what can be achieved historically, scientifically and practically. Different models may be used for each type of products. For example, a wider limit of 90%CI 0.5-2.0 for bronchodilators could be adequate. This is based on a specific model for bronchodilators and the details are provided in Appendix I (see attached).</p>  <p>C:\Documents and Settings\jqiu\Desktop</p> <p>Based on the literature and available data to date, the limit proposed in the guideline has not been achieved in the studies that have been carried out for the known bronchodilators. As shown in the Appendix I, it is almost impossible to conduct such studies to achieve the proposed limit in a methacholine challenge study.</p> <p>Proposed change: The use of a wider limit such as 90% CI of 0.75-1.33 when intra-subject variability exceeds 30% should be considered. In addition, an even wider limit (i.e., 90% CI 0.5-2.0) could also be considered when the dose response slope is flat (i.e., ≤ 0.7).</p>	<p>EWP comment:</p> <p><i>This aspect has been discussed within the group. A widening of acceptance boundary should be a case by case decision (possible condition for widening: please compare updated BE guideline to this issue). However, a widening of AUC is not possible. It is recommended to seek for a scientific advice.</i></p>

340	<p><u>IPAC-RS / Pfizer:</u></p> <p>The relevance of the bioequivalence criteria may differ for different drug mechanisms (e.g., wider criteria for anti-inflammatory drugs still produce therapeutic equivalence) and low levels of drug in the plasma at the LLQ of the assay may result in greater variability in estimation of PK parameters as acknowledged in 4.3.1.</p> <p><u>Proposed change:</u> Provide scientific justification for the bioequivalence criteria as applied to safety end points, or allow for flexibility for sponsors to justify criteria to be applied for individual products.</p>	<p><u>EWP comment:</u></p> <p><i>From our point of view relevant points have been adequately mentioned. The final evaluation of relevant safety aspects should be done in a case by case manner. In this context, please compare aforementioned comment and the updated BE-guideline.</i></p>

340-345	<p>EFPIA: Further guidance on what is considered appropriate evidence of equivalent safety would be useful. The relevance of the bioequivalence criteria may differ for different drug mechanisms (e.g. wider criteria for anti-inflammatory drugs still produce therapeutic equivalence) and low levels of drug in the plasma at the LLQ of the assay may result in greater variability in estimation of PK parameters as acknowledged in 4.3.1. Proposed change: Provide scientific justification for the bioequivalence criteria as applied to safety end points, or allow for flexibility for sponsors to justify criteria to be applied for individual products.</p> <p>IPAC-RS: Further guidance on what is considered appropriate evidence of equivalent safety would be useful. Proposed change: Provide further guidance or points to consider.</p>	<p>EWP comment: <i>From our point of view relevant points have been adequately mentioned. The final evaluation of relevant safety aspects should be done in a case by case manner.</i></p>
340-342	<p>TEVA: These two lines are related to systemic exposure from possible PK studies. It may cause some confusion from the section 4.3.1.2.</p> <p>A wider limit of 90%CI 0.75-1.33 should be applied if the intra-subject variability exceed 0.30 (e.g. the root mean square error in the ANOVA crossover model exceeds 0.30, suggesting high intra-subject variability). If the intra-subject coefficient of variation exceeds 0.30, a wider confidence interval is appropriate and is also recommended for highly variable drug product by the CHMP (CPMP/EWP/QWP/1401/98 and EMEA/CHMP/EWP/40326/2006). Specifically, this degree of variability would indicate that even if the same device were administered to the same patient on two separate occasions, the CI would need to be wider in order to establish similarity. That is, a wider confidence interval is needed in order to eliminate the false conclusion that two different formulations are in fact different, and not merely a reflection of the expected variability in the PK measurements.</p>	<p>EWP comment: <i>Please compare aforementioned issue.</i></p>

	Proposed change: Safety: If possible bioequivalence (<i>from pharmacokinetic studies</i>) with respect to total systemic exposure should be demonstrated (the 90% confidence interval must be contained entirely within 80-125%. However, <i>when the intra-subject variability, measured as the root mean square error in the ANOVA crossover model, exceeds 30%, a wider interval e.g. 0.75-1.33 may be acceptable as long as the interval is prospectively defined.</i>	
341 - 343	EGA: Please refer to section 4.3.1.2, lines 282-285 and section 4.3.2.2, lines 341-343.	EWP comment: <i>An amendment has been implemented.</i>
344	IPAC-RS: “...frequency of adverse events” is not adequate. Proposed change: Change to “...safety profile”.	EWP comment: <i>The frequency has been pointed out. In this section single examples for the safety profile are described. Please take into consideration the whole sentence: ‘There should be no evidence that the test product is worse than the reference product in respect of changes in vital signs, biochemical parameters and frequency of adverse events.’ From EWP point of view no important modification is needed.</i>
344-345	EFPIA: It is suggested to rephrase the sentence for a better clarity. Proposed change: “Also there should be no important difference between the test product and evidence that the test product is worse than the reference product in respect of changes in vital signs, biochemical parameters, safety profile frequency of adverse ”	EWP comment: <i>We have considered this proposal. However we do not take over this proposed wording. The definition/meaning of ‘important differences’ is not clear. As usual, safety aspects should be analysed descriptively.</i>

4.3.2.2.1 Bronchodilatation studies		
Line no. ²³ + paragraph no.	Comment and Rationale	Outcome
348	IPAC-RS:	EWP comment:

²³ Where applicable

	<p>Indicates the primary and secondary endpoints can be investigated for efficacy, yet line 338 discusses the primary endpoint only. How should both endpoint types be used? Do all have to demonstrate equivalence?</p> <p>Proposed change: Include a clarification, e.g., “Demonstrating equivalence for the primary endpoint would be sufficient”.</p> <p>Schering Plough:</p> <p>Indicates the primary and secondary endpoints can be investigated for efficacy, yet LINE 338 discusses the primary endpoint only. How should both endpoint types be used? Do all have to demonstrate equivalence?</p> <p>Proposed change: Language should be clarified.</p>	<p><i>This is a statistical question. Of course the primary efficacy parameter which should be appropriate is deciding. However, this primary efficacy parameter should be supported by some relevant secondary parameters. If test and reference product has been equivalent it would have to be expected that all secondary endpoints should be in line with the primary endpoint.</i></p>
354-355	<p>EFPIA:</p> <p>Please clarify the rationale for incorporating at least two dose levels in a bronchodilatation study. Is demonstration of a dose-response required?</p> <p>EGA:</p> <p>Please refer to all other comments concerning two (or more) dose levels.</p>	<p>EWP comment:</p> <p><i><u>Rationale:</u> Showing of assay sensitivity. This aspect has been sufficiently mentioned within the final version of the guideline. However, additional references to all other comments concerning two (or more) dose levels seem to be confusing. A development of a new hybrid product requires taking note of the complete guideline.</i></p>

4.3.2.2.2 Bronchoprotection studies		
Line no. ²⁴ + paragraph no.	Comment and Rationale	Outcome
356-366	<p>EFPIA / IPAC-RS:</p> <p>The recommendations for appropriate primary variables in clinical trials to prove therapeutic equivalence do not seem always to be useful; e.g. Induced sputum remains an assessment that is primarily used in research. eNO will be unable to differentiate any dose response of an ICS.</p>	<p>EWP comment:</p> <p><i>The guideline clearly states that eNO, sputum etc. is another efficacy endpoint and not the primary endpoint. However, it is generally expected that the chosen primary endpoint should be validated and justified.</i></p>

²⁴ Where applicable

	<p>This comment is also valid for lines 436- 437.</p> <p>Proposed change: Add: <i>“The endpoints used in the clinical trials should be appropriately validated.”</i></p> <p>and delete the mention of exhaled nitric oxide because it is not a validated marker and therefore is inappropriate for establishing therapeutic equivalence.</p>	
365-366	<p>EGA:</p> <p>Please refer to all other comments concerning two (or more) dose levels.</p>	<p>EWP comment:</p> <p><i>Additional references to all other comments concerning two (or more) dose levels seem to be confusing. A development of a new hybrid product requires taking note of the complete guideline.</i></p>

4.3.2.3.1 Bronchodilators		
Line no. ²⁵ + paragraph no.	Comment and Rationale	Outcome
380-383	<p>Innovata Biomed Limited:</p> <p>Clarification is requested with regard to the duration of cumulative dose clinical studies.</p>	<p>EWP comment:</p> <p><i>Previously cumulative dose studies have been used to proof equivalence for SABA. Although this study design is no longer considered appropriate to conclude therapeutic equivalence it might be used to show equivalent safety of two SABAs. Usually these cumulative dose studies use increasing single doses within the duration of action of the test product.</i></p>
381	<p>IPAC-RS / Pfizer:</p> <p>It is unclear what is meant by ‘relative potency comparison’ and ‘demonstration of therapeutic equivalence on the y axis’. There is also no indication of the subject numbers likely to be required for cross-over or parallel group designs.</p> <p>Proposed change: Clarify exactly what study designs are being proposed or remove this wording.</p>	<p>EWP comment:</p> <p><i>Some aspects to the several designs of the different kinds of studies have been implemented in the final version of the guideline. (Please compare the published final guideline). The implementation of a figure explaining the meaning of RP would be beyond the scope of this guideline. Here a strong view in relevant statistical text book could help. However, some more explaining sentences have been added.</i></p> <p><i>Sample size calculation depends on the actual study design and can therefore not be covered by a guideline. Special questions should be discussed in a frame of a national or European SA case by case.</i></p>

²⁵ Where applicable

383-400	<p>EGA: For LABAs, there is no reason to specifically assess the onset of action and the maximum response more critically than for SABAs. Intuitively, these parameters are less important for LABAs than for SABAs, which require prompt drug action. Hence, it should not be necessary to consider these two parameters in the design of the bronchodilation study of LABAs. Clarification in this regard would be welcome.</p>	<p>EWP comment: <i>Please take the whole paragraph into account. In comparison to the study design of SABA the longer duration of action has to be considered in order to measure the endpoint during the relevant time of action.</i> <i>In contrast to LABAs, SABAs are only used as rescue medication. LABAs are basically indicated as maintenance treatment. For the maintenance treatment of LABAs it is important to demonstrate that the duration of action is equivalent to the reference product.</i></p>
384-385	<p>TEVA: 1.) Terminology for a single dose study with different dose levels versus a repeat dose study should be provided in the definition list (line 540) to avoid potential confusion. 2.) It states “Initial requirements in the assessment of therapeutic ... as for the SABAs”. It is not clear if there are more studies are required after this “initial” therapeutic equivalence studies. If there are, what would be the situations or conditions? The “Initial requirements...” needs to be explained or removed. Proposed change: 1.) Change to “Initial requirements in the assessment are the single <i>treatment</i> comparative studies of either bronchodilation or ...” 2.) Change to “Requirements in the assessment ... as for the SABAs.” Or the “initial requirements...” should be explained.</p>	<p>EWP comment: <i>The proposals have been considered.</i></p>
384-90	<p>Orion Pharma: Here it is stated only that “the longer duration of effect of the LABA must be taken into consideration in the design of the study.” The specific meaning of this statement is then explained under 4.3.2.3.3 Combination products. It would be advantageous to give the specific piece of advice here too. Proposed change: The specific requirement to measure “bronchodilation over at least 80% of the duration of action” given on lines 490-1 (section 4.3.2.3.3) should be stated here too.</p>	<p>EWP comment: <i>Agreed. A modified wording has been implemented.</i></p>
384-390	<p>Schering Plough:</p>	<p>EWP comment:</p>

	<p>The guidelines indicate that a single dose bronchial challenge study would be adequate. Reduced delivery of active would result mainly in shorter duration that can be more evident over time due to potential beta-agonist tolerance, suggesting the need for confirmation of equivalence with multi-dose studies.</p> <p>Proposed change: Revised the guideline to additionally require longer-term study. We note that the asthma guidance suggests studies for as long as 6- months to establish efficacy. While shorter studies may be adequate to establish therapeutic equivalence, the duration of study should be justified.</p>	<p><i>It has to be distinguished between requirements for NCE and hybrid (generic) products. The requested requirements seem to be unrealistic for known active substances.</i></p>
386	<p>EFPIA / IPAC-RS: FEV₁ increase of 12% and 200ml is generally accepted as the most appropriate definition of onset of action.</p> <p>In addition, a similar wording could be mentioned for SABAs as equally important for these products.</p> <p>Proposed change: “However, the onset of action (defined as FEV₁ increase of 15% or 12% and 200ml, from baseline) ...”</p>	<p>EWP comment: <i>The proposed criterion is well accepted in Europe. However some studies are conducted in other continents/countries (e.g. US). Differences exist between Europe and America in this aspect. Therefore we should be flexible in this point.</i> <i>Therefore, it has to be emphasized that this raised aspect has been transferred in the section of definitions at the end of the guideline (please compare final version of the guideline). Here onset of action is defined as follows: “For example - an increase in FEV₁ of 200 millilitres from baseline or the time to 50% of the maximum response or a percent of the maximum response achieved at a given time, either 5 or 10 minutes from baseline, where the maximum change in FEV₁ is at least 15%.”</i></p>
394 – 395	<p>ANDI-VENTIS: It is known that it is difficult to show dose-response with bronchodilators because even low doses achieve increments in FEV₁ that are close to peak response in asthmatics. As an example, in the case of a new formulation of formoterol, it appears problematic to show dose-response in a study in which formoterol is administered at, say,</p>	<p>EWP comment: <i>The mentioned aspect has been revised (compare the modified guideline). The chosen limits have to be adequately justified by the applicant, always.</i> <i>One point has to be clarified. The investigation of one strength would be adequate in the case described by EFPIA. Nevertheless, in this case for</i></p>

<p>6µg and 12µg.</p> <p>No study has been published yet in which LABAs were studied with the relative potency approach. Even recent studies²⁶ have compared one dose of formoterol of the test and reference inhalers versus placebo, therefore did not follow the relative potency approach although the authors made reference to the methods of “relative potency” in the “Introduction” of their paper.</p> <p>We think that the fixed equivalence interval, i.e. 80 – 125% is very tight and it will be difficult for a new generic LABA inhalator to enter the market if these limits are confirmed. One of the only two published studies which we have found on the practical application of the relative potency is the one by Ahrens et al.²⁷ (NOTE: a study with SABA!). The predetermined 90% CI for equivalence was 0.5 – 2.0 (NOTE: well beyond what the CHMP guideline requires). The actual result of the trial showed that the relative potency of the test DPI inhaler (Spiros) was equivalent to 1.12 with 90% CI 0.68 – 1.94 (larger, both on the left and right, than 0.8 – 1.25 that the CHMP guideline requires).</p> <p>In another study on SABA and relative potency by Newhouse et al. on salbutamol Clickhaler DPI²⁸, the equivalence interval was not defined <i>a priori</i> but the 90% CI was calculated. The results showed that the relative potency was 1.29 with 90% CI: 1.04 – 1.63. Therefore, also in this study the CI were outside the 0.8 – 1.25 interval (only on the right in this case).</p> <p><i>There is no literature on clinical studies with LABAs which supports the equivalence interval limits set up by the CHMP guideline. The limited available published literature is relevant to SABAs and appears to indicate that the set interval of equivalence is very difficult to meet.</i></p> <p><u>Proposed change:</u> In studies of either bronchodilation or bronchoprotection with LABAs, the sensitivity of the sample size (i.e., the “room for improvement”) can be evaluated by the clinically</p>	<p><i>reasons of assay sensitivity at least two doses have to be investigated.</i></p>
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²⁶ Lipworth et al. Bronchoprotection with formoterol via dry powder and metered-dose inhalers in patients with asthma. *Ann Allergy Asthma Immunol* 2005; 95: 283-290

²⁷ Ahrens RC et al. Therapeutic equivalence of Spiros dry powder inhaler and Ventolin MDI. *Am J Respir Crit Care Med* 1999;160:1238-1243

²⁸ Newhouse MT et al. Protection against methacholine-induced bronchospasm: salbutamol MDI vs. Clickhaler DPI. *Eur Respir J* 2003; 21: 816-820

	<p>significant response of patients to administration of the reference drug at the screening visit.</p> <p>The rationale of studying two dose levels of the test and reference drugs is to estimate their relative potency. The required equivalence interval, 80-125%, should be justified or allow flexibility to justify alternative criteria being applied.</p> <p>EFPIA:</p> <p><i>LABA therapeutic equivalence:</i> Demonstrating dose-response for efficacy may be problematic if only one dose is licensed e.g. salmeterol 50mcg</p> <p>Possible rewording as thus proposed.</p> <p>Proposed change: Assuming <i>in-vitro</i> evidence for LABA dose proportionality, state that it is acceptable to compare only one dose where only a single dose of the comparator is licensed.</p> <p>Or,</p> <p>“The dose range <i>approved for the reference product</i> should be explored in the single dose studies with assessment of low and high doses to enable demonstration of dose-response”.</p> <p>Pfizer:</p> <p><i>LABA therapeutic equivalence:</i> Demonstrating dose-response for efficacy may be problematic if only one dose is licensed e.g. salmeterol 50mcg.</p> <p>Proposed change: Assuming in-vitro evidence for LABA dose proportionality, state that it is acceptable to compare only one dose where only a single dose of the comparator is licensed.</p>	
394-395	<p>TEVA:</p> <p>It should be also noted that although two doses of test and reference may be explored using either bronchodilation or bronchial challenge studies, a dose-response may not be detectable (e.g. formoterol, inhaled corticosteroids).</p> <p>Proposed change: Illustration by an example for such a study could be very useful.</p>	<p>EWP comment:</p> <p><i>An example would be beyond the scope of the guideline. However, a scientific advice should be sought in the described case.</i></p>

400	<p>EGA: Please clarify the meaning of the term “maximum recommended dose regimen”, i.e. should the highest recommended single dose be used?</p>	<p>EWP comment: <i>The definition of the highest recommended dose should be clear and is reflected in the informative texts of the reference product.</i></p>
401-405	<p>EFPIA: 1.) In contrast to S(L)ABAs, safety with respect to anticholinergics is not mentioned. 2.) In contrast to S(L)ABAs, short-acting versus long-acting antimuscarinic/anticholinergic agents are not differentiated. It is proposed to revise the header. Proposed change: 1.) “The investigation of therapeutic equivalence in respect of anticholinergic drugs (<u>e.g. pupillometry (pupil diameter, pupillary reflex), intraocular pressure, and salivary secretion</u>) is similar to that of SABAs and LABAs”. 2.) “<u>Short-acting and long-acting</u> anticholinergic drugs”</p> <p>IPAC-RS: In contrast to S(L)ABAs, safety with respect to anticholinergics is not mentioned. Proposed change: The following methods can contribute to assess the safety of anticholinergic drugs: pupillometry (pupil diameter, pupillary reflex), intraocular pressure, and salivary secretion.</p>	<p>EWP comment: <i>Agreed. Aspects have been implemented in a modified version.</i></p>

4.3.2.3.2 Inhaled glucocorticosteroids		
Line no. ²⁹ + paragraph no.	Comment and Rationale	Outcome
406-439	<p>IPAC-RS: The section acknowledges the difficulty associated with demonstrating dose-response with inhaled steroids given lack of assay sensitivity of different clinical models, though the draft guidelines maintain a requirement to demonstrate a significant dose-response relationship. Proposed change: Clarity regarding what is considered a significant dose response relationship in the setting of literature precedence would be helpful.</p>	<p>EWP comment: <i>The requirements for proof of therapeutic equivalence of the several kinds of active substances via pharmacodynamic studies have been well described in the final version of the updated guideline. In addition proposals and recommendation were addressed to reach a sensitive proof of TE.</i></p>
406-414	<p>EFPIA / Pfizer: The section acknowledges the difficulty associated with demonstrating dose-response with inhaled steroids given lack of assay sensitivity of different clinical models, though the draft guidelines maintain a requirement to demonstrate a significant dose-response relationship. Clarity regarding what is considered a significant dose response relationship in the setting of literature precedence would be helpful. Proposed change: Assuming <i>in-vitro</i> evidence for ICS dose proportionality, it is proposed that demonstrating therapeutic equivalence at a single strength of an ICS containing product would be adequate.</p>	<p>EWP comment: <i>Yes, the investigation of one strength would be adequate in the described case. Nevertheless, in this case for reasons of assay sensitivity at least two doses have to be investigated.</i></p>
407 -	<p>EGA: As pointed out in the general comments above, the demonstration of a significant dose response relationship with 2 or more doses of test versus the reference product is extraordinarily difficult and should be taken into account in this section. The demonstration of a significant dose-response relationship, which requires testing of more than one dose of both the test and reference</p>	<p>EWP comment: <i>The previous practice of only one dose (of one strength) investigation is no longer acceptable due to reasons of assay sensitivity. The main question is the method of patient's recruiting, however we discuss about frequent and chronic diseases. To sum it up, the requirements are feasible.</i></p>

²⁹ Where applicable

	<p>products, for demonstrating therapeutic equivalence of ICS products is problematic as many ICS are known to have a very flat dose-response curve on pulmonary functions (e.g., FEV₁), thereby requiring hundreds to thousands of patients to achieve reasonable power to pass.</p> <p>Hence, if a steeper dose-response relationship can be achieved with other efficacy measures such as the anti-inflammatory markers (e.g., sputum eosinophils), they should be used as the primary efficacy measure. Otherwise, demonstration of therapeutic equivalence on the y-axis at one dose level should also be acceptable if a dose at the middle portion of the dose-response curve is used.</p>	
408 – 410	<p>ANDI-VENTIS:</p> <p>It is known that the dose-response curve for the effect of ICS on morning PEF (and FEV₁ as well) is flat. In the FACET study³⁰, patients who had asthma for at least six months and had been treated with an ICS for at least three months, were enrolled. The study had a 4-week run-in period, followed by 12 months of randomized treatment. All patients entering the run-in phase received inhaled budesonide at a dose of 800 µg twice daily (total daily dose, 1600µg), plus 250 µg of inhaled terbutaline as needed. Following the run-in phase, eligible patients were randomly assigned to receive one of the following treatments (each dose was given twice daily) for a period of 12 months: 100 µg of budesonide (total daily dose, 200 µg) plus placebo; 100 µg of budesonide plus 12 µg of formoterol (Oxis, total daily dose 24 µg); 400 µg of budesonide (total daily dose, 800 µg) plus placebo; or 400 µg of budesonide plus 12 µg of formoterol. An <u>8-fold decrease</u> in the daily dose of budesonide (from 1600 µg during run-in to 200 µg in the lower-dose budesonide), resulted only in <u>a decrease of the mean morning PEF of only 15 L/min</u> (it is generally considered that a clinically significant difference for PEF is <u>20L/min</u>). While there was a <u>4-fold difference</u> in the daily dose of inhaled budesonide between the higher-dose and the lower-dose arms, <u>there was only a 10 L/min difference in the mean morning PEF</u>. The FACET study clearly demonstrates that the dose-</p>	<p>EWP comment:</p> <p><i>This statement based on the experiences of the European assessors. Several studies were conducted in this way in the past and it has to be concluded: 'IT WORKS.' The main question is the method of patient's recruiting, however we discuss about frequent and chronic diseases. Fully controlled asthmatic patients should not be included definitely. To sum it up, it is feasible.</i></p> <p><i>However, section 'Inhaled corticosteroids) has been comprehensively modified (please compare final version of the updated guideline).</i></p>

³⁰ Pauwels et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11

	<p>response curve for the effect of ICS on morning PEF (and FEV₁) is very flat.</p> <p><i>We maintain that it is problematic to show dose-response with two adjacent doses of inhaled corticosteroids, as required by the guideline.</i></p> <p><u>Proposed change:</u> In studies with ICS, the sensitivity of the sample size (i.e., the “room for improvement”) can be evaluated by the clinically significant response of patients at the end of study. To reach this evidence, the inclusion/exclusion criteria must be carefully defined to select patients that are suitable to the study, e.g. by presence of clinical symptoms and by a run-in period during which the steroid dose is tapered down until symptoms manifest.</p> <p>The rationale of studying two dose levels of the test and reference drugs is to estimate their relative potency. The required equivalence interval, 80-125%, should be justified or allow flexibility to justify alternative criteria being applied.</p>	
408-409	<p><u>TEVA:</u></p> <p>Again reference is made to ‘demonstration of a significant dose-response’ but this may not be possible with all inhaled corticosteroids. It is stated that for inhaled glucocorticosteroids a successful therapeutic equivalence study requires demonstration of a significant dose response relationship with the study of at least two doses of the test drug compared with, if possible, two doses of the reference product. However, there are both ICS and LABAs, for example, where only a single dose is approved. For this situation, no guidance has been provided.</p> <p>In addition, it is mentioned in lines 415-417 that a double blind, randomised, parallel group comparison is the most well/used study design. More clarity with regards to the design of such studies (e.g. two doses in parallel group study design, a cumulative dose study with a single dose or a single dose cross-over study or one dose in a parallel group repeat dose study design). The selection of two doses is mentioned in several areas. For a product that has two or more strengths, it is not clear how the two does are to be selected (e.g. two doses to be tested per strength or two doses of one strength). Further</p>	<p><u>EWP comment:</u></p> <p><i>A guideline is always a recommendation. Therefore, using of alternative models would be possible if adequately justified. However, from the current point of view the proposed alternative models/methods seem to be insensitive.</i></p>

	<p>clarification is required.</p> <p>Proposed change: As acknowledged by the guideline, it is difficult (almost impossible) to establish dose-responses for ICSs. In addition, studies of approved ICS that have been carried out to date generally have not achieved, or even evaluated the dose-response relationship that the guideline is requesting (i.e., although dose ranging is always carried out, it is done using different dose ranges in distinct populations and not a full dose response in a single population). Therefore, alternative models (described below) should be considered.</p> <p><u>An alternative model</u></p> <ul style="list-style-type: none"> • A four week efficacy study comparing test product, reference product, placebo or another less potent treatment such as leukotriene antagonists • For ICS, the dose of the test and reference product should be selected based on the patient's asthma severity. • Demonstration of the assay sensitivity by showing that both test and reference products are superior to the placebo or the alternative treatment • Therapeutic equivalence to be demonstrated between the test and the reference products within a normal dose range 	
418-423	<p>EFPIA:</p> <p>Line 422 states that for crossover studies, carryover effects between treatment periods must be at least equal. It is not clear if this is a statement of principle or if there is a requirement that this be demonstrated from the data collected.</p> <p>The latter is not really possible in practice. Instead the guideline should ask for a washout period between treatment periods of sufficient length to ensure that there are no residual effects of the previous treatment.</p> <p>IPAC-RS:</p> <p>The text states that for crossover studies, carryover effects between treatment periods must be at least equal. It is not clear if this is a statement of principle or if there is a requirement that this be demonstrated from the data collected. The latter is not really possible in</p>	<p>EWP comment:</p> <p><i>It should be demonstrated that the carryover effect is equal. If this is not possible a cross over design will not be considered adequate. However, please take into account that the section 'Inhaled corticosteroids' has been comprehensively modified (compare updated guideline).</i></p>

	<p>practice.</p> <p>Proposed change: Clarify the intent. For example, state it is acceptable to have different but quantifiable carryover (e.g., greater carryover at higher dose) that can be adjusted for in the analysis. Alternatively, the guideline should ask for a wash-out period between treatment periods of sufficient length to ensure that there are no residual effects of the previous treatment.</p> <p>Pfizer: The text states that carry-over must be at least equal.</p> <p>Proposed change: State it is acceptable to have different but quantifiable carryover (e.g. greater carryover at higher dose) that can be adjusted for in the analysis.</p>	
424-426	<p>EFPIA / Pfizer: The draft guideline states “Patients recruited should have demonstrable room for improvement in pulmonary function to respond differently to the two doses of the inhaled corticosteroid and should be symptomatic”. Given issues with demonstrating dose-response to ICS, that such a design would require at least a 2 month run-in to assess dose-response and that to our knowledge this type of study design has not been described in the literature, we have concerns that the approach is being recommended in the guidelines given lack of precedence and concerns regarding technical and logistic feasibility. In addition, this might be quite challenging in COPD patients as opposed to asthmatics.</p> <p>Proposed change: Please provide supporting literature regarding this approach or delete this requirement.</p> <p>IPAC-RS: The recommended ICS design would require at least a 2 month run-in to assess dose-response and to our knowledge this type of study design has not been described in the literature.</p>	<p>EWP comment: <i>This statement based on the experiences of the European assessors. Several studies were conducted in this way in the past. The main question is the method of patient’s recruiting, however we discuss about frequent and chronic diseases. To sum it up, it is feasible. However, section ‘Inhaled corticosteroids) has been comprehensively modified (please compare final version of the updated guideline). In this context some statements should be taken into account in the section “General comment”.</i></p>

426-429	<p>EFPIA / Pfizer:</p> <p>The text states that the patient population should be as homogeneous as possible and should also be the target population. However realistic numbers can only be achieved by narrowing the population so that the population used for bioequivalence is a sub-population of the target populations.</p> <p>Proposed change: By definition to achieve a more homogenous population a sub-population of the target population must be used. Therefore state acceptability of using a sub-population of the target population for the purpose of demonstrating therapeutic equivalence.</p> <p>IPAC-RS:</p> <p>The text states that the patient population should be as homogeneous as possible and should also be the target population. However, realistic numbers can only be achieved by narrowing the population so that the population used for bioequivalence is a sub-population of the target populations.</p> <p>Proposed change: By definition, to achieve a more homogenous population, a sub-population of the target population must be used. <u>The guideline should therefore state acceptability of using a sub-population of the target population for the purpose of demonstrating therapeutic equivalence. The sub-population chosen should be representative of the target population.</u></p>	<p>EWP comment:</p> <p><i>We want to see studies in the intended patient population, but we do not require the entire target population.</i></p> <p><i>A small amendment has been implemented in the final version of the updated guideline.</i></p>
426-429	<p>TEVA:</p> <p>This paragraph contains some assumptions that may not be valid, and some contradictions :</p> <p>Asthma patients requiring high or low dose corticosteroids usually have different severities of asthma and therefore will not form a ‘homogeneous population’ and will be more variable in their symptoms / airway function. Again, it is assumed that a significant dose-response may be present but this is not always the case and is highly dependent on the corticosteroid and the part of the dose-response curve that is examined. Is it intended that different doses (e.g. high and low) should</p>	<p>EWP comment:</p> <p><i>We want to see studies in the intended patient population, but we do not require the entire target population. In the described issue the target population can be defined as patients suffering from persistent asthma. Within this population it should be searched for patients with partly controlled disease in order to fulfil the requirements of sensitivity. However, a small amendment has been implemented.</i></p> <p><i>(This new approach is considered to be more ethically justifiable than the claims addressed in the CFC regulation. The CFC regulation has required steroid-naïve patients.)</i></p>

	<p>be examined in different studies / asthma populations, or two doses within the same population? This needs clarification.</p> <p>In addition, there could be ethical concerns regarding exposing mild-moderate asthma patients to high dose inhaled corticosteroids suitable for severe asthmatics only.</p> <p>Proposed change: In reality, to achieve this “homogeneous population” is going to be very challenging and is unlikely to impact the probability of successfully demonstration of a dose response. It is recommended to use GINA guideline on classification of asthma severity for a targeted population (e.g. intermittent, mild persistent, moderate persistent, severe persistent) or internationally recognised guideline (e.g. BTS). See also the response above for lines 408-409.</p>	
430-431	<p>EFPIA:</p> <p>Clarity regarding the intent of the recommendation to measure FEV₁ in the clinic every 2 weeks would be appreciated given that FEV₁ trough at endpoint would be the usual primary efficacy variable and that in the setting of a 3 month study this would most likely drive additional clinic visits. Domiciliary FEV₁ will be a less robust measure of FEV₁ and drive greater subject numbers. In addition, collection of daily peak flow should be captured electronically to ensure reliability of data.</p> <p>Proposed change: “The primary efficacy variable should be a pulmonary function measure and preferably FEV₁ measured regularly <u>at defined visit</u>, if possible daily at home or at least every two weeks in the clinic. [Regular measurement of FEV₁ is a more sensitive measure of pulmonary function than peak expiratory flow rate (PEFR) which <u>could</u> should be recorded daily at home as a secondary efficacy variable.]”.</p> <p>IPAC-RS / Pfizer:</p> <p>Clarity regarding the intent of the recommendation to measure FEV₁ in the clinic every 2 weeks would be appreciated given that FEV₁ trough at endpoint would be the usual primary efficacy variable and that in the setting of a 3 month study this would most likely drive additional clinic visits. Domiciliary FEV₁ will be a less robust measure of FEV₁ and</p>	<p>EWP comment:</p> <p><i>This topic was discussed by the EWP. The final wording has been modified (please compare).</i></p>

	drive greater subject numbers. Proposed change: Remove requirement for 2 weekly measurement of FEV ₁ . State clinic rather than domiciliary FEV ₁ .	
430-437	Innovata Biomed Limited: Innovata Biomed Limited believes that more emphasis on patient handling studies and <i>in vitro</i> and <i>in vivo</i> flow rate studies should be given, especially for follow on/generic products. FEV ₁ is considered to be a harder manoeuvre for paediatric patients to perform than PEF. It is only recommended for use in children aged 6 years and over, whereas a reference product may be indicated in younger children, for example down to 4 years old. It is more difficult to obtain an accurate and reproducible result in this population, where lung function tests are particularly unreliable. PEF is a more simple measure than FEV ₁ and repeat measurements can be more easily performed. There is a good correlation between PEF and FEV ₁ , which could allow for the use of PEF as a surrogate for FEV ₁ . It could be considered that it is preferable to keep the primary endpoint the same in adult and paediatric studies and the PEF should be used throughout the studies.	EWP comment: <i>Several studies have shown that FEV₁ is a more robust parameter than PEF. Particularly with adults able to manage the inhalation manoeuvre required for a proper FEV₁ assessment this parameter should be used. The situation in children has to be considered separately. Therefore, a clear separation between requirements for the paediatric and the adult population has been addressed in the final version of the guideline (please compare).</i>
432	EGA: FEV ₁ may be considered more sensitive, but can also be shown to be more variable unless it is limited to clinic visits as such. It should be weighed against the power of obtaining larger amounts of more robust, but less sensitive, population data from PEFR.	EWP comment: <i>Here we can not agree. This requirement has been developed to general practice by now.</i>
434	Pfizer: States that electronic diary cards should be used “if at all possible”. This sounds a bit proscriptive and should be reworded for greater flexibility. Proposed change: Suggest, “the use of electronic diary cards is desirable and should be used when possible”.	EWP comment: <i>The wording has been amended in the final version of the guideline.</i>
435-436	EGA:	EWP comment:

	Concerning primary efficacy variables apart from pulmonary function measure (sputum eosinophils, etc), there is no sufficient information available in the literature concerning the variability and the clinically relevant equivalence margins. Without this information, an equivalence study cannot be planned.	<i>The guideline clearly states that eNO, sputum etc. is another efficacy endpoint and not the primary endpoint. However, it is generally expected that the chosen primary endpoint should be validated and justified. Other efficacy endpoints can be analysed descriptively.</i>
438-439	<p>EFPIA: The treatment period for demonstrating therapeutic equivalence for an ICS has been increased from the current guideline which states 6-8 weeks. It is unclear why this change has been made. In addition, duration of treatment period should be specified / clarified for Asthma and COPD. Proposed change: “The duration of treatment periods should be at least six-eight eight (if not twelve) weeks, any shorter treatment period should be justified.”</p> <p>EGA: The requirements laid out in this section are unclear. Please clarify whether treatment periods of 8 weeks are generally acceptable or under which circumstances 12 weeks are mandatory.</p> <p>IPAC-RS: The treatment period for demonstrating therapeutic equivalence for an ICS has been increased from the current guideline which states 6-8 weeks. It is unclear why this change has been made. Proposed change: Please provide references supporting the need for the recommended duration.</p> <p>Pfizer: The treatment period for demonstrating therapeutic equivalence for an ICS has been increased from the current guideline which states 6-8 weeks. It is unclear why this change has been made. Proposed change: Suggest ‘The duration of treatment periods should be at least 6-8 weeks’</p>	<p>EWP comment: <i>Sensitive studies are required. If 6 to 8 weeks studies are sufficient to show TE in a sensitive way (!) then the study will be accepted. The proposed wording keeps as it is.</i></p>

443-446	<p>EGA:</p> <p>See general comments and comments on line 407.</p> <p>On lines 443-446 it is stated that specific safety investigations must be carried out following inhalation of the maximum recommended daily dose of ICS regularly over time in both adults and children, and, if possible, systemic safety should be demonstrated through pharmacokinetic bioequivalence and measurement of pharmacodynamic parameters in adults and children. As with other therapeutic classes, single-dose PK bioequivalence without measurement of PD parameters should be sufficient to assure systemic safety. This is consistent with the conventional PK bioequivalence study of orally administered drugs where similarity of drug concentration in the systemic circulation assures similar systemic safety of the test and reference products. The reason is that any systemic side effect of the drug is triggered by the drug molecules that were absorbed into the systemic circulation. The same can be said for ICS. Hence, PK bioequivalence alone should be sufficient. Furthermore, a single-dose design in healthy subjects should be allowed for the PK bioequivalence study because it is more sensitive for detecting differences in drug absorption. The multiple-dose design can be an option if the drug levels in plasma are too low to be measured accurately and precisely or if the PK parameters are too variable. With the use of PK bioequivalence, there is also no need to study systemic safety in children because any differences or lack of differences, in absorption between products predicted by the study should also apply to children. This is, again, consistent with the practice of conventional PK bioequivalence study of orally administered drugs where only adult volunteers are employed even though the drugs may be prescribed for chronic use in children. Please refer to the General comments on paediatric studies.</p>	<p>EWP comment:</p> <p><i>The paragraph ‘specific safety investigations must be carried out following inhalation of the maximum recommended daily dose of ICS regularly over time in both adults and children, and, if possible, systemic safety should be demonstrated through pharmacokinetic bioequivalence and measurement of pharmacodynamic parameters in adults and children’ has been amended. Furthermore, the complete section discusses requirements for clinical studies in patients with asthma. This section does not deal with PK studies primarily. PK is only mentioned as additional parameter for safety assessment. The influence of PK differences on classically systemic safety parameters has to be assessed in this context. It is known that the inhalation manoeuvre is different in obstructive patients and healthy volunteers. Therefore we would like to see this investigation in patients and not in healthy volunteers. In case of ICS, a PK measurement would be recommended at the beginning and at the end of the study, for instance. Multiple dose design should be in line with ethical considerations and should be clinically relevant. From our experiences using of x-fold higher doses are not necessary to measure plasma levels.</i></p> <p><i>The requirements for the paediatric population have been intensively reconsidered. The paediatric items have been included in the main guideline. Therefore, please compare the final version of the guideline.</i></p>
443-446	<p>TEVA:</p> <p>It states “ In addition, specific safety investigation must be carried out ...”</p> <p>Does this mean that separate safety studies with high dose ICS must be</p>	<p>EWP comment:</p> <p><i>1.) Agreed. Safety studies have to be carried out in the highest applied strength. If this strength is already used to assess efficacy no additional study is necessary.</i></p>

	<p>carried out both in adults and children, in addition to PK / PD equivalence studies in both populations (or healthy adults?) Why both populations?</p> <p>What is 'regularly over time' [e.g. how long, how regularly (line 444)]? Is this referring to the text provided in lines 447-464) (e.g. HPA axis in adult patients: 8 or 12 weeks; HPA axis study in healthy adult volunteers: 4 weeks). If this is the case, it should be referenced in the text. Additionally, two weeks duration of treatment is more than adequate to assess HPA axis effects. Since most inhaled CS half lives are several hours in duration, steady state for most of currently available inhaled drugs can be achieved in 2-3 days; therefore, two weeks duration is adequate from a PK perspective and is adequate time for the HPA axis effects to reach steady state.</p> <p>It is not clear what the recommendation is for the duration required for a knemometry study in children.</p> <p>Proposed change:</p> <p>1.) PK systemic exposure is very good surrogate and a long term safety study [specify the length] is required only when PK data shows a higher systemic exposure for the test product.</p> <p>2.) Clarification is required on the duration required for paediatric studies.</p>	<p>2.) <i>The paediatric items have been intensively re-considered. All relevant paediatric aspects have been included in the main part of the final guideline. Please compare.</i></p>
445-446	<p>EGA:</p> <p>A PK bioequivalence study in adults (preferably healthy volunteers) should be sufficient, as PK studies in children are critical: The necessary amount of blood samples for AUC measurement cause especially in younger children an unacceptable high blood loss. Please refer to the General comments on paediatric studies.</p>	<p>EWP comment:</p> <p><i>Once again, from our point of view, PK studies should be conducted in patients and not in healthy volunteers. Because we discuss about a very common disease the recruiting of appropriate patients should be feasible. Furthermore, in the final version of the guideline, paediatric issues are included in the main part of the guideline. It is clearly addressed what is expected in certain circumstances. Concerning the necessary amount of blood samples for AUC measurement modifications can be considered case by case (e.g. depending on age of included children).</i></p>
447-450	<p>EFPIA:</p> <p>If <i>in vitro</i> comparative testing and demonstration of <i>in vivo</i> clinical efficacy and comparable PK parameters are shown for a medicinal product relative to the reference product, please clarify why there is a</p>	<p>EWP comment:</p> <p><i>From EWP point of view this aspect has been adequately reflected in the final version of the updated guideline. To sum it up, clinical studies are not always necessary (please take the hierarchical approach into</i></p>

	requirement for studies to investigate the systemic effects of inhaled corticosteroids. Why should patients, in particular children, be put through the rigors of HPA testing when it has already been demonstrated that PK is equivalent?	<i>account).</i>
447-450	<p><u>TEVA:</u> <u>Systemic safety of ICS in children</u> The knemometry approach may be another possibility but such studies are long in duration and have not been well-correlated with effects of ICS on asthma in children. There is no mention of 24 hr (or 12 hr overnight) urinary cortisol measurements in children as an acceptable non-invasive method and this can also be built into a therapeutic study. No guidance is provided on what constitute equivalence between tow inhalers. <u>Proposed change:</u> Clarification is required on the equivalence limit for the safety measurements (also see comments above).</p>	<p><u>EWP comment:</u> <i>An assessment of safety via knemometry does usually not require longer term investigations. A fortnight investigation could be sufficient. The requirements for evaluation of safety aspects in children have been completely re-considered. Please compare the final version of the guideline.</i></p>
448-450	<p><u>Innovata Biomed Limited:</u> Innovata Biomed Limited believes that knemometry is not a technique that is adequately sensitive enough to use for comparison purposes for follow on/generic products. The ability to detect differences between products /doses by this method is questioned. The company acknowledges that the methodology has some use in assessing safety of new actives against normal growth but is not accurate, validated or reproducible in comparative product studies. <i>The use of an indwelling cannula to assess HPA impact through plasma cortisol levels in children is also deemed to be “far from robust or even satisfactory”. These matters have been extensive discussed during our EMEA Scientific Advice procedure and Innovata Biomed Limited request that these lines are deleted.</i></p>	<p><u>EWP comment:</u> <i>We do not really share this opinion. There is a lot of experience with knemometry surveys. Additionally, the special situation in the paediatric population has been considered critically. However, this section has been comprehensively modified (please compare final version of the guideline).</i></p>
451-453	<p><u>Innovata Biomed Limited:</u> This section leaves the company in the position of no choice but to go with 12 weeks or to expect issues during assessment if a duration of less than 12 weeks chosen. We request that the guideline is amended to</p>	<p><u>EWP comment:</u> <i>What study duration deems necessary depends always also on the particular study design and can not be answered in a guideline. Sensitive studies are required. For example, if 8 weeks (as requested in the final</i></p>

	provide clarification on the exact study duration required or duration of treatment if the company should undertake a crossover study.	<i>guideline) bronchodilating studies are sufficient to show TE in a sensitive way then the study will be accepted.</i>
451-453	<p><u>Siegfried Pharma Development GmbH:</u></p> <p>The recommendation of 24-hour urinary-free cortisol measurements are not in-line with the available evidence on the large variability of urinary free-cortisol measurements relative to 24-hour plasma- or serum-cortisol measurements, that are commonly considered the methodological “golden standard”.</p> <p><u>Proposed change:</u></p> <ul style="list-style-type: none"> a) Would it be acceptable to recommend the “golden standard” for HPA – axis studies in adults i.e. assessment of 24h plasma / serum cortisol profiles unless otherwise indicated (due to evidence of large variability of urinary free-cortisol). b) We suggest to remove the recommendation for the “coupling methodology” of the 24 hour urinary free cortisol with repeated measures of plasma cortisol c) We propose the guideline includes the option of assessment of salivary cortisol concentrations in children as an alternative to the proposed 24 hour urinary cortisol assessment, as the former correlates more closely with plasma / serum concentration? 	<p><u>EWP comment:</u></p> <p><i>A modification has been implemented. Please compare final version of the published guideline.</i></p>

451-453	<p><u>IPAC-RS / Schering Plough:</u> Requirement for urinary cortisol measurements in addition to 24-hour plasma profiles is unnecessary. <u>Proposed change:</u> Delete the requirement.</p>	<p><u>EWP comment:</u> <i>The requirement for evaluation of the safety aspect for ICS has been partly amended. Please compare the final version of the guideline.</i></p>
454-456	<p><u>TEVA:</u> These seem to be recommending several different approaches – whereas the impression is that a 4-week high ICS dose PD study of plasma cortisol with Synacthen stimulation in healthy subjects is really being favoured. It needs to be made clear whether such a study can supplant the need for repeated high dose cortisol safety studies in asthmatic adults and children. Additionally, the administration of high dose ICS to healthy children raises ethical concerns. Since systemic effects following inhaled administration can vary between patients and healthy volunteers, PD studies in children should be done in patients rather than healthy children whereas in adolescent and adult patients either population could be considered.</p>	<p><u>EWP comment:</u> <i>This section has been modified. It should be emphasised that the PD studies should always be conducted in patients.</i></p>
453 –	<p><u>EGA:</u> Please refer to Section 4.3.2.3.2 lines 438 - 439.</p>	<p><u>EWP comment:</u> <i>We do not see the need of any amendment.</i></p>
458 (& 473)	<p><u>EFPIA:</u> We disagree with the suggested use of the ACTH stimulation test to assess the systemic effects of ICS on the HPA axis. This is a measure of adrenal function reserve and not of systemic exposure. Normal clinical doses of inhaled corticosteroids are unlikely to reduce the ACTH stimulation test so the method is not sensitive enough or appropriate. In addition, this indicates that an ACTH stimulation test can be conducted in healthy subjects. Some inhaled products have different systemic exposure in healthy as compared with patients and therefore the study in healthy may not be predictive of what happens in disease. A</p>	<p><u>EWP comment:</u> <i>Agreed. This paragraph has been removed. Overall, the section dealing with the clinical requirements for inhaled corticosteroids has been comprehensively modified. Please compare final version of the updated guideline.</i></p>

	<p>rewording is thus proposed.</p> <p><u>Proposed change:</u> <i>“In cases where it has been shown that PK is similar in healthy subjects and asthmatics, a further alternative method....”</i></p> <p><u>Innovata Biomed Limited:</u> The effects of corticosteroids on the HPA axis can be measured in a number of different ways such as 24 hour urinary cortisol, 2-hourly plasma cortisol measured over 12 or 24 hours. An alternative test is the low dose Synacthen test but as yet a reference range for the dose response has not been established and there are few comparative studies determining its reproducibility. In particular Innovata Biomed Limited believe that the repeated interventions may not be acceptable for the paediatric population and the test is not sufficiently robust to give an accurate measure of the differences in the delivered doses. Clinical opinion is not currently in favour of this end point. Following scientific advice received Innovata Biomed Limited request that these lines are deleted, as this test is not appropriate for all patient populations.</p> <p><u>IPAC-RS:</u> We disagree with the suggested use of the ACTH stimulation test to assess the systemic effects of ICS on the HPA axis. This is a measure of adrenal function reserve and not of systemic exposure. Normal clinical doses of inhaled corticosteroids are unlikely to reduce the ACTH stimulation test so the method is not sensitive enough or appropriate. <u>Proposed change:</u> Delete suggested use of the ACTH stimulation test.</p>	
458-464	<p><u>Siegfried Pharma Development GmbH:</u> There is limited evidence available that HPA-axis stimulation tests would offer any additional qualitative or quantitative information of clinically value or significance over that of the 24-hour plasma/serum cortisol assessment. <u>Proposed change:</u> Would it be possible to propose the ACTH short stimulation test for the assessment of the systemic effects of ICS on the</p>	<p><u>EWP comment:</u> <i>The ACTH-test has been removed in the final version of the guideline. All in all, this section has been completely updated.</i></p>

	HPA axis in adults only as second line test that may provide supplementary information compared to the 24 – hour plasma / serum cortisol measurement.	
462 + 4.3.2.3.2	<p>Orion Pharma: The proposed 4-week duration for a HPA axis suppression study using the Synacthen short stimulation test in healthy volunteers treated with doses of ICS at the upper limit of the dose range seems excessive and such a protocol is likely to be found ethically unacceptable.</p> <p>Proposed change: Alternative short-term study approaches in healthy volunteers should be considered acceptable. For example, Brus (Arch Intern Med. 1999;159:1903-8) has demonstrated that a single dose of ICS causes significant reductions in cortisol–AUC₂₄ compared with placebo, and there is no difference between single and multiple doses for steroids other than fluticasone propionate (which appears to accumulate). For single doses of budesonide and fluticasone, a clear dose–response in cortisol suppression has also been demonstrated (Grahnen et al. Br J Clin Pharmacol. 1994;38:521-5). It thus appears that a single dose study should suffice to characterise differences between products.</p>	<p>EWP comment: <i>This section has been completely amended.</i></p>

4.3.2.3.3 Combination products		
Line no. ³¹ + paragraph no.	Comment and Rationale	Outcome
480-502	<p>TEVA: This section regarding combination products is extremely unclear and needs rewriting. Given that the principle of a combination product (e.g., budesonide-formoterol and fluticasone-salmeterol) is now well-</p>	<p>EWP comment: <i>PK studies should always be considered before conducting comprehensive PD / clinical studies.</i> <i>New fixed combination products should be compared to the free</i></p>

³¹ Where applicable

	<p>established as a therapeutic option with advantages over both monocomponents, there should only be the necessity to compare a new generic combination of the same drug and dose combination to the corresponding dose combinations of the originator. Studies of the generic combination product against the individual monocomponents should be unnecessary.</p> <p>The choice of an acceptable study design and method needs to be clarified for comparing two similar combination products – the guideline is too vague in these respects. Separate studies comparing the efficacy of each component are unnecessary and should be simplified into one study since the endpoints (lung function, symptoms) are common to both.</p> <p>New combination products with no established originator would not come under the scope of a generic product development programme.</p> <p><u>Proposed change:</u></p> <p>Dosing of ICSs is usually based on the severity of patients' conditions. As mentioned above, demonstration of dose-responses is almost impossible even for the monoproducts. It is not clear about how to establish dose-responses for the combination product. Especially since this was not required of the combination product originally. Having this type of requirement will make the development of a generic product essentially impossible. Alternative models should also be considered and an example is proposed below:</p> <ul style="list-style-type: none"> • a single or repeat dose PK study with the 2 combinations at the same strengths to show exposure of the old and new combo is the same. • A four-week efficacy study comparing test, reference and ICS alone • Demonstration of study sensitivity by showing superiority of both test and reference to the monoproduct (ICS) • Demonstration of therapeutic equivalence between test and reference products within a normal dose range 	<p><i>combination and additionally with the mono-substances as far as possible.</i></p>
481-486	<p><u>EFPIA:</u></p> <p>The first sentence of paragraph may be misunderstood. It is thus</p>	<p><u>EWP comment:</u></p> <p><i>This depends on the available reference product: if a fixed combination</i></p>

	<p>proposed to revise it.</p> <p>Proposed change: “For fixed combination products of known active substance therapeutic equivalence <i>with the free combination</i> should be demonstrated for each/all of the component actives of a fixed-dose combination product and study design will depend on the specific actives in the combination...”</p> <p>IPAC-RS: The first sentence of paragraph may be misunderstood.</p> <p>Proposed change: Add “<i>with the free combination</i>” in the first sentence, i.e.: “...known active substance therapeutic equivalence <i>with the free combination</i> should....”.</p>	<p><i>reference product is available, the comparison to this fixed combination will be preferred.</i></p>
481-486	<p>EFPIA / Pfizer: The proposal to use co-primary endpoints complicates the potential study design and statistical analysis and is unnecessary if the in vitro and PK data support the proposal that the new product is identical in all key parameters to the reference product.</p> <p>Proposed change: Suggest trough FEV₁ as primary endpoint for both components (assuming an ICS/LABA combination) with FEV₁ AUC as a secondary endpoint where bioequivalence is supported by <i>in vitro</i> and PK parameters.</p> <p>IPAC-RS: The proposal to use co-primary endpoints complicates the potential study design and statistical analysis and is unnecessary if the in vitro and PK data support the proposal that the new product is identical in all key parameters to the reference product.</p> <p>Proposed change: Suggest trough FEV₁ as primary endpoint for both components (assuming an ICS/LABA combination) with FEV₁ AUC as a secondary endpoint where bioequivalence is supported by in vitro and PK parameters.</p>	<p>EWP comment: <i>We see your point but we still think that fixed combinations need one primary endpoint for each active substance.</i></p>
481 - 494	ANDI-VENTIS:	EWP comment:

	<p>The recommendations in this section are not clear. According to our interpretation, there are two ways to demonstrate therapeutic equivalence for this class of products:</p> <p>A. A single study in which the outcomes relevant to each of the two components, i.e. ICS and LABA are measured separately. Not clear how to define an outcome capable of assessing both active components separately? Does it mean that the outcome for the ICS component, i.e. FEV₁ should be measured after at least 8 weeks of treatment, while the effects of LABA should be evaluated by a bronchodilation or bronchoconstriction study? What should be the comparator drug?</p> <p>B. Two separate studies in which the two components, ICS and LABA, are assessed through separate studies assessing each separate active. What should be the comparator in these studies? Should the COMBO be compared vs. the LABA in one study and the COMBO vs. the ICS in another study? These would be superiority studies! Or, should we instead compare the COMBO vs. the extemporaneous combination (ICS + LABA) in both studies?</p> <p>In any case, we will be confronted by the problem of the “relative potency” approach: two dose levels for each of the tested products and the very tight CI, as detailed in the previous comments.</p>	<p><i>In seldom cases, it can be that only one strength has to be investigated (depend on the kind of the reference product), however for reasons of assay sensitivity more than one dose should normally be examined.</i></p>
487	<p><u>EFPIA / Pfizer:</u></p> <p>Demonstration of dose-response for different ICS strengths of LABA/ICS containing products will be even more problematic given the LABA component will most likely diminish assay sensitivity further.</p> <p>Does the statement “two doses of each combination product (the test and the reference combination product)” mean 4 arms, i.e. 2 new, 2 reference product arms? Please clarify.</p> <p><u>Proposed change:</u> Assuming <i>in-vitro</i> evidence for ICS dose proportionality, propose that demonstrating therapeutic equivalence at a single strength of an ICS containing product would be adequate.</p>	<p><u>EWP comment:</u></p> <p><i>Single strengths but more than one dose when ever possible. The number of arms depends on the investigated product. In the concrete question, yes the statement is correct.</i></p>

	<p><u>IPAC-RS:</u> Demonstration of dose-response for different ICS strengths of LABA/ICS containing products will be even more problematic given the LABA component will most likely diminish assay sensitivity further.</p> <p><u>Proposed change:</u> Assuming in-vitro evidence for ICS dose proportionality, propose that demonstrating therapeutic equivalence at a single strength of an ICS containing product would be adequate.</p>	
487-488	<p><u>EGA:</u> For combination products the LABA component is usually only available in one strength. Guidance should be added as to which type of study is required if the maximum (and only) registered single dose of the reference product is one single actuation. The introduction of a second dose would mean that patients would be treated with (at least) twice the maximum registered dose. The same applies to the glucocorticosteroid component in the paediatric indication, where one actuation of the lowest registered strength is the maximum daily single dose. For the requested two dose levels (especially in DPIs with high flow rate dependency) children would consequently have to be treated with an overdose (i.e., a dose twice as high as the registered dose) for both the LABA and the corticosteroid component, which raises ethical concerns. This is a general problem if demonstration of dose sensitivity is requested in children. Please refer to the General comments on paediatric studies.</p>	<p><u>EWP comment:</u> <i>It can be that only one strength has to be investigated (depend on the kind of the reference product), however for reasons of assay sensitivity more than one dose should normally be examined.</i> <i>In case of a paediatric indication we would like to refer to the completely revised final version of the guideline. Here, all the requirements are clearly addressed.</i></p>
487-8	<p><u>Orion Pharma:</u> It is proposed that two doses of each combination product (test and reference) should be included to show a dose–response relationship. For the LABA component, such demonstration should not pose major practical hurdles in the proposed single-dose studies. For the steroid component, however, this requirement taken literally will effectively prevent any second-entry ICS+LABA combinations from the market.</p>	<p><u>EWP comment:</u> <i>Regarding the non-inferiority the same applies to combination products as applies to the single components. Single strengths but more than one dose when ever possible is recommended. Assay sensitivity has to be proven.</i></p>

	<p>(On line 407, the present draft correctly notes that “demonstration of therapeutic equivalence of ICS is difficult.” When it is the ICS component of a combination, demonstration of equivalence along the lines proposed here becomes insurmountable.) Firstly, the selection of the patient population is problematic, since the majority of patients are already well-controlled with a low dose of a combination, and demonstration of dose–response in such patients is unfeasible in practice. In patients with severe asthma, demonstration of dose–response might be feasible, but subjecting a large number of patients to treatment <i>a priori</i> known to be substandard for them (and less effective than the treatment they are already on) poses major ethical concerns (albeit the treatment periods were restricted to 8–12 weeks).</p> <p><u>Proposed change:</u> We propose that demonstration of non-inferior efficacy of the test product to the reference, with one dose of each product, and demonstration of superiority over ICS alone would be considered sufficient proof of equivalence.</p>	
491-492	<p><u>IPAC-RS / Schering Plough:</u></p> <p>The guideline allows for assessment for LABA combinations over only 80% of the duration of action rather than requiring equivalent trough level effect. Lesser delivery can result in reduced duration, perhaps more visibly than lower peak effect, and this would be most evident at the end of the dosing interval.</p> <p><u>Proposed change:</u> Revise the guideline to additionally require equivalence at the end of the dosing interval.</p> <p><u>TEVA:</u></p> <p>"at least 80% of the duration of action". What is the definition for duration of action? Is it 12 hour for a drug that is administered twice daily? In that case, you could measure the efficacy for formoterol or salmeterol in combination products for at least 9.6 hours (80% of 12 hours), which is quite short.</p> <p><u>Proposed change:</u> Clarification is required. The duration of action may differ slightly between two different doses for the same product (e.g. it is c. 10 hrs for 6 mg formoterol, compared to c.12 hrs for 12 mcg</p>	<p><u>EWP comment:</u></p> <p><i>We appreciate your point. It is expected that in the last 20 % of the duration of action corresponds with the decreasing part of the curve. Here, changes are expected to be minimal so that extrapolation should be possible even if duration of action is shorter for one of the comparators</i></p>

	formoterol) and different products. The rationale should be provided.	
495-6	<p>Orion Pharma:</p> <p>It is proposed that for “new fixed combination products with no approved fixed combination reference product the inclusion of an additional treatment arm in which patients would receive the ICS component alone...”. It is not obvious what “additional” refers to (since there is no reference product); additional to what? Please clarify.</p>	<p>EWP comment:</p> <p><i>PK studies should always be considered before conducting comprehensive PD studies. New fixed combination products should be compared to the free combination and additionally with the mono-substances as far as possible.</i></p>
495-500	<p>EFPIA:</p> <p>This paragraph implies that all combination products would be combinations which include ICS as one of the components. It is proposed to remove the paragraph as new combination products are clearly outside the scope of this guideline.</p> <p>Proposed change: “For new fixed combination products with no approved fixed combination reference product the inclusion of an additional treatment arm in which patients would receive the ICS component alone is necessary with further reference to the CPMP Note for Guidance on Fixed Combination Medicinal Products CPMP/EWP/240/95. The ICS alone treatment group could receive the same dose of corticosteroid as in the combination product or alternatively receive a higher dose, although care should be taken to ensure that patients are not then over treated.”</p>	<p>EWP comment:</p> <p><i>A small modification has been addressed in this paragraph. However, we can not agree with the statement that the paragraph addressing the requirements of new combination products are clearly outside the scope of this guideline. In the past some new fixed combination products were developed that consisted of known active substances.</i></p>

4.3.2.3.4 Sodium cromoglycate and nedocromil sodium		
Line no. ³² + paragraph no.	Comment and Rationale	Outcome
504-505	<p>EFPIA:</p> <p>There is insufficient scientific evidence for demonstrating the therapeutic equivalence of sodium cromoglycate and nedocromil sodium based on bronchial challenge studies.</p>	<p>EWP comment:</p> <p><i>Clinical studies would be the last step. At the beginning, the applicant should try to show equivalence in vitro and/or in vivo via PK studies. If this procedure was not successful, PD studies would be necessary.</i></p>

³² Where applicable

	Proposed change: Please consider deleting the section.	<i>However, it should be kept in mind that both sodium cromoglycate and nedocromil sodium do no account to the hybrid 'blockbusters'. Few experiences exist in showing TE with this drug class.</i>
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4.4 Clinical trials and change of pharmaceutical specifications		
Line no. ³³ + paragraph no.	Comment and Rationale	Outcome
507-512	<p>EFPIA: The requirements for setting of specifications based on the pharmaceutical results of the batches used in trials etc is unnecessarily restrictive, (Particularly in relation to considerations of process capability) and is covered in the guideline on pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/49313/2005)</p> <p>Specifications will contain tests not related to aerosol performance. Moreover, some tests of aerosol performance may not be clinically relevant in some cases. A more appropriate statement is thus proposed.</p> <p>Proposed change: 1.) Remove this paragraph from the guideline, or refer to the pharmaceutical guideline. 2.) "A widening of <u>clinically relevant test acceptance criteria on a specification</u> cannot be supported at a later date, when..."</p> <p>Pfizer: Specifications will contain tests not related to aerosol performance. Moreover, some tests of aerosol performance may not be clinically relevant in some cases.</p> <p>Proposed change: It would be more appropriate to state "A widening of clinically relevant test acceptance criteria on a specification....."</p>	<p>EWP comment: <i>A reference to the pharmaceutical guideline has been already implemented at the beginning of the guideline. With regard to the second proposal, a slightly modified wording has been implemented. However, the proposed wording 'A widening of clinically relevant test acceptance criteria on a specification.....' seems to be not clear enough. What does 'clinically relevant test acceptance criteria' mean?</i></p>

³³ Where applicable

	<p><u>IPAC-RS:</u> Specifications will contain tests not related to aerosol performance. Moreover, some tests of aerosol performance may not be clinically relevant in some cases.</p> <p><u>Proposed change:</u> It would be more appropriate to state “<i>A widening of clinically relevant test acceptance criteria on a specification.....</i>”</p>	
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4.5 COPD		
Line no. ³⁴ + paragraph no.	Comment and Rationale	Outcome
513	<p><u>EFPIA / IPAC-RS / Pfizer:</u> The guideline recognises that COPD is different to asthma but provides no guidance on design/duration of studies to demonstrate Therapeutic Equivalence (TE) but instead refers to existing guidance which is only intended for New Chemical Entity development programmes. This could be interpreted to mean that (TE) is not demonstrable in COPD and that a full clinical programme is required where a reference product is for COPD only. Please provide further guidance on design/duration of TE studies for COPD as a standalone application. We understand that the guideline is pushing for clinical development with asthma and does not allow getting an asthma indication if clinical comparative development has been carried for COPD. Please clarify. <u>Proposed change:</u> Provide further guidance on design/duration of TE studies for COPD as a standalone application.</p>	<p><u>EWP comment:</u> <i>In repetition of previous statement, the focus of this guideline is more to asthma for reasons of feasibility. In case of approval of the reference product only for COPD, the normal procedure (in vitro / in vivo etc.) should also be considered. If clinical studies (PD studies dealing with COPD) are necessary, the concrete clinical studies will be discussed in a national or European SA. Imaginable endpoints could be time to or number of severe exacerbation in patients suffering from very severe COPD. However, the described situation may be possible, but do not reflect the normal situation on the European market.</i></p>

4.4 Clinical trials and change of pharmaceutical specifications		
Line no. ³⁵ + paragraph	Comment and Rationale	Outcome

³⁴ Where applicable

no.		
521	<p>EFPIA: The first sentence is not consistent with the title of this section aimed at discussing new excipients to be used in inhalation products. It is thus proposed to delete the sentence.</p> <p>Proposed change: “The safety profiles of active drug substances as currently formulated are not in question. However, <i>potential</i> safety concerns do arise, both from...”</p> <p>IPAC-RS: The first sentence of section 4.7 should be revised to address the topic of the header of this section. Proposed change: Proposed change: “<i>The safety profiles of currently used excipients do not cause questions to the safety of currently authorised product.</i>”</p>	<p>EWP comment: <i>A small modified wording has been implemented.</i></p>
521-539	<p>EGA: If the new excipients are well known and have been used in other inhalation products without any documented problems, extended safety data in animals or patients should not be needed.</p>	<p>EWP comment: <i>We do not demand toxicological data about well-known excipients. However, it could be necessary that the interaction aspect has to be discussed.</i></p>
527	<p>EFPIA: "Full animal toxicology" for excipients used for the first time in inhalation is an ambiguous requirement. Please provide more specific guidance.</p>	<p>EWP comment: <i>This aspect is beyond the scope of this guideline. There is no need for action.</i></p>

SAFETY OF NEW EXCIPIENTS		
Line no. ³⁶ + paragraph no.	Comment and Rationale	Outcome

³⁵ Where applicable

³⁶ Where applicable

DEFINITIONS		
Line no. ³⁷ + paragraph no.	Comment and Rationale	Outcome
540-556	<p>EFPIA / Pfizer: A number of the definitions (e.g. delivered/emitted dose) are inconsistent with the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products. It would be useful to harmonise with this earlier guideline.</p> <p>IPAC-RS: The definition of the <i>delivered/emitted dose</i> is inconsistent with the <u>EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products</u>. Proposed change: Standardise definitions with the referenced earlier guideline.</p>	<p>EWP comment: <i>Thanks for this comment. We have modified and extended the section of definition.</i></p>
540	<p>IPAC-RS: The guideline uses the terms “<i>reference product</i>”, “<i>comparator</i>”, and “<i>authorised product</i>” seemingly interchangeably.</p>	<p>EWP comment: <i>A definition of a reference product has been added in the glossary. The guideline has been modified with regard to this aspect.</i></p>
543-4	<p>Orion Pharma: A “negative” definition for linearity is only given. Please define linearity in this context. Proposed change: Use a single term, e.g., “<i>Reference Product</i>”, and provide a definition, e.g., “<i>The authorized innovator product against which therapeutic equivalence is claimed.</i>”</p>	<p>EWP comment: <i>Agreed. A modified wording has been implemented.</i></p>
549	<p>IPAC-RS: “<i>Also called a holding chamber</i>” is not a definition. Furthermore, there may be important differences between “spacing devices” and “holding chambers” because the former have no means of retaining the aerosol</p>	<p>EWP comment: <i>Absolutely correct, a definition has been implemented. In the most publications “spacing device” and “holding chamber” are used in a similar context. It should be avoided any further confusion by</i></p>

³⁷ Where applicable

	<p>(preventing aerosol from escaping) before a patient's inhalation. This difference may influence the aerosol particle size distribution, among other things.</p> <p>Proposed change: Include a meaningful definition for “<i>spacing device</i>” (or, rather, “<i>spacer</i>”, to be consistent with EMEA/CHMP/QWP/49313/2005corr.), e.g., “<i>An accessory that increases the distance between the inhaler and the patient's mouth but which does not retain the emitted aerosol.</i>”</p> <p>Also include a separate definition for “<i>holding chamber</i>”, e.g. “<i>An accessory comprising a volume between the inhaler and the patient's mouth, enabling it to contain the aerosol following an actuation</i>”.</p> <p>Make the use of these terms consistent throughout the guideline.</p>	<p><i>additional separations.</i></p>
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Comments on the requirements for studies in children and adolescents

General Comments on Appendix 1 – Overview

EFPIA (European Federation of Pharmaceutical Industries and Associations)

EFPIA do support the principles espoused on page one of the draft appendix regarding the differences in children's airways compared to adult and agree that products shown to be equivalent in adults may not be equivalent in children. EFPIA are proposing that this Paediatric Annex 1 becomes integrated into the main guideline.

EWP Comment:

*The EWP agreed. It was always the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults **and** for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline.*

This draft document relies heavily on demonstration of *in vitro* equivalence and/or therapeutic equivalence in adults to support a claim of equivalence in children without the need for specific studies. These concerns need to be adequately addressed in order to provide meaningful comments on the paediatric proposals. In addition, when demonstration of therapeutic equivalence to a reference product in an abridged application in children is to be considered, *in vitro* and clinical requirements should always be considered and balanced. The use of a decision tree would be a benefit to sponsors.

EWP Comment:

The EWP agreed with the concerns raised. The section entitled "Clinical Requirements" has been reviewed and has been completely rewritten.

As previously mentioned in our comments on the draft guideline for Orally Inhaled products (CPMP/EWP/4151/00), EFPIA would welcome the opportunity for further discussion on this subject and respectfully requests an Interested Parties meeting led by the EWP.

EWP Comment:

The EWP discussed this proposal but following the receipt of all comments and following numerous discussions with the Profession and extensive rewriting of this section of the Guideline a meeting of Interested Parties was thought to be unnecessary.

In addition to other detailed comments in the following pages, we would like to highlight the following:

1. Appendix 1 uses the condition that "the inhalation device of the test product is (or: is not) pharmaceutically identical to that of the reference product". The term "identical" is inappropriate, unless the same (identical) inhaler from the same manufacturing source is used as test and reference inhaler. Moreover, the combined term "pharmaceutically identical" is neither defined in the parent guideline, nor in the Appendix, and is therefore not suitable as a prerequisite to take or not to take further action, i.e. to perform clinical studies.

EWP Comment:

The EWP commented that the phrase “pharmaceutically identical” will be changed to “identical”. It was intended that the inhalation device of the test product should be identical to the reference product to allow a bridge without any clinical studies or minimal handling studies.

2. The wording of the Appendix does not take adequately into account the fact that the performance of an inhalation product is in most cases (and for dry powder inhalation products, always) a combination of the properties of inhaler and formulation. It could therefore be a significant difference, if for example in paragraph 2 the test inhalation device is an HFA MDI already approved in the intended paediatric population, or if this is a dry powder inhaler with performance characteristics predominantly influenced by the powder formulation.

EWP Comment:

The EWP commented that the inclusion of the criteria that the “*in vitro* criteria for equivalence have all been fulfilled” takes into account the performance of the combination of the properties of the inhaler and formulation.

3. In the clinical development of orally inhaled products, generally, any new product which may claim equivalence with the innovator must demonstrate:
- Safety: systemic exposure to the active ingredient should be equivalent or lower than that with the innovator product (“non-superiority”)
 - Efficacy: pharmacodynamic (PD) equivalence, as a surrogate for efficacy, should be demonstrated. In an especially vulnerable population like children, an abbreviated programme for demonstration of PD equivalence may be acceptable (e.g. single-dose crossover). In contrast, if e.g. the test product has been shown to have lower systemic exposure of the active ingredient than the innovator, equivalence of efficacy (as per PD) may need to be based on more extensive data..

EWP Comment:

The EWP agreed with the comment – see the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 6.

EGA (European Generic Association)

The EGA has already contributed to the revision of the “Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)” (CHMP/EWP/4151/00 Rev.1). We welcome the publication of Appendix 1 which relates to specific paediatric clinical concerns.

Before discussing specifics of the appendix 1, EGA member companies would like to outline a very significant and pressing issue which would deserve careful evaluation by the EMEA CHMP or the CMD(h). In re-drafting this guideline a noticeable effect has been to undermine the confidence of assessors in assessing current applications and indeed for assessors to predict the outcome and pre-emptively implement changes.

It is worth noting that assessors have also begun to defer assessments and to hold back on completing assessments already begun, pending the outcome of this review. This is likely to leave applicants in a “regulatory vacuum” until Q3-2008 at the optimistic earliest.

The EGA would urge the EMEA to provide the necessary guidance to assessors within the agencies on how best to manage the interim “vacuum” in guidance when assessing applications, as this has now become of paramount importance to the industry.

EWP Comment:

The EWP accepted the difficulties which might be encountered during this interim period. It was the intention of all those involved in the Drafting Group and in the EWP that this very important Guideline would be finalised and adopted by the CHMP within the shortest possible timeframe. Clinical programmes currently underway would be assessed alongside the previously available CHMP guidance in this area but in order that Marketing Authorisations can be granted appropriate therapeutic equivalence in respect of both efficacy and safety in the intended patient population must be demonstrated.

In addition to this important remark, the EGA would like to highlight other important areas where clarification is sought:

- The paediatric studies are addressed in the present document but also partially in the main guideline. These documents were released separately for public consultation.

In order to maintain consistency and to consolidate the relevant information, we would request that all information relating to the paediatric studies be put in one place, either in the main guideline or in the Appendix. Cross references should be introduced in the main text of the guideline.

In addition, the assessment by the EMEA of answers to the public consultation should be carried out when responses are available on both documents (end of May) as it will then be more meaningful and complete.

EWP Comment:

It was always the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline.

- The guideline suggests a stepwise approach and in effect a hierarchy of equivalence testing, ie, from *in vitro*, PK, PD and TE studies. It is to be acknowledged that this approach runs completely contrary to the current thinking whereby agencies have suggested that locally acting respiratory medicines needed TE (ie, lung function endpoint studies) to show patient-delivery interaction. In practice it remains to be clarified whether all agencies will pursue recognising the former studies as being capable of proving clinical equivalence or whether questions will be repeatedly raised whereby the clinical package will in effect become a combination of all the studies suggested. EGA member companies believe acceptance of PK equivalence for systemic exposure is fundamental and that requirements for long term safety studies in particular need to be reconsidered. The guideline and subsequently issued appendix would require further qualification (throughout) as to how they have been worded against the *in vitro* – PK - PD - TE approach.

EWP Comment:

A stepwise approach, from in vitro data through pharmacokinetic and pharmacodynamic studies through to full clinical development, as required, is the recommended route in the development of orally inhaled products where the objective is the demonstration of therapeutic equivalence between two inhaled products. The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 describes this approach in detail in Section 6; however at this stage in our knowledge, in general therapeutic equivalence, particularly in respect of efficacy, will require demonstration through appropriate pharmacodynamic and/or clinical studies.

However this stepwise approach becomes more difficult in the development of orally inhaled products in children as it is felt that pulmonary deposition studies in

children are not appropriate. Pharmacokinetic studies as a surrogate for efficacy only imply efficacy, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence. Imaging studies in children are also not appropriate.

The situation in respect of the assessment of systemic safety in children differs slightly regarding the use of pharmacokinetic studies and situations where such studies might be used are described in the Final Adopted CHMP Guideline – Sections 6 and 9. In situations where pharmacokinetic studies are not appropriate for the assessment of systemic safety, pharmacodynamic studies will be required.

- A decision tree (or flow chart) to suggest possible studies and approval routes under various situations would be a useful addition to the revised guideline and its appendix 1. This is perceived as an essential tool to prevent differences in interpretation of the guidance by the various stakeholders.
A summary of each study type and clear rationale of their objectives would be useful.

EWP Comment:

The EWP agreed with this proposal. However in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 a late decision was made not to include a decision tree/flow chart.

- Particular attention should be given to the choice of words employed in order to limit the degrees of interpretation.
The use of highlighted terms such as “might”, “may”, “generally not”, etc. should be avoided in that it leads to confusion as to what is really expected.

EWP Comment:

The EWP agreed with this proposal.

- Clarifications should be brought on the need for applicants to apply upfront for a PIP waiver.

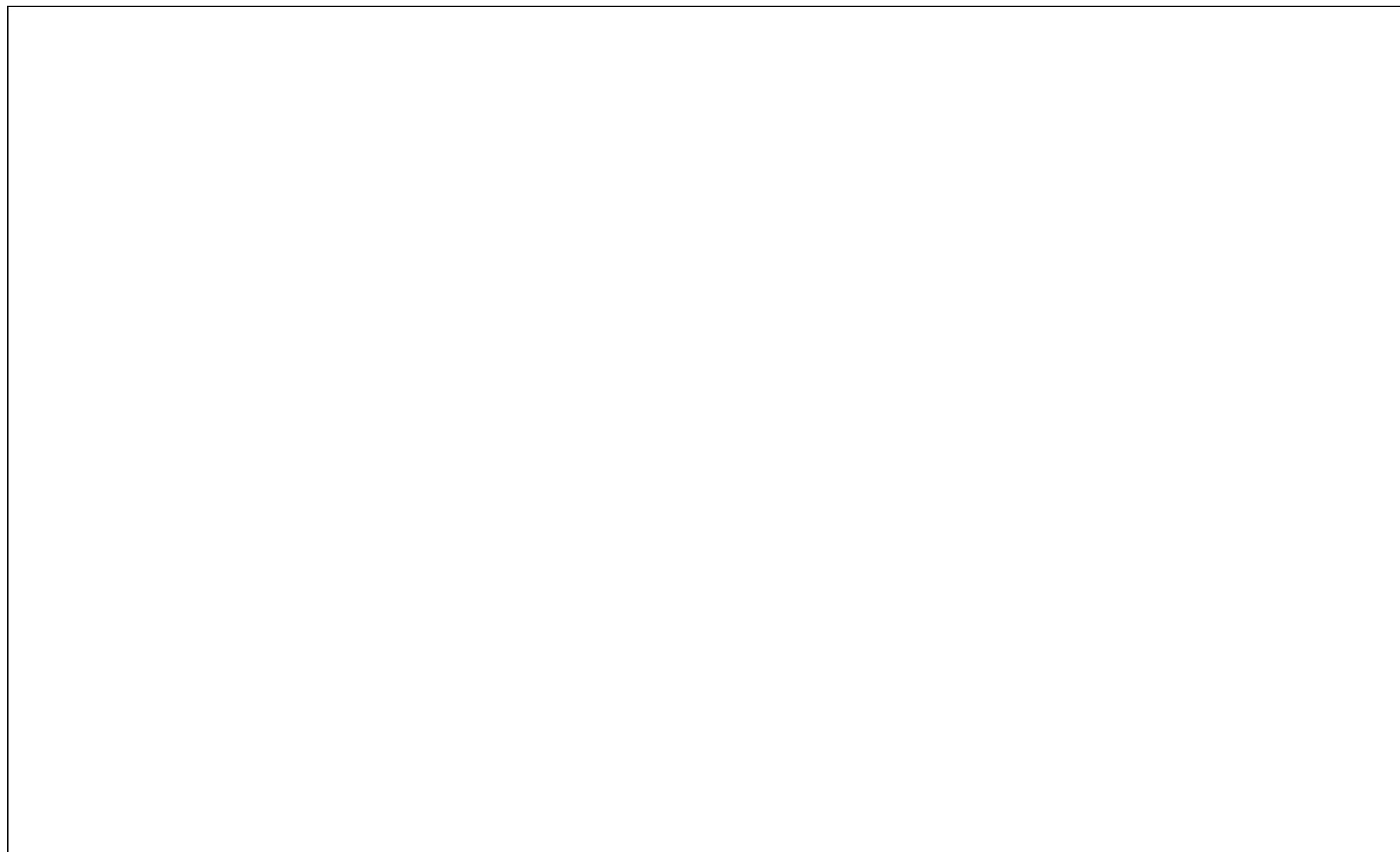
EWP Comment:

The requirements for a PIP waiver were deemed to be outside the scope of this Guideline.

- EGA member companies would like to highlight here that although children are defined as a label population (ie, 4 to 12 years of age), as noted in the appendix, it constitutes a range in physiological and cognitive functions which will have an impact on the demonstration of equivalence (therefore more defined guidance is required on the acceptability of an adult bioequivalence package and need for specified bridging studies)

EWP Comment:

The Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 describes clearly the scenarios which may arise resulting in differing clinical requirements in the development of orally inhaled products in children and states that if none of the three given scenarios arises clinical development of the product in children will be required with demonstration of therapeutic equivalence in respect of both efficacy and safety. Interpolation from data generated in studies in adults may be possible for development in adolescents (aged between 12 and 17 years). Section 6 of the Final Adopted Guideline describes how orally inhaled products should be studied and developed in children and looks at the sub-groups of children aged 6 to 12 years and the pre-school child aged 3 to 6 years and 2 to 6 years.



- Conversely, as currently drafted the main guideline also remains unclear as to the ability to use proof of equivalence in adults as a surrogate to license products in children (for example by referring to cannulation in children ie, inferring but not guiding on the practicality and not least ethics of paediatric PK studies).

Therefore certain sections of the appendix appear to be contradicting the main guideline text (eg, problem statements, scenarios) in that they infer the requirement for specific studies in children without having clearly defined what these should be.

EWP Comment:

The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009, Section 9, states clearly the situations when clinical development in children will or will not be required. In the vast majority of situations clinical development in children will be required. It is felt that pulmonary deposition studies in children are not appropriate, pharmacokinetic studies as a surrogate for efficacy only imply efficacy, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence. Imaging studies in children are also not appropriate. The situation in respect of the assessment of systemic safety in children differs slightly regarding the use of pharmacokinetic studies and situations where such studies might be used are described in the Final Guideline. In situations where pharmacokinetic studies are not appropriate for the assessment of systemic safety, pharmacodynamic studies will be required.

- Consideration should be given to those reference products for which the labelling of the posology section is limited, for example referring only to a “minimum posology” in patients above 4 years and the clinical implications this may have on generic medicines against such reference product (eg, Flixotide).

EWP Comment:

If therapeutic equivalence between the test (new) product and the reference product is deemed to have been demonstrated the labelling in respect of the posology in children will be identical to that of the reference product. If there is a thought for clinical need for the labelling in respect of the posology of the new product to differ from that of the reference product, or if the posology does differ from that of the reference product, a full development of the new product will be required and the dose, the dose range and the dose regimen in the paediatric population will need to be defined. The product labelling will have to reflect this clearly.

EPAG (European Pharmaceutical Aerosol Group)

We appreciate the additional information provided in this annex and support the concept and structure of the guidance provided. We have some comments that we would appreciate you to consider in your review process.

EWP comment:

*See later in the section **Specific Comments on Text.***

IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)

We support the principles espoused on page 1 of the draft Appendix regarding the differences in children's airways compared to adult and agree that products shown to be equivalent in adults may not be equivalent in children.

We consider that these differences are such that clinical safety-related PK/PD data would almost always be necessary to "provide assurance that the safety profile is unchanged" in children unless otherwise justified by reference to the criteria outlined under points 1-3 of the Clinical Requirements.

There appears to be an opportunity to introduce a decision tree as a part of the guideline. The use of a decision tree would be a benefit to sponsors. This comment was also raised on the draft guideline itself. We would welcome the opportunity to collaborate with EWP in producing a decision tree for the main guideline and for the Appendix.

We would propose that the pediatric annex becomes integrated into the main guideline.

We welcome the opportunity for further discussion on this subject and respectfully request an Interested Parties meeting led by the EWP.

EWP Comment:

The EWP accepted the comments regarding the use of a decision tree and sees the benefits. However following lengthy discussions on the Guideline text and the provision of a huge amount of detail regarding both the in vitro and the clinical requirements (pharmacokinetic, pharmacodynamic and clinical) a decision was reached that a decision tree/flow chart would not be included in the Guideline.

*The EWP agreed that Appendix 1 regarding development in children should be integrated into the main Guideline. It was always been the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults **and** for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline.*

The EWP discussed the request for a meeting of Interested Parties led by the EWP. However following receipt of all comments and following numerous discussions with the Profession and extensive rewriting of this section of the Guideline a meeting of Interested Parties was thought to be unnecessary.

<u>Orion Pharma</u>
None
<u>Siegfried Pharma Development GmbH</u>
None
<u>TEDDY (Task-force in Europe for Drug Development for the Young)</u>
<p>TEDDY Experts consider the document an excellent proposal, very carefully written and of great value for introducing new paediatric drug formulations in this field particularly relevant for the paediatric population.</p> <p>However, few comments are related below.</p> <p><u>EWP Comment:</u></p> <p><i>See later in the section Specific Comments on Text.</i></p>
<u>TEVA Pharmaceuticals Europe</u>
<p>In general, the guideline is welcomed.</p> <p>We would recommend a decision tree for the clinical requirements outlined on page 4 of the Appendix I, including criteria for each option to illustrate the proposed stepwise approach.</p> <p><u>EWP comment:</u></p> <p><i>The EWP accepted the comments regarding the use of a decision tree and sees the benefits. However following lengthy discussions on the Guideline text and the provision of a huge amount of detail regarding both the in vitro and the clinical requirements (pharmacokinetic, pharmacodynamic and clinical) a decision was reached that a decision tree/flow chart would not be included in the Guideline.</i></p>
<p>This Appendix should be combined with the main guideline CPMP/EWP/4151/00 Rev 1 as one guideline.</p> <p><u>EWP Comment:</u></p> <p><i>The EWP agreed that Appendix 1 regarding development in children should be integrated into the main Guideline. It was always been the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline.</i></p>

SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	Comment and Rationale – Proposed change (if applicable)	EWP Comment
2 nd paragraph 2 nd bullet	<p><u>EFPIA (European Federation of Pharmaceutical Industries and Associations)</u></p> <p>The statement “<i>Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child</i>” is inconsistent with the <u>CHMP Reflection Paper on Paediatric Formulations</u> which indicates that children can be taught to use breath operated MDIs. While spacers may be useful in particular circumstances, e.g., for patients who have difficulties with coordination or patients trying to reduce the probability of topical side effects from ICS, there is no evidence that spacers increase efficacy in general. Moreover, some spacers increase systemic absorption for certain drugs, e.g., inhaled corticosteroids with high first pass metabolism.</p> <p>It is suggested to reword this statement to ensure consistency between this guideline and the <u>CHMP Reflection Paper on Paediatric Formulations</u>.</p> <p>The need for a spacer should only be required where a specific product type (e.g., a high-dose steroid) is indicated for specific patient populations (e.g., children), as recommended in Appendix III of the <u>Guideline on Pharmaceutical Quality of Inhalation and Nasal</u></p> <p><u>Proposed change</u></p> <p>“the requirement that <i><u>spacers are recommended for use with pMDIs and should be especially considered when a pMDI is used by a child</u></i> a child should always use a pressurised metered dose inhaler together with a specific spacing device, with and/or</p>	<p><u>EWP Comment:</u></p> <p><i>The requirement for children to use a spacing device, or at least have a spacing device available for use, with a pressurised metered dose inhaler has been discussed at length with the Profession and the following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.3):</i></p> <p><i>If a non-breath-operated (standard) pMDI is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacer(s) which will then be named in the SmPC, the package leaflet and possibly also on the product labelling. A specific named spacer should <u>always</u> be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask. The spacer has to be appropriate for the age groups of intended use.</i></p>

	without a face mask, and the effect that such a device may have on the amount of the active moiety reaching the lung and the amount reaching the systemic circulation.”	
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2 nd paragraph	<p>It is proposed to add a fifth bullet.</p> <p><u>Proposed change</u> <u>The need to stratify by different paediatric age groups</u></p>	<p><u>EWP Comment:</u> <i>The EWP accepted this comment and an appropriate statement has been written into the final guideline.</i></p>
4 th paragraph	<p>Depending on age of the child, you may mention that children 5 years and older may be capable of using ipMDI inhalers without a spacer. In addition, a rewording is proposed.</p> <p><u>Proposed change</u> The dose range for use in children must be defined and the lowest limit of the dose range for the reference product as authorised for use in children must be achievable with the new product <u>together with a specific spacing device if needed</u>, if a claim of therapeutic equivalence is to be made.</p>	<p><u>EWP Comment:</u> <i>The EWP accepted this comment.</i></p>
5 th paragraph	<p>It is proposed to strengthen the wording with regard to request for equivalence of systemic exposure (or lower, compared to innovator). We consider pharmacodynamic data should always be required unless a link between pharmacokinetic and pharmacodynamic data has been established in children or can be extrapolated from adults.</p> <p><u>Proposed change</u> In addition to the demonstration of equivalent efficacy assurance must be provided that the safety profile is unchanged (or improved on) compared with that of the reference medicinal product, particularly in respect of systemic safety (and this may need to <u>should</u> be based on pharmacokinetic data and/or if necessary relevant <u>on</u> pharmacodynamic data <u>unless a link between pharmacokinetic and pharmacodynamic data has been established in children or can be extrapolated from adults</u>; For example, for inhaled corticosteroids investigation of the hypothalamic pituitary adrenocortical axis function and/or growth) at the top of the proposed dose range, such that the</p>	<p><u>EWP Comment:</u> <i>The EWP accepted this comment which is particularly pertinent to the assessment of the systemic safety of inhaled corticosteroids. The following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009:</i></p> <p><u>In children safety data cannot be extrapolated from data generated in adults with asthma or from a surrogate adult population. The circumstances/scenarios when evaluation of safety in children is necessary are described in section 9, below. Systemic safety should be demonstrated through pharmacodynamic equivalence using two different but relevant tests or through pharmacokinetic equivalence if this is possible and if justifiable (see also section 9). The use of pharmacokinetic data will be dependent on the drug and the quality of the assay and should be considered only if there is sufficient published information on the systemic effects of the reference product on the HPA axis in children. If the use of pharmacokinetic data can be fully justified, pharmacokinetic data alone may be sufficient in the assessment of</u></p>

	benefit/risk ratio remains unchanged or is improved compared with the reference product	<i>equivalent systemic safety in children.</i>
Points 1-5	It would be helpful to provide specific guidance or example(s) on acceptable non-inferiority margins for children.	<p><u>EWP Comment:</u></p> <p><i>This was considered and similarly to the adult section of the Guideline it was felt that it was not appropriate to specify a general acceptable non-inferiority or equivalence margin in children. The choice will depend on the specific population studied taking into account the severity of asthma in the patient population and hence a decision on whether or not the chosen margin is appropriate will be taken on a case by case basis.</i></p>
Point 1	<p>The draft guidance outlines three criteria where clinical trials are generally not required, namely where 1) the <i>in vitro</i> criteria outlined in the main guidance have been fulfilled 2) where therapeutic equivalence in adults has been indisputably demonstrated and the test and reference product are pharmaceutically identical. However, the main guideline only requires therapeutic equivalence to be demonstrated where the <i>in vitro</i> criteria are not met. The proposed guidance would appear to establish a requirement to establish therapeutic equivalence clinically where one does not exist in the main guidance.</p> <p>In addition, the draft guidance uses the term “where therapeutic equivalence in adults has been indisputably demonstrated”. The use of the term “indisputably” inappropriately implies degrees of demonstration of therapeutic equivalence.</p> <p>Finally, the term “pharmaceutically identical” is introduced but is not defined. It is understood that similarity to existing devices is required to ensure operation by paediatric patients is possible but it is not necessary for devices to be identical in every aspect.</p> <p>A new wording is thus proposed. It is also suggested if Appendix 1 is incorporated into the main guideline, to define the</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>

	<p>expression ‘pharmaceutically identical’ in a glossary.</p> <p><u>Proposed change</u> “If the <i>in vitro</i> criteria for equivalence have all been fulfilled and <u>or</u> therapeutic equivalence has been demonstrated indisputably in adults, and the instructions for use of the inhalation device of the test product <u>are similar</u> the inhalation device is pharmaceutically identical to that of the reference product which is approved in the intended paediatric population, clinical studies in children are generally not required.”</p>	
Points 2-5	<p>The second bullet point on page 3 of the appendix (under the CHILDREN section) talks to the impact a spacing device with and/ or without a facemask may have on drug delivery in children.</p> <p>Consideration should be given in points 2-5 to the use of spacers with MDIs as the overall delivery system and the impact this may have on establishing therapeutic equivalence.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p> <p><i>The requirement to develop a specific and appropriate spacing device(s) for use with the pressurised metered dose inhaler when used by a child is discussed in the main Guideline/general text – see Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4.1.3.</i></p>
Point 2	<p>The general comments relating to the requirement for fulfilling <i>in vitro</i> criteria demonstrating therapeutic equivalence, use of the term “indisputably” and the concept of devices being pharmaceutically identical outlined above for Point 1, applies equally to point 2.</p> <p><u>Proposed change</u> “If the <i>in vitro</i> criteria for equivalence have all been fulfilled (see section 4.2.2 of the Draft Guideline) and <u>or</u> therapeutic equivalence has been demonstrated indisputably in adults, and the instructions for use of the inhalation device of the test product <u>are not similar</u> the inhalation device is pharmaceutically identical to that of the reference product but is approved in the</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>

	intended paediatric population containing another active substance, clinical studies in children are generally not required.”	
Point 3	<p>Guidance is made for the applicant to fulfil all the <i>in vitro</i> requirements outlined in the main guidance and under specific circumstances conduct paediatric-handling studies. In addition it is required to support the requirements by “Comparative <i>in vitro</i> data which must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range and air volume which are clinically applicable to children.”</p> <p>However, the later requirement would appear superfluous, as the main draft guidance requires as part of the <i>in vitro</i> requirements that “The complete individual stage particle size distribution profile should be provided In case of flow rate dependency, the comparative <i>in vitro</i> data should be obtained with a range of flow rates. This range should be justified in relation to the intended patient population. The minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate should be investigated.</p> <p>Moreover, the text in the main draft guidance is more informative and is also consistent with the requirements outlined on this subject in the Guideline on Pharmaceutical Quality of Orally Inhaled and Nasal Drug Products”.</p> <p>Taking into account what was proposed for previous points, a rewording is thus, proposed.</p> <p>We would appreciate to get clarification on the followings:</p> <ul style="list-style-type: none"> - Some details are needed for this handling study - And the requested “comparative <i>in vitro</i> data”; are they different than “the <i>in vitro</i> criteria for equivalence” mentioned at the beginning of this section? <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements. Reference is made within Section 9 to earlier sections in the Final Adopted CHMP Guideline, Sections 4.4 and 5.2.</i></p>

	<p>“If the <i>in vitro</i> criteria for equivalence have all been fulfilled (see section 4.2.2 of the Draft Guideline) and <u>or</u> therapeutic equivalence has been demonstrated indisputably in adults, but the instructions for use of the inhalation device of the test product are is not pharmaceutically identical <u>similar</u> to that of the reference product and is not approved in the intended paediatric population, as an absolute minimum clinical requirement a handling study in this young age group will be required. This must be further supported by comparative <i>in vitro</i> data which must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range and air volume which are clinically applicable to children.”</p>	
Point 4	<p>The guideline states that in this circumstances outline clinical studies will be required in children “unless an appropriate surrogate patient population can be justified”. We are not aware of a model which could be considered “<i>an appropriate surrogate patient population</i>”. Unless the guidance can clarify that a known surrogate patient population exists for paediatrics this wording should be amended or an example provided.</p> <p><u>Proposed change</u> “If any of the <i>in vitro</i> criteria for equivalence are not fulfilled (see section 4.2.2 of the Draft Guideline) or when equivalence cannot be demonstrated on the basis of the <i>in vitro</i> comparison, some clinical development of the product in children will be required unless an appropriate surrogate patient population can be <u>otherwise</u> justified.</p> <p>The word “some” should be deleted, because the extent of clinical studies will be specific to the case and must be justified. The meaning of the sentence will then be in line with lines 236-238 of the parent guideline.</p> <p>Further explanation is required on what data is needed to</p>	<p><u>EWP Comment:</u> <i>The EWP agreed with the comment made regarding the lack of an appropriate surrogate patient population and this reference has been deleted.</i></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p> <p>.</p> <p><u>EWP Comment:</u> <i>The EWP agreed with the comment made.</i></p> <p><u>EWP Comment:</u></p>

	<p>establish “demonstration of equivalent drug distribution”, while safety data should always be required.</p> <p>The word “might” is a grey zone; please clarify “might” based on what?</p> <p><u>See given paragraph</u> Demonstration of equivalent drug distribution combined with safety data (bioequivalence based on pharmacokinetic data and/or measurement of pharmacodynamic parameters, in as far as possible) generated following inhalation of the maximum recommended total daily dose regimen over an appropriate time period dependent on the active substance might be considered as sufficient demonstration of therapeutic equivalence.”</p>	<p><i>This whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Point 5	<p>Regarding “<i>clinically relevant age-dependent endpoints</i>”, we would suggest also including PEF, which can be measured in ages 4 and above.</p> <p>Further clarification on how to demonstrate equivalence based on symptoms would be useful.</p> <p><u>Proposed change</u> “In these circumstances clinically relevant age-dependent endpoints must be evaluated (spirometric endpoints in the older child, 6 years and older, <u>PEF in ages 4 and above</u> and clinical symptom scores in the younger child, 5 years and younger).”</p>	<p><u>EWP Comment:</u> <i>Efficacy endpoints for use in children are described in detail in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 6. Peak expiratory flow is listed but as a secondary endpoint of function only.</i></p>
7th paragraph	<p>The statement is made that “If a pressurised metered dose inhaler is to be used in children it must be developed for use together with a specific appropriate spacing device(s)....”</p> <p>This statement is inconsistent with the <u>CHMP Reflection Paper on Paediatric Formulations</u> which indicates that children can be</p>	<p><u>EWP Comment:</u> <i>The requirement for children to use a spacing device, or at least have a spacing device available for use, with a pressurised metered dose inhaler has been discussed at length with the Profession and the following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.3):</i></p>

	<p>taught to use breath operated MDIs. While spacers may be useful in particular circumstances, e.g., for patients who have difficulties with coordination or patients trying to reduce the probability of topical side effects from ICS, there is no evidence that spacers increase efficacy in general. Moreover, some spacers increase systemic absorption for certain drugs, e.g., inhaled corticosteroids with high first pass metabolism.</p> <p>It is recommended to ensure consistency between this guideline and the <u>CHMP Reflection Paper on Paediatric Formulations</u>. The need for a spacer should only be required where a specific product type (e.g., a high-dose steroid) is indicated for specific patient populations (e.g., children), as recommended in Appendix III of the <u>Guideline on Pharmaceutical Quality of Inhalation and Nasal Drug Products</u>.</p> <p>A rewording is thus proposed.</p> <p><u>Proposed change</u> <i><u>“Spacers are recommended for use with pMDIs and should be especially considered when a pMDI is used by a child</u></i> If a pressurised metered dose inhaler is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacing device(s) which will then be named in the SPC, the Patient Information Leaflet and possibly also on the product labelling.”</p>	<p><i>If a non-breath-operated (standard) pMDI is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacer(s) which will then be named in the SmPC, the package leaflet and possibly also on the product labelling. A specific named spacer should <u>always</u> be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask. The spacer has to be appropriate for the age groups of intended use.</i></p>
Last paragraph	<p>This paragraph is unclear and would need clarification. Data extrapolation from adult to adolescent is understandable and accepted, but why adding: “if studies have been conducted in children less than 12 years”? Is it because these 2 different age groups have different physiologic characteristics?</p> <p>The last sentence would need clarification. A rewording is thus</p>	<p><u>EWP Comment:</u> <i>The EWP is of the opinion that if children less than 12 years of age and adults 18 years and over have been studied it may be possible to cover use in the adolescent, aged 12 to 17 years, through interpolation from data generated in studies in adults. However if this is not possible a sufficient number of adolescents should be recruited to the adult studies such that the entire age range of intended use (12 years through to the elderly) has been</i></p>

	<p>proposed.</p> <p><u>Proposed change</u></p> <p>“In these circumstances the demonstration of equivalent <u>pharmacodynamics, as a surrogate of efficacy, and systemic exposure (equivalent or lower than innovator), as a surrogate of drug distribution</u> combined with safety may be sufficient.”</p>	<p><i>studied. If studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population.</i></p> <p><i>See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2000 – Sections 6 and 9.</i></p>
	<u>EGA (European Generic Association)</u>	
Page 3-4	<p>Non-inferiority margins are a parameter (δ) defined in both equivalence and non inferiority studies.</p> <p>Clarification is sought as to whether equivalence and/or non-inferiority studies are acceptable.</p>	<p><u>EWP Comment:</u></p> <p><i>Normally equivalence is required. If superior efficacy is seen reassurance would be required that this did not have a negative impact on the safety of the product.</i></p>
Page 3, section “Children”, 1 st bullet point	<p>We would suggest adding the following clarification to the sentence “either for follow-on or originator medicinal products, or both”.</p> <p><u>Proposed change</u></p> <p>“The internal resistance of a dry powder inhaler device may be such that the device [either for follow-on or originator medicinal products, or both] is more difficult for a child to use than an adult”</p>	<p><u>EWP Comment:</u></p> <p><i>EWP did not consider that the proposed wording added any further clarification.</i></p>

Page 3, section “Children”, 2 nd bullet point	<p>We would suggest to remove the term ‘always’ from this scenario and replace it by ‘should consider using’.</p> <p><u>Proposed change</u> “The requirement that a child should always consider using a metered dose inhaler together with a specific spacing device...”</p>	<p><u>EWP Comment:</u> <i>The requirement for children to use a spacing device, or at least have a spacing device available for use, with a pressurised metered dose inhaler has been discussed at length with the Profession and the following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009:</i></p> <p><i>If a non-breath-operated (standard) pMDI is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacer(s) which will then be named in the SmPC, the package leaflet and possibly also on the product labelling. A specific named spacer should <u>always</u> be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask. The spacer has to be appropriate for the age groups of intended use.</i></p>
Page 3, section “Children”, 2 nd bullet point	<p>The use of a spacer tends to improve drug delivery to the child, especially for inefficient formulation/device. This can reduce differences in drug delivery between medicinal products and then increase the chance of demonstrating bioequivalence between them. Hence, this factor should not be included as a likely scenario.</p> <p><u>Proposed change</u> Please remove this scenario from the 4 proposed ones.</p>	<p><u>EWP Comment:</u> <i>See the EWP Comment above.</i></p>
Page 3, section “Children”, 3 rd bullet point	<p>It should be clarified whether any scenarios exist for which it can be certainly excluded that any differences that are clinically irrelevant in adults might be clinically irrelevant in children as well or whether this will be questioned in any case.</p>	<p><u>EWP Comment:</u> <i>The reasons why children need to be studied as a separate population are addressed in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p>
Page 3, section “Children”, 4 th bullet point	<p>The “need to develop a lower dose and/or a lower strength product for use in a child” implicates that this dose/strength does not exist for the reference/originator product. Therefore the requirements on page 4 cannot be fulfilled as equivalence cannot</p>	<p><u>EWP Comment:</u> <i>The EWP agreed. The 4th bullet point has not been included in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009.</i></p>

	<p>be demonstrated if no reference product in the respective strength is available.</p> <p>Clarification is requested as to what would be an appropriate approach in such situation.</p>	
Page 3, section “Children”, 5 th paragraph	<p>It should be clarified whether such scenarios must be considered in any case or whether there is any possibility to dispel all doubts argumentatively.</p>	<p><u>EWP Comment</u> <i>The three listed scenarios in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 should be considered in the development of all products for which an indication for use in children is sought.</i></p>
Page 3, section “Children”, 5 th paragraph	<p>the sentence ending with “ is appropriate is required” should be corrected. See the general comment section on the structure of this clinical guideline.</p> <p><u>Proposed change</u> ““ is appropriate is required”</p>	<p><u>EWP Comment:</u> <i>The EWP did not accept the proposed revision to the text.</i></p>
Page 3, section “Children”, 6 th paragraph	<p>In many products a dose range for the use in children is not available for the originator product. Please clarify the requirements in such cases.</p>	<p><u>EWP Comment:</u> <i>The dose range for use in children, which might simply be a single dose regimen, should always be defined. The revised statement in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 is as follows:</i></p> <p><i>.... The dose range for use in children must be defined and the lowest limit of the dose range for the reference product as authorised for use in children must be achievable with the new product (both with and without a specific appropriate spacer if the active substance is delivered via a pMDI); sometimes the development of a new lower strength will be required. However if the reference product is not authorised for use in children full clinical development of the new product in children, which must include determination of the dose range, the dosing interval, the minimally effective dose and the maximum total daily dose, will be required. In addition to the demonstration of equivalent efficacy assurance must be provided that the safety profile is unchanged or</i></p>

		<i>improved compared with that of the reference medicinal product, particularly in respect of systemic safety at the top of the proposed dose range.</i>
Page 3, section “Children”, 7 th paragraph	“(and this may need to be based on pharmacokinetic data and/or if necessary relevant pharmacodynamic data...”: According to CPMP/EWP/4151/00 Rev.1 pharmacodynamic studies should only be performed if demonstration of in vitro equivalence in the first step and in the second step of equivalent pulmonary deposition (in combination with safety data) is not possible. This 3 step approach should also be reflected in Appendix I consistently.	<p><u>EWP Comment:</u> <i>A stepwise approach, from in vitro data through pharmacokinetic and pharmacodynamic studies through to full clinical development, as required, is the recommended route in the development of orally inhaled products where the objective is the demonstration of therapeutic equivalence between two inhaled products. The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 describes this approach in detail in Section 6; however at this stage in our knowledge, in general therapeutic equivalence, particularly in respect of efficacy, will require demonstration through appropriate pharmacodynamic and/or clinical studies.</i></p> <p><i>However this stepwise approach becomes more difficult in the development of orally inhaled products in children as it is felt that pulmonary deposition studies in children are not appropriate. Pharmacokinetic studies as a surrogate for efficacy only imply efficacy, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence. Imaging studies in children are also not appropriate.</i></p> <p><i>The situation in respect of the assessment of systemic safety in children differs slightly regarding the use of pharmacokinetic studies and situations where such studies might be used are described in the Final Adopted CHMP Guideline – Sections 6 and 9. In situations where pharmacokinetic studies are not appropriate for the assessment of systemic safety, pharmacodynamic studies will be required.</i></p>
Page 3, section “Children”, 7 th	“at the top of the proposed dose range...”: In many products a dose range for the use in children is not available for the	<p><u>EWP Comment:</u> <i>See EWP Comment next but one above.</i></p>

paragraph	originator product (see also comment above).	
Page 3, section “Children”, 7 th paragraph	Systemic safety is assessed by PK bioequivalence study. The PK study conducted in healthy adults should be applicable to children as with conventional bioequivalence study for orally administered drugs. Hence, there is no need to repeat the PK bioequivalence study in children. If the concern is about the high flow rate dependency in the deposition characteristics of DPI products in children, <i>in vitro</i> testing at different flow rate can be used to test equivalence of the products for the paediatric population.	<p><u>EWP Comment:</u> <i>The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 discusses a number of differences between adults and children and particularly the younger child (and between children with asthma and children with normal airway function) which might influence efficacy and safety in children and in the light of these differences states that extrapolation from studies in adults, or from studies in adults coupled with in vitro data, or the study of a surrogate adult population or the study of normal healthy children may be unsafe and difficult to justify. Products may be equivalent in adults but may not be equivalent in children.</i></p> <p><i>In Section 6 of the Guideline and in the paragraphs pertaining to inhaled glucocorticosteroids (6.2.3.2) the following statement in respect of the use of pharmacokinetic data in the assessment of systemic safety in children is made:</i></p> <p><i><u>In children safety data cannot be extrapolated from data generated in adults with asthma or from a surrogate adult population. The circumstances/scenarios when evaluation of safety in children is necessary are described in section 9, below. Systemic safety should be demonstrated through pharmacodynamic equivalence using two different but relevant tests or through pharmacokinetic equivalence if this is possible and if justifiable (see also section 9). The use of pharmacokinetic data will be dependent on the drug and the quality of the assay and should be considered only if there is sufficient published information on the systemic effects of the reference product on the HPA axis in children. If the use of pharmacokinetic data can be fully justified, pharmacokinetic data alone may be sufficient in the assessment of equivalent systemic safety in children.</u></i></p>
Page 4, section “Clinical Requirements”	In this section, the inference is that there is a greater risk from the follow-on product. However, we would recommend that this clinical guideline appendix be drafted so as to refer to applicants	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January</i></p>

	justifying the potential safety for a follow-on product in terms of its comparative use and safety when used by children	<i>2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i>
Page 4 section Clinical Requirements	<p>“generally not ” needs to be clarified.</p> <p>See general comment on the overall wording used in the main guideline and its appendix.</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Page 4, sections 1., 2.	"pharmaceutically identical" should be defined or clarifications should be brought as to how this relates to the dosage form (which should be similar as a prerequisite to <i>in vitro</i> equivalence, as per the main guideline CPMP/EWP/4151/00 Rev.1 Section 4.2.2)	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements. The term “pharmaceutically identical” is not used at all within the text of the Final Adopted CHMP Guideline.</i></p>
Page 4, section “Clinical requirements”, 1.-4.	<p>We, as an organisation, know that the current originator medicinal product information on posology for children and/or spacer used is often poor. In addition, in Europe the number of commercially available spacers is high.</p> <p>This can be problematic when it comes to show <i>in vitro</i> equivalence. We would propose that studies be carried out in comparison with the originator medicinal product alone, unless specifics for spacers are included in the reference product labelling.</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP does not accept the point raised. A spacing device must be developed for use with a pressurised metered dose inhaler but particularly so if the pressurised metered dose inhaler is to be used by a child.</i></p> <p><i>The requirement for children to use a spacing device, or at least have a spacing device available for use, with a pressurised metered dose inhaler has been discussed at length with the Profession and the following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.3):</i></p> <p>....</p>

		<p><i>If there are no specific recommendations for the use of a specific spacer given in the Summary of Product Characteristics (SmPC) for the reference product, the test product used both with and without a spacer should be compared with the reference product used without a spacer. If a specific spacer is named in the SmPC for the reference product, the reference product should be used in accordance with the specific spacer as stated.</i></p> <p>.... ..</p> <p><i>If a non-breath-operated (standard) pMDI is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacer(s) which will then be named in the SmPC, the package leaflet and possibly also on the product labelling. A specific named spacer should <u>always</u> be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask. The spacer has to be appropriate for the age groups of intended use.</i></p> <p><i>(There are a number of other statements in this Section of the Guideline pertaining to the use of spacing devices).</i></p>
Page 4, sections 1.-3.	<p>The phrase “If the <i>in vitro</i> criteria for equivalence have all been fulfilled... and therapeutic equivalence has been demonstrated indisputably in adults...” seems to be contradictory to CPMP/EWP/4151/00 Rev.1:</p> <p>According to CPMP/EWP/4151/00 Rev.1 therapeutic equivalence studies are only required if both the demonstration of <i>in vitro</i> equivalence and of equivalent pulmonary deposition (in combination with safety data) are not possible.</p> <p>EGA member companies would welcome clarification about what is required in the <i>in vitro</i> testing that would allow the</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>

	<p>extrapolation of therapeutic equivalence in adult to children, with the understanding from the main guidance that if the <i>in vitro</i> criteria for equivalence are met, no clinical studies are needed to demonstrate therapeutic equivalence.</p> <p>The guideline and subsequently issued appendix would require further qualification (throughout) as to how they have been worded against the; <i>in vitro</i> - PK - PD - TE approach.</p>	
Page 4, Clinical requirements section 3.	What kind of handling study in children is required?	<p><u>EWP Comment:</u></p> <p><i>A handling study is required to ensure that the intended population is able to use the device correctly, that is that the user/child can generate the minimal peak inspiratory flow to trigger the inhalation device.</i></p>
Page 4, Clinical requirements section 4.	What does "equivalent drug distribution" refer to?	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Page 4, section 4.	<p>“bioequivalence based on pharmacokinetic data and/or measurement of pharmacodynamic parameters, in as far as possible”: Is the demonstration of equivalent pulmonary deposition according to 4.3.1 of CPMP/EWP/4151/00 Rev.1 sufficient (although ethically and practically such studies are very difficult to perform in children)?</p> <p>See general comment on the heterogeneity of the children population.</p>	<p><u>EWP Comment:</u></p> <p><i>The statement bioequivalence based on pharmacokinetic data and/or measurement of pharmacodynamic parameters, in as far as possible is referring to the demonstration of equivalence in respect of systemic safety (not efficacy); pulmonary deposition is a surrogate for efficacy. However the EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Page 4, section 4.	Please provide examples for possible “surrogate patient populations”. Does this mean “adults”? If so, we would suggest	<p><u>EWP Comment:</u></p> <p><i>Following extensive discussions it was agreed that in the light of a number of differences between adults and children and particularly the younger</i></p>

	to explicitly use the term ‘adults’ to remove any ambiguity.	<i>child (and between children with asthma and children with normal airway function) which might influence efficacy and safety in children, extrapolation from studies in adults, or from studies in adults coupled with in vitro data, or the study of a surrogate adult population or the study of normal healthy children may be unsafe and difficult to justify. Products may be equivalent in adults but may not be equivalent in children. Therefore all references to the use of surrogate populations have been removed from the Guideline.</i>
Page 4, section 4.	Does “appropriate time period” mean the time periods specified in CPMP/EWP/4151/00 Rev.1 section 4.3.2, for the different therapeutic classes? Please clarify.	<u>EWP Comment</u> <i>The reference to appropriate time period refers to the duration of study required, depending on the active drug, in order to reach steady state in the assessment of systemic safety.</i>
Page 4, section 5.	Are the specified age-dependent endpoints optional to be used as primary or secondary efficacy criteria, i.e. are they intended to be used for the confirmatory analysis?	<u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i> <i>Endpoints are discussed in detail in Section 6 (6.2) of the final Guideline and are described for children 6 years of age and older and the pre-school child.</i>
Page 4, 5 th paragraph	<p>In adults the commonly accepted equivalence margins are differences of absolute values, i.e. ± 200 ml for FEV1. As the justification of absolute margins in children is extremely difficult, we propose that percentage values be used and that this should be reflected in the guideline.</p> <p>In addition, we cross refer here to our comments on the main guideline where the EGA suggested that specific references to non validated studies (eg, knemometry) be removed from the guideline text in favour of a reference to “validated study</p>	<u>EWP Comment:</u> <i>This was considered and it was not felt appropriate to specify a general accepted equivalence margin in adults or children. If it is considered extremely difficult to specify an absolute margin for children it is not clear how it is easier to specify an acceptable percentage value.</i> <i>Knemometry is considered to be validated study methodology.</i>

	methodology”.	
Page 4, 8 th paragraph	“sufficient number”: Please clarify for which type of analysis the number should be sufficient for.	<p><u>EWP Comment:</u></p> <p><i>The use of the term sufficient number is used in the context of ensuring that the studies in adults see the recruitment of adolescents aged between 12 and 17 years, to bridge the gap between studies in adults (often seeing recruitment of adults aged 18 years and older only) and studies in children (less than 12 years of age), if the adolescent age group is not being studied in its own right. The statement as presented in the Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 requests that studies set up in adults and including recruitment of adolescents aged 12 to 17 years need not necessarily be stratified for age, but data generated from the two age groups (18 years and above and 12 to 17 years) should be documented and analysed separately , if possible.</i></p> <p><i>However if studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population.</i></p>
Page 4, 8 th paragraph	<p>The rationale for the requirement for specific studies in children to allow interpolation from adult data to adolescents is not understood as airways in children differ from both adolescents and adults while it is generally accepted that the airways in adolescents resemble those of adults.</p> <p>Besides, please clarify for which therapeutic classes studies in adolescents are required if studies in children have not been conducted.</p>	<p><u>EWP Comment:</u></p> <p><i>See the EWP Comment to the point raised immediately above.</i></p> <p><i>The requirement to endeavour to include adolescents in the adult studies – when studies have also been carried out in children less than 12 years of age – is to bridge the gap and simply ensure that some data are generated in the adolescent age group. However if studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population. Such decisions may need to be made on a case by case basis.</i></p>
Page 4, last sentence	<p>”equivalent drug distribution”: Is the demonstration of equivalent pulmonary deposition according to 4.3.1 of CPMP/EWP/4151/00 Rev.1 sufficient?</p> <p>If yes, are separate studies necessary or would it be sufficient if</p>	<p><u>EWP Comment:</u></p> <p><i>Demonstration of equivalent pulmonary deposition combined with an appropriate assessment equivalence in respect of systemic safety may be sufficient. See the Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1</i></p>

	<p>for example in pharmacokinetic studies in adults, adolescents are included as well? Otherwise please specify the criteria for equivalence in drug distribution.</p>	<p>January 2009 – Sections 9 and 6 (6.1).</p>
	<p><u>EPAG (European Pharmaceutical Aerosol Group)</u></p>	
General	<p>We believe that it would be most helpful and consistent if harmonisation with GINA guidance could be established.</p> <p><u>Proposed change</u> It is important that these guidelines be harmonised with the GINA guidelines, e.g. age range and types of devices that can be used.</p>	<p><u>EWP Comment:</u> <i>It was not felt appropriate to reference the GINA Guidelines.</i></p>
General	<p>We note that the guidance does not refer to breath actuated pressurised metered dose inhalers.</p> <p><u>Proposed change</u> The annex should refer to use of Breath-actuated pMDIs and that they may be used.</p>	<p><u>EWP Comment:</u> <i>The EWP always intended that Appendix 1 regarding development in children should be integrated into the main Guideline. Breath-operated metered dose inhalers are discussed in the Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.2).</i></p>
Page 4	<p>Clinical Requirements Section Bullet No. 1: '... inhalation device of the test product is <u>pharmaceutically identical</u> to that of the reference product...'</p> <p><u>Proposed change</u> We have difficulty in understanding the terminology, 'pharmaceutically identical' and believe you are referring to the ability of paediatrics to operate the device. We suggest a change in text to '... inhalation device of the test product <i>operates in a similar</i> way to that of the reference product. If this is not what is being referred to, then please clarify further what it is that is being referred to.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements. The term “pharmaceutically identical” is not used at all within the text of the Final Adopted CHMP Guideline.</i></p>

Page 4	<p>This above comment applies thorough out the Clinical requirements section where ‘pharmaceutically identical’ is mentioned.</p> <p><u>Proposed change</u> Modify text where required as described above.</p>	<p><u>EWP Comment:</u> <i>See the EWP Comment to the point raised immediately above.</i></p>
Page 4, pen ultimate para	<p>If a pressurised metered dose inhaler’,</p> <p><u>Proposed change</u> We recommend a change to If a non-breath actuated pressurised metered dose inhaler. Later in paragraph change to non-breath actuated pressurised metered dose inhaler.</p>	<p><u>EWP Comment</u> <i>The EWP agreed and the change to the text has been made. The whole paragraph has been re-sited and apperas in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 in Section 4 (4.1.3 last paragraph).</i></p>
<p><u>IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)</u></p>		
Page 3. “Executive Summary”	<p>Should the Executive Summary be a summary of the Appendix? At the moment, it is only referencing the main guideline, which does not seem appropriate.</p> <p><u>Proposed change</u> Consider providing an executive summary specific to the Appendix.</p>	<p><u>EWP Comment:</u> <i>It had always been the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline.</i></p>

Page 3. “Children”. First paragraph	<p>The paragraph describes the differences between adults and children with respect to lung function.</p> <p>Proposed change It would be helpful if the differences were discussed in the context of more specific age ranges.</p>	<p>EWP Comment: <i>It was considered that such detail was not required in this Guideline.</i></p>
<p>Page 3. Section “Children”. Bullet 2 and</p> <p>Page 4. Second paragraph after Points 1-5.</p>	<p>The statements “<i>Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child.</i>” (page 3) and “<i>If a pressurized metered dose inhaler is to be used in children it must be developed for use together with a specific appropriate spacing device(s).....</i>” (page 4) are inconsistent with the EMEA/CHMP/PEG/194810/2005 <u>Reflection Paper: Formulations Of Choice For The Paediatric Population</u> (http://www.nppg.scot.nhs.uk/misc/choicepaper0605.pdf) which indicates that older children can be taught to use breath operated MDIs.</p> <p>While spacers may be useful in particular circumstances, e.g., for patients who have difficulties with coordination or patients trying to reduce the probability of topical side effects from ICS, there is no evidence that spacers increase efficacy in general. Moreover, some spacers increase systemic absorption for certain drugs, e.g., inhaled corticosteroids with high first pass metabolism.</p> <p>Proposed change Ensure consistency between this guideline and the EMEA/CHMP/PEG/194810/2005 <u>Reflection Paper: Formulations Of Choice For The Paediatric Population</u> (http://www.nppg.scot.nhs.uk/misc/choicepaper0605.pdf).</p> <p>The need for a spacer should only be required where a specific product type (e.g., a high-dose steroid) is indicated for specific patient populations (e.g., children), as recommended in Appendix III of the <u>Guideline on Pharmaceutical Quality of Inhalation and Nasal Drug Products</u>. Change to “<i>Spacing devices are recommended for use with pMDIs and should be especially</i></p>	<p>EWP Comment: <i>The requirement for children to use a spacing device, or at least have a spacing device available for use, with a pressurised metered dose inhaler has been discussed at length with the Profession and the following text appears in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.3):</i></p> <p>....</p> <p><i>If there are no specific recommendations for the use of a specific spacer given in the Summary of Product Characteristics (SmPC) for the reference product, the test product used both with and without a spacer should be compared with the reference product used without a spacer. If a specific spacer is named in the SmPC for the reference product, the reference product should be used in accordance with the specific spacer as stated.</i></p> <p>....</p> <p><i>If a non-breath-operated (standard) pMDI is to be used in children it <u>must</u> be developed for use together with a specific appropriate spacer(s) which will then be named in the SmPC, the package leaflet and possibly also on the product labelling. A specific named spacer should <u>always</u> be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask. The spacer has to be appropriate for the age groups of intended use.</i></p>

	<p><i>considered when a pMDI is used by a child.”</i></p> <p>Consider mentioning that children 5 years and older may be capable of using pMDIs without a spacer.</p> <p>In addition, mention that the generic product must prescribe the use of the same named spacing device(s) as the reference product prescribes for use in children.</p> <p>Inclusion of spacer information in the SPC should be sufficient.</p>	<p><i>(There are a number of other statements in this Section of the Guideline pertaining to the use of spacing devices).</i></p>
<p>Page 3.</p> <p>First paragraph after bullet points.</p>	<p>The paragraph suggests that the focus is on children under 12 years, but this might be clearer if stated up front. Also, it is later suggested that adult data cannot be extrapolated to adolescents, but if the listed issues are limited to children under 12 years, then the requirement for adolescent data does not seem supported.</p> <p><u>Proposed change</u> Please clarify the age scope of the recommendations in the Appendix.</p>	<p><u>EWP Comment:</u> <i>The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 provides guidance on the clinical documentation required for adults, children less than 12 years of age and adolescents 12 to 17 years of age.</i></p>
<p>Page 3.</p> <p>First paragraph after bullet points.</p>	<p>Strengthen the wording regarding adolescents: <i>“To this end, children with asthma and younger than 12 years <u>may need to be studied in their own right</u>”</i></p> <p><u>Proposed change</u> Change “<i>may need to</i>” to “<i>should</i>”.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p>
<p>Page 3, second paragraph after bullet points.</p>	<p>By only stating that the lowest limit of the dose range of the reference must be “<i>achievable</i>” by the generic, the Appendix suggests that quite a wide range of dose delivery from the generic is acceptable.</p> <p><u>Proposed change</u> The criteria that have been set for demonstration that a generic is therapeutically equivalent to a reference product need clarification.</p>	<p><u>EWP Comment:</u> <i>The statement refers to the situation whereby the test product is formulated such that the lowest dose which can be delivered from the reference product is not achievable from the test product and therefore the lowest dose/dose regimen for the reference product cannot be achieved by the test product, an issue which would be particularly pertinent if the test product is to be used in children.</i></p> <p><i>However this whole section of the Guideline has been re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January</i></p>

		2009 – Section 9.
Page 3, last paragraph.	<p>The last paragraph starts with the assumption that equivalent efficacy has been demonstrated, presumably in children. This is not consistent with the text that follows where, in certain cases, therapeutic equivalence in children is not required to be demonstrated.</p> <p>Proposed change Please clarify the text and intention of the paragraph.</p>	<p>EWP Comment: <i>However this whole section of the Guideline has been re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p>
Page 3, last paragraph.	<p>The appendix states that systemic safety “<i>may need to be based on pharmacokinetic data and/or if necessary relevant pharmacodynamic data</i>”. We consider pharmacodynamic data should always be required unless a link between pharmacokinetic and pharmacodynamic data has been established in children or can be extrapolated from adults.</p> <p>Proposed change Change the text in the final paragraph on page 3 regarding systemic safety to “<i>should be based on pharmacokinetic data and/or if necessary relevant pharmacodynamic data unless a link between pharmacokinetic and pharmacodynamic data has been established in children or can be extrapolated from adults</i>”</p>	<p>EWP Comment: <i>This whole section of the Guideline has been re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Sections 9 and 6 (6.2 and more particularly 6.2.3.2).</i></p> <p><i>Equivalent safety should only be demonstrated through paramacokinetic equivalence if possible and if justifiable. The use of pharmacokinetic data will be dependent on the drug and the quality of the assay and should be considered only if there is sufficient published information on the systemic effects of the reference product in children. If the use of pharmacokinetic data can be fully justified, pharmacokinetic data alone may be sufficient in the assessment of equivalent systemic safety in children.</i></p>
Page 4. Title “Clinical Requirements”	<p>The subheading “<i>Clinical Requirements</i>” does not represent the numbered paragraphs that follow, as they do not give details of the clinical assessment required, only that some clinical data may be needed.</p> <p>Consider including further information about clinical requirements or re-naming the section.</p>	<p>EWP Comment: <i>The EWP accepts the comment. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 this sub-heading has been changed to reflect more accurately the scenarios described which may arise resulting in differing clinical requirements. The requirements for clinical studies in children are described in Section 6 of the Final Adopted CHMP Guideline.</i></p>
Page 4. Title “Children”	<p>The overall title of Appendix 1 indicates that its scope is defining therapeutic equivalence in pediatric subjects, so the subheading “Children” seems redundant or not sufficiently specific.</p> <p>Proposed change</p>	<p>EWP Comment: <i>It had always been the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic</i></p>

	Consider re-naming the section.	<i>equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline which now has a title which fully reflects the objectives of the Guideline.</i>
Page 4. Point 1.	<p>The term “<i>pharmaceutically identical</i>” is introduced but is not defined. It is understood that similarity to existing devices is required to ensure operation by pediatric patients is possible but it is not necessary for devices to be identical in every aspect.</p> <p><u>Proposed change</u> Change to “<i>The method of operation for the device is the same</i>” or “<i>The instructions for use of the inhalation device are similar</i>”.</p> <p>If Appendix 1 is incorporated into the main guideline, define the expression “pharmaceutically identical” in a glossary.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements. The term “pharmaceutically identical” is not used at all within the text of the Final Adopted CHMP Guideline.</i></p>
Page 4. Point 2.	The wording of the Appendix does not take adequately into account the fact that the performance of an inhalation product is in most cases (and for dry powder inhalation products: always) a combination of the properties of inhaler and formulation. It could therefore be a significant difference, if for example in point 2 the test inhalation device is an HFA MDI already approved in the intended paediatric population, or if this is a dry powder inhaler	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p> <p><i>The Final Adopted CHMP Guideline – Section 9 states clearly the</i></p>

	<p>with performance characteristics predominantly influenced by the powder formulation.</p> <p><u>Proposed change</u></p> <p>Reconsider the intent and wording of the requirements in light of different inhaler types. Also, the outcome should be that clinical studies in children are generally not required, but may be required depending on the attributes of the drug product which cause it not to be pharmaceutically identical.</p>	<p><i>situations when clinical development in children will or will not be required and specific reference is made to the pressurised metered dose inhaler used with the same spacing device in the first scenario listed on page 20/26. In the vast majority of situations clinical development in children will be required. It is felt that pulmonary deposition studies in children are not appropriate, pharmacokinetic studies as a surrogate for efficacy only imply efficacy, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence. Imaging studies in children are also not appropriate. The situation in respect of the assessment of systemic safety in children differs slightly regarding the use of pharmacokinetic studies and situations where such studies might be used are described in the Final Guideline. In situations where pharmacokinetic studies are not appropriate for the assessment of systemic safety, pharmacodynamic studies will be required.</i></p>
<p>Page 4. Point 3.</p>	<p>The Appendix recommends that the applicant fulfill all the <i>in vitro</i> requirements outlined in the main guideline and under specific circumstances conduct pediatric handling studies. In addition it is required to support the requirements by “<i>Comparative in vitro data which must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range and air volume which are clinically applicable to children.</i>”</p> <p>However, the later requirement would appear superfluous as the main guideline requires as part of the <i>in vitro</i> requirements that “<i>The complete individual stage particle size distribution profile should be provided. In case of flow rate dependency, the comparative in vitro data should be obtained with a range of flow rates. This range should be justified in relation to the intended patient population. The minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate should be investigated.</i>” (lines 219-222 of the main guideline).</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP accepts the comment. However the statement has been retained in the text of the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9, second and third scenarios listed on pages 20/26 and 21/26, in order to re-inforce the requirement that the test and the reference product must demonstrate comparable particle size distribution through the flow rate, pressure drop range and air volume clinically applicable to children.</i></p>

	<p>Moreover, the text in the main guideline is more informative and is also consistent with the requirements outlined on this subject in the <u>Guideline on Pharmaceutical Quality of Orally Inhaled and Nasal Drug Products</u>.</p> <p><u>Proposed change</u> Delete the statement “ <i>Comparative in vitro data which must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range and air volume which are clinically applicable to children</i>”</p>	
Page 4. Point 3.	<p>What would the EMEA expect to see for a “<i>handling study</i>”? This is especially complicated if spacers are to be included in the evaluation.</p> <p>In general, handling studies in children may not be sufficient because if the use of the test inhaler is not approved in the intended pediatric population, and the test inhaler can differ to an unspecified extent from the reference inhaler (i.e. it is “not pharmaceutically identical”), then the performance of the test product can differ significantly and clinically relevant from the reference product.</p> <p><u>Proposed change</u> It would be helpful to have some guidance on what a “<i>handling study</i>” involves.</p>	<p><u>EWP Comment:</u> <i>A handling study is required to ensure that the intended population is able to use the device correctly, that is that the user/child can generate the minimal peak inspiratory flow to trigger the inhalation device.</i></p>
Page 4. Points 1-3.	<p>The draft Appendix uses the term “<i>where therapeutic equivalence in adults has been indisputably demonstrated..</i>”. The use of the term “<i>indisputably</i>” inappropriately implies degrees of demonstration of therapeutic equivalence.</p> <p><u>Proposed change</u> Remove the term “<i>indisputably</i>”.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed to delete the term “indisputably”.</i></p>

Page 4. Points 1-3	<p>Appendix 1 uses the condition that “<i>the inhalation device of the test product is (or: is not) pharmaceutically identical to that of the reference product</i>”. First, the term “<i>identical</i>” would imply that the same (identical) inhaler from the same manufacturing source is used as test and reference inhaler, which seems inconsistent with the scope and intent of the Appendix and main guideline. Second, the combined term “<i>pharmaceutically identical</i>” is neither defined in the parent guideline, nor in the Appendix, and is therefore not suitable as a prerequisite to take or not to take further action, i.e. to perform clinical studies.</p> <p><u>Proposed change</u> A better term than “<i>identical</i>” is needed. A definition of “<i>pharmaceutically identical</i>” is needed. Further clarification is necessary on the data required to establish two products as being “<i>pharmaceutically identical</i>”.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements. The term “pharmaceutically identical” is not used at all within the text of the Final Adopted CHMP Guideline.</i></p>
Page 4. Point 4.	<p>The Appendix states that in this circumstances outline clinical studies will be required in children “<i>unless an appropriate surrogate patient population can be justified</i>”. Unless the Appendix can clarify “surrogate patient population” for pediatrics this wording should be amended.</p> <p><u>Proposed change</u> Clarify the term “surrogate patient populations”. Alternatively, amend wording to state that clinical studies will be required in children in the circumstances outlined “unless otherwise justified”.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that the use of a surrogate population for the study of orally inhaled products in children was not appropriate. This is stated clearly in the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p>
Page 4. Point 4.	<p>Third line: The word “some” should be deleted, because the extent of clinical studies will be specific to the case and must be justified. The meaning of the sentence will then be in line with lines 236-238 of the parent guideline.</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9. The word “some” in relation to the need for clinical development has been deleted.</i></p>

	Delete “some” in line 3.	
Page 4. Point 4.	<p>The term “equivalent drug distribution” is unclear.</p> <p><u>Proposed change</u> Please clarify.</p>	<p><u>EWP Comment:</u> <i>This whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Page 4. Points 1-4.	<p><i>In vitro</i> data alone may be sufficient to establish equivalence in the case of a variation/extension to a marketing authorization (point 1). However, to establish therapeutic equivalence to a reference medicinal product (points 2-4) both <i>in vitro</i> and clinical data should be required.</p> <p><u>Proposed change</u> Add clinical data requirements to points 2-4.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p> <p><i>In the Final Adopted Guideline – Section 9 describes clearly the scenarios which may arise resulting in differing clinical requirements in the development of orally inhaled products in children and states that if none of the three given scenarios arises clinical development of the product in children will be required with demonstration of therapeutic equivalence in respect of both efficacy and safety. Interpolation from data generated in studies in adults may be possible for development in adolescents (aged between 12 and 17 years). Section 6 of the Final Adopted Guideline describes how orally inhaled products should be studied and developed in children and looks at the sub-groups of children aged 6 to 12 years and the pre-school child aged 3 to 6 years and 2 to 6 years.</i></p>
Page 4. Point 5.	<p>What is the rationale for proposing symptom scores for children 5 years and younger, vs. spirometry for children 6 years and older?</p> <p><u>Proposed change</u> Please clarify.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p> <p><i>Clinically validated and relevant age-dependent efficacy variables must be evaluated. The evidence base to date in respect of the best methods to use in the assessment of either bronchodilatation or bronchoprotection in children is limited and therefore cases may</i></p>

		<i>need to be handled on an individual basis taking into account the current literature and the views of experts in the field. Justification should be provided to support the chosen efficacy variables. See the Final Adopted CHMP Guideline Sections 9 and 6.</i>
Page 4. Points 2-5.	<p>The second bullet point on page 3 of the appendix talks to the impact a spacing device with and/ or without a face mask may have on drug delivery in children.</p> <p><u>Proposed change</u> Consideration should be given in points 2-5 to the use of spacers with MDIs as the overall delivery system and the impact this may have on establishing therapeutic equivalence.</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p> <p>The spacing device is now also alluded to in the first scenario listed in the Final Adopted Guideline – Section 9 page 20/26. However spacing devices and holding chambers are discussed fully in the Final Adopted Guideline – Section 4 (4.1.3).</p>
Page 4. Point 4.	<p><i>“Demonstration of equivalent drug distribution combined with safety data might be considered as sufficient demonstration of therapeutic equivalence!.</i></p> <p><u>Proposed change</u> Further explanation is required on what data is needed to establish “equivalent drug distribution”. Safety data should always be required.</p>	<p><u>EWP Comment:</u> <i>This whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>
Page 4. Point 5.	<p>Regarding “clinically relevant age-dependent endpoints”, we would suggest also including PEF, which can be measured in ages 4 and above.</p> <p><u>Proposed change</u> Include PEF as a recommended measurement and provide further clarification on how to demonstrate equivalence based on symptoms.</p>	<p><u>EWP Comment:</u> <i>This comment has been considered and it is accepted that clinically validated and relevant efficacy variables must be evaluated. The evidence base to date in respect of the best methods to use in the assessment of either bronchodilatation or bronchoprotection in children is limited and therefore cases may need to be handled on an individual basis taking into account the current literature and the views of experts in the field. Justification should be provided to support the chosen efficacy variables. See the Final Adopted CHMP Guideline Sections 9 and 6. In Section 6 specific efficacy variables as discussed with reference to the use of peak expiratory flow as a primary or secondary measure in sub-section 6.2.3.2.</i></p>
Page 4. 1 st para	<i>“For detailed discussion on the clinical development...”</i>	<u>EWP Comment:</u>

after points 1-5.	<p>Proposed change It would be helpful to provide specific guidance or example(s) on acceptable non-inferiority margins for children.</p>	<p><i>This was considered and it was not felt appropriate to specify a general accepted equivalence margin in adults or children.</i></p>
Page 4. 2 nd para after points 1-5.	<p>The last sentence in this paragraph seems redundant, since it is already stated that pMDIs for use in children must be developed with a specific and appropriate spacer.</p> <p>Proposed change Consider deleting the last sentence.</p>	<p>EWP Comment: <i>The main discussion on the use of spacing devices and holding chambers has been moved to the more general sections of the Guideline. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.3). In this Section (final paragraph) the statement “The spacer has to be appropriate for the age groups of intended use” is more acceptable.</i></p>
Page 4, last paragraph.	<p>The need for specific studies in adolescents should be justified in terms of differences between adults and adolescents (as outlined on page 3, if these criteria also apply to adolescents - which is why we suggest some ages be attached to the points that are made).</p> <p>Proposed change It would be helpful to include some guidance on what is considered “a sufficient number of adolescents”.</p>	<p>EWP Comment: <i>The use of the term sufficient number is used in the context of ensuring that the studies in adults see the recruitment of adolescents aged between 12 and 17 years, to bridge the gap between studies in adults (often seeing recruitment of adults aged 18 years and older only) and studies in children (less than 12 years of age), if the adolescent age group is not being studied in its own right. The statement as presented in the Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 requests that studies set up in adults and including recruitment of adolescents aged 12 to 17 years need not necessarily be stratified for age, but data generated from the two age groups (18 years and above and 12 to 17 years) should be documented and analysed separately, if possible.</i></p> <p><i>However if studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population.</i></p>
Page 4, last paragraph.	<p>Strengthen the last sentence “<i>In these circumstances the demonstration of equivalent drug distribution combined with safety may be sufficient</i>”.</p> <p>Proposed change</p>	<p>EWP Comment: <i>The EWP agreed that the last sentence should be deleted from the general section on adolescents (which can be found in Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9, penultimate paragraph) and referred the reader to the</i></p>

	Change to “ <i>In these circumstances the demonstration of equivalent pharmacodynamics, as a surrogate of efficacy, and systemic exposure (equivalent or lower than innovator), as a surrogate of safety, may be sufficient.</i> ”	<i>Final Adopted CHMP Guideline – Section 6 (6.1 – Pharmacokinetics and 6.2 – Pharmacodynamics).</i>
	Orion Pharma	
P. 3/4, last paragraph	<p>It is proposed that the safety profile of the applied product can be unchanged or better than that of the reference product. This is logical and we strongly favour this approach. Nevertheless, this is discrepant with the current draft of the guideline proper (CPMP/EWP/4151/00 Rev. 1), where the possibility for a “better” safety profile of the applied product is de facto excluded.</p> <p><u>Proposed change</u> Keep as is in Appendix 1 and rewrite appropriate sections in the guideline proper (CPMP/EWP/4151/00 Rev. 1) to match the “non-inferiority” paradigm.</p>	<p><u>EWP Comment:</u> <i>The EWP accepted the comment. The Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 does state that there should be no evidence that the test product is worse than the reference product in respect of changes in vital signs, biochemical parameters and frequency of adverse events; however equivalence in respect of systemic exposure should be demonstrated through the use of pharmacokinetic studies if possible, if not through the use of pharmacodynamic studies. It is accepted that if the test product is shown to be less systemically available than the reference product (which can only be beneficial in respect of systemic safety) it must be shown that is at least equivalent in respect of efficacy to (and not inferior to) the reference product.</i></p>
P. 4/4, first paragraph	<p>These requirements are not consistent with the guideline proper. If “therapeutic equivalence” is substantiated based on in vitro data alone (i.e. when all the listed criteria are satisfied), there will be no in vivo studies to start with. So how then can the second condition (“therapeutic equivalence has been demonstrated indisputably in adults”) be satisfied, when there are no clinical data? Or is this to be interpreted so that clinical data in adults are needed in addition to <i>in vitro</i> data, if children are part of the target population? If so, why then not study children directly?</p> <p><u>Proposed change</u> Please rewrite the sentence as follows: “If the <i>in vitro</i> criteria for equivalence have all been fulfilled (see section 4.2.2 of the Draft Guideline) and the inhalation device of the test product is pharmaceutically identical to that of the reference product which is approved in the intended paediatric population, clinical studies</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 where only three scenarios are described each of which will result in differing clinical requirements when the in vitro criteria for equivalence have all been fulfilled. If none on the scenarios applies clinical development of the product in children will be required.</i></p>

	in children are generally not required.	
	<u>Siegfried Pharma Development GmbH</u>	
Page 4	<p>It is unclear what is meant by a "pharmaceutically identical device". Section 4.2.2 CPMP/EWP/4151/00 Rev.1 contains a definition, which is based on requirements on vitro data and drug product criteria. This definition includes some elements that could be relevant in the definition of "pharmaceutically identical device" (same instructions, resistance, etc). It would be valuable to know if there are other criteria for "pharmaceutically identical device" apart from those mentioned in section 4.2.2.</p> <p><u>Proposed change</u> Would it be possible to clarify the definition of "pharmaceutically identical device" and, if appropriate, to revise the definition of Section 4.2.2 in CPMP/EWP/4151/00 Rev.1 to avoid overlap?</p>	<p><u>EWP Comment:</u> <i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9. The term “pharmaceutically identical” has been deleted from the text.</i></p>
	<u>TEDDY (Task-force in Europe for Drug Development for the Young)</u>	
3	<p>A further inclusion to be considered.</p> <p><u>Proposed change</u> It should be included the followings: New inhaler devices should be tested with paediatric breathing patterns.</p>	<p><u>EWP Comment:</u> <i>The EWP accepted that breathing patterns may be important considerations during the in vitro testing; however details of in vitro testing is outside the scope of this Guideline.</i></p>
3	<p>A further inclusion to be considered.</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u> <i>The EWP accepted that breathing patterns may be important considerations during the in vitro testing; however details of in vitro</i></p>

	A recommendation on the use of ‘old drugs’ with new inhalation devices for different age groups is missing. This includes the newer very effective inhalers which nebulize ‘intelligently’ during specific parts of the breathing cycle. Some of these inhalers make use of computerized systems that take vital capacity into account.	<i>testing is outside the scope of this Guideline.</i>
	<u>TEVA Pharmaceuticals Europe</u>	
Page 3, 1st bullet	<p>This point needs to specify the resistance differences that would be considered problematic. As written, it is very vague and specific guidance is needed</p> <p><u>Proposed change</u></p> <p>To use In-check device to identify the optimum inspiratory flow rate for a device that can be achieved by children</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP disagreed with this comment. Providing such definitions is deemed to be outside the remit of this Guideline.</i></p>
Page 3, 2nd bullet	<p>A spacer may not be needed or appropriate for a BAI type. This type of device needs to be delineated separately and not grouped in with all other MDI type devices or DPIs. Spacers are only considered necessary for a MDI containing steroids and for helping patients to coordinate inhalation with actuation</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u></p> <p><i>The EWP accepted that a spacing device is for use with a non-breath-operated (standard) pressurised metered dose inhaler only and the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.1 and 4.1.3) reflects this.</i></p> <p><i>The EWP did not fully accept that spacing devices are only considered necessary for pressurised metered dose inhalers containing corticosteroids and for aiding co-ordination of inhalation of breath with actuation of the pMDI. The use of a spacing device is recommended for all patients but should always be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask – see the Final Adopted CHMP Guideline – Section 4 (4.1.3).</i></p>
Page 3, 3rd bullet	This point needs to specify the magnitude of differences and the type of parameters that would be considered problematic. As	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See</i></p>

	<p>written, it is very vague and specific guidance is needed</p> <p><u>Proposed change</u></p>	<p><i>the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p> <p><i>It is impossible to give specific guidance as it depends on the specific product and patient population studied.</i></p>
<p>Page 3, 3rd paragraph after the bullets</p>	<p>A statement is made about equivalent efficacy needing to be demonstrated, but no mention has yet been made about the requirements for equivalence so this statement seems premature and is at odds with what is on page 4 where options 1 and 2 state that no studies in children may even be required.</p> <p>It states that systemic safety studies should be “at the top of the proposed dose range”, but a clarification is required as to whether or not this means the top single dose if a single dose is examined or daily dose if a multiple dose regimen is examined. Either type of dosing may be appropriate for a safety study depending on the drug.</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Sections 9 and 6.</i></p>
<p>Page 4: “Clinical Requirements” No. 1</p>	<p>“pharmaceutically identical” for an inhalation device has not been defined and needs to be specifically defined – i.e., precise guidance here is needed</p> <p><u>Proposed change</u></p> <p>The <i>in vitro</i> criteria outlined in section 4.2.2 of the Draft Guideline (CPMP/EWP/4151/00Rev1) should also be repeated for this section if the Appendix is a separated guideline.</p>	<p><u>EWP Comment</u></p> <p><i>It had always been the intention that this Guideline should address the requirements for clinical documentation for orally inhaled products (OIPs) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents. However the general sections and the adult sections of the Guideline were ready for release for consultation earlier than the sections on children and adolescents and therefore in order to maximise the time for consultation the general</i></p>

		<p><i>and adults sections were released first and prior to the completion of the sections on children and adolescents. Therefore the sections of the Guideline relating to children and adolescents were presented as Appendix 1 to avoid confusion. Appendix 1 was always intended as a temporary measure for use in the development of the Guideline and for ease of consultation only. In the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 Appendix 1 has been fully integrated into the main Guideline which now has a title which fully reflects the objectives of the Guideline.</i></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline – Section 9. The term “pharmaceutically identical” has been deleted from the text.</i></p>
<p>Page 4: “Clinical Requirements” No. 2</p>	<p>“Pharmaceutically not equivalent” is not defined, but is assumed to mean excipients are not identical. As such, it needs to be clarified that adult data showing equivalence are an acceptable surrogate and that if the dose(s) are the same in children with the new versus old devices, no further studies are needed</p> <p><u>Proposed change</u></p> <p>It should be made very clear that if the <i>in vitro</i> pharmaceutical performance of the test product is not affected by the difference between the devices (pharmaceutically not equivalent devices), no studies are required.</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline – Section 9.</i></p>
<p>Page 4: “Clinical Requirements” No.3</p>	<p>What is meant by a handling study? More specific guidance is required here.</p> <p>For the paediatric specific <i>in vitro</i> matching, more information regarding the standards for comparability is required, i.e. both how the test conditions (flow rate, pressure drop, air volume) are to be defined and how the standard is to be met.</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u></p> <p><i>A handling study is required to ensure that the intended population is able to use the device correctly, that is that the user/child can generate the minimal peak inspiratory flow to trigger the inhalation device.</i></p> <p><i>This whole section has been re-written. See the Final Adopted CHMP Guideline – Section 9 where only three scenarios are described each of which will result in differing clinical requirements.</i></p>

	<p>Clarification and more guidance are required. The current text suggests that investigation of all three parameters: flow rate and pressure drop and air volume are all required.</p> <p>An illustrative example would be helpful as representative of a range of options.</p>	<p><i>Both the second and third scenario listed request that comparative in vitro data between the test and the reference product demonstrating comparable particle size distribution through the flow rate, pressure drop range and air volume clinically applicable to children, are available.</i></p> <p><i>Reference is made within Section 9 to earlier sections in the Final Adopted CHMP Guideline – Sections 4.4 and 5.2 which are applicable both to adults and children.</i></p>
<p>Page 4: “Clinical Requirements” No.4</p>	<p>This is so vaguely written as to be unhelpful. The need for a PK and PD study is specified. However, what is an appropriate period of time? Guidance needs to be more specific and guidance on what PD parameters are acceptable (HPA vs knemometry) needs to be spelled out. Finally, what is meant by “might”? What would be the criteria where these studies would not be adequate to demonstrate equivalence and if they are not adequate, what would be expected or required?</p> <p>Additionally, at the end of the paragraph it recommends a PK study “following inhalation of the maximum recommended total daily dose regimen over an appropriate time period. Clarification is required on whether this is recommending that the maximum single dose allowed is to be used for single dose studies, while the maximum daily dose is to be used for multiple dose regimens.</p> <p>The meaning of “surrogate patient population” is not clear and should be defined.</p> <p><u>Proposed change</u></p> <p>More guidance is required on the following:</p> <ul style="list-style-type: none"> Exactly which type of studies are acceptable for showing equivalence of two inhalers in children 	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline – Section 9.</i></p> <p><i>In the Final Adopted Guideline – Section 9 describes clearly the scenarios which may arise resulting in differing clinical requirements in the development of orally inhaled products in children and states that if none of the three given scenarios arises clinical development of the product in children will be required with demonstration of therapeutic equivalence in respect of both efficacy and safety. Interpolation from data generated in studies in adults may be possible for development in adolescents (aged between 12 and 17 years). Section 6 of the Final Adopted Guideline describes how orally inhaled products should be studied and developed in children and looks at the sub-groups of children aged 6 to 12 years and the pre-school child aged 3 to 6 years and 2 to 6 years.</i></p> <p><i>The EWP agreed that the use of a surrogate population for the study of orally inhaled products in children was not appropriate. This is stated clearly in the Final Adopted CHMP Guideline – Section 9.</i></p> <p><i>The EWP agreed with the proposal to include flow charts within the Guideline. However in the Final Adopted CHMP Guideline a late</i></p>

	<ul style="list-style-type: none"> - PK studies (but repeated blood sampling would be an issue)? - PD studies (e.g. FEV1 / PEFr AUC over 12 hours)? - Bronchial challenge studies? <ul style="list-style-type: none"> • How many doses need to be examined for efficacy? (two doses – top and bottom of intended dose range ?) <p>Clarification is also required on whether or not the approaches proposed in the Draft Guideline (CPMP/EWP/4151/00Rev1) are applicable.</p> <p>A flow-chart decision process for all the five types of requirements is highly recommended.</p>	<p><i>decision was made not to include these.</i></p>
<p>Page 4, “Clinical Requirements”</p> <p>No.5</p>	<p>How is equivalence to be demonstrated based on symptom scores in children <5 yrs?</p> <p>More guidance is required. It suggests that full efficacy and safety studies are needed – but it is not clear concerning the duration required and these versus established reference NCE as equivalence studies or versus placebo (PBO) and why symptom scores and not PEF in the 4-6 year olds?</p> <p><u>Proposed change</u></p> <p>More guidance on the exact equivalence criteria and what are considered as age-dependent endpoints are required.</p>	<p><u>EWP Comment:</u></p> <p><i>The EWP agreed that this whole section should be re-written. See the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9.</i></p> <p><i>In the Final Adopted Guideline – Section 9 describes clearly the scenarios which may arise resulting in differing clinical requirements in the development of orally inhaled products in children and states that if none of the three given scenarios arises clinical development of the product in children will be required with demonstration of therapeutic equivalence in respect of both efficacy and safety. Interpolation from data generated in studies in adults may be possible for development in adolescents (aged between 12 and 17 years). Section 6 of the Final Adopted Guideline describes how orally inhaled products should be studied and developed in children and looks at the sub-groups of children aged 6 to 12 years and the</i></p>

		<p><i>pre-school child aged 3 to 6 years and 2 to 6 years.</i></p> <p><i>It is accepted that clinically validated and relevant age-dependent efficacy variables must be evaluated. The evidence base to date in respect of the best methods to use in the assessment of either bronchodilatation or bronchoprotection in children is limited and therefore cases may need to be handled on an individual basis taking into account the current literature and the views of experts in the field. Justification should be provided to support the chosen efficacy variables. See the Final Adopted CHMP Guideline Sections 9 and 6. In Section 6 specific efficacy variables as discussed with reference to the use of peak expiratory flow as a primary or secondary measure in sub-section 6.2.3.2.</i></p>
<p>Page 4, 2nd paragraph after “Point 5”</p>	<p>See comment above as well.</p> <p>Why has it been assumed that any pMDI must be developed with a spacer? If the originator product does not require use of a spacer there can be no justification for requiring spacer studies with a comparator inhaler. Surely spacing devices are only necessary with ICS to limit local and systemic side effects. If a comparator inhaler has been shown to be equivalent to an originator inhaler in terms of <i>in vitro</i> deposition without spacers what justification can there be to seek further studies to determine the effects of a spacer on a product (this assumes that deposition is somehow inferior without a spacer?)</p> <p>BOIs – spacers not necessary surely? Why has no reference been made to the use of BOIs in children (which are particularly applicable to this age group) in this document?</p> <p><u>Proposed change</u></p>	<p><u>EWP Comment:</u></p> <p><i>The EWP did not accept the comments made regarding the development of a spacing device – that there is no justification for such a development if the reference product does not seem to require that a spacing device be used and that spacing devices are only considered necessary for pressurised metered dose inhalers containing corticosteroids.</i></p> <p><i>The use of a spacing device is recommended for all patients but should always be available for use with a pMDI, and be considered for use with a pMDI, when a pMDI is prescribed for use by a child (which may not be the case when used in adults) and may need to be used with and/or without a face mask – see the Final Adopted CHMP Guideline – Section 4 (4.1.3).</i></p> <p><i>The EWP accepted that a spacing device is for use with a non-breath-operated (standard) pressurised metered dose inhaler only and the Final Adopted CHMP Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 4 (4.1.1 and 4.1.3) reflects this.</i></p>
<p>Page 4, 3rd paragraph</p>	<p>It is not clear about the requirements for “a sufficient number of adolescents”. Since the stratification for this group is not</p>	<p><u>EWP Comment:</u></p> <p><i>The use of the term sufficient number is used in the context of</i></p>

after “Point 5”	<p>required, what is the validity of inclusion of some numbers of adolescent patients?</p> <p><u>Proposed change</u></p> <p>Clarification is required.</p>	<p><i>ensuring that the studies in adults see the recruitment of adolescents aged between 12 and 17 years, to bridge the gap between studies in adults (often seeing recruitment of adults aged 18 years and older only) and studies in children (less than 12 years of age), if the adolescent age group is not being studied in its own right. The statement as presented in the Final Adopted Guideline CHMP/EWP/4151/00 Rev. 1 January 2009 – Section 9 requests that studies set up in adults and including recruitment of adolescents aged 12 to 17 years need not necessarily be stratified for age, but data generated from the two age groups (18 years and above and 12 to 17 years) should be documented and analysed separately , if possible.</i></p> <p><i>However if studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population.</i></p>
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