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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS

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EXECUTIVE SUMMARY

This guideline is a revision of the *CPMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) CPMP/EWP/4151/00.* It clarifies the requirements for clinical documentation for abridged applications for orally inhaled formulations and variations/extensions to a marketing authorisation, and including both single active substance products and combination products, in respect of the demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma and chronic obstructive pulmonary disease in adults and the management and treatment of asthma in children and adolescents.

1. INTRODUCTION (BACKGROUND)

This guideline describes the clinical requirements for inhalation products 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.

2. SCOPE

Existing CHMP documents which discuss the clinical requirements for the development of inhaled products - *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma CPMP/EWP/2922/01* and *Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) CPMP/EWP/562/98* - discuss primarily the development of new active substances. This guideline is directed particularly at the requirements for demonstration of therapeutic equivalence between two inhaled products, in the context of abridged applications or variations / extensions to a marketing authorisation, used in the management and treatment of adult patients with asthma and/or COPD and children and adolescents with asthma.

This guideline will address data required which are often dependent on the performance of the device from which the active substance is inhaled. This document 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. In cases where an approach other than that outlined in this guidance is proposed the applicant is encouraged to seek scientific advice.

Further to clinical performance in respect of the clinical efficacy and safety of the product administered via the inhaler device, knowledge of the *in vitro* performance, and particularly the flow-dependent particle size distribution of the product, is important and will have some influence on the clinical development programme.

This guideline is relevant for the following pharmaceutical dosage forms i.e. medicinal products administered via:

- pressurised metered dose inhalers (i.e. non-breath-operated (standard) pressurised metered dose inhalers);
- breath-operated metered dose inhalers;
- pressurised metered dose inhalers with spacers or holding chambers;
- non-pressurised metered dose inhalers;
- solutions and suspensions for nebulisation;
- dry powder inhalers using a reservoir and metering mechanism or a pre-dispensed dose.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles and part I, II of the Annex I to Directive 2001/83/EC as amended and Commission Regulation (EC) No 1085/2003. In particular, this guideline has to be seen as additional to the following existing CHMP Guidance:

- *EMEA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products;*

- *CPMP/EWP/239/95: Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents;*
- *CPMP/180/95: Guideline for PMS Studies for Metered Dose Inhalers with New Propellants;*
- *CPMP/EWP/240/95 Rev.1: Guideline on the Clinical Development of Fixed Combination Medicinal Products;*
- *CPMP/III/5378/93-Final: Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products;*
- *CPMP/ICH/363/96: Note for Guidance on Statistical Principles for Clinical Trials;*
- *CPMP/EWP/QWP/1401/98 Rev.1 Guidance on the Investigation of Bioequivalence;*
- *CPMP/ICH/364/96 Note for Guidance on Choice of Control Group in Clinical Trials;*
- *EMEA/CPMP/EWP/2158/99 Guideline on the Choice of the Non-inferiority Margin (this guideline is referenced for its comments on non-inferiority margins and to assist in the choice of equivalence margins).*

The existing CHMP Guidance referred to in the first paragraph in section 2 above and which discusses primarily the requirements for the development of new active substances, may also need to be considered.

4. INHALATION DEVICES

Pressurised and non-pressurised metered dose inhalers, dry powder inhalers and nebulisers have different flow-dependent pulmonary deposition patterns. Handling of these devices – and the resultant patient preference – differs. Therefore some general considerations concerning the requirements for *in vitro* characterisation and clinical documentation in respect of these devices are presented below.

4.1 Pressurised metered dose inhalers

4.1.1 Non-breath-operated (standard) pressurised metered dose inhalers

Non-breath-operated (standard) pressurised metered dose inhalers (pMDIs) contain different propellants and other excipients, and may use different delivery systems, all of which may result in differing clinical outcomes. The standard pMDI requires co-ordination of actuation of the device with inspiration of breath; breath-operated devices and the use of spacers with pMDIs reduce the need for such co-ordination. Spacers are required to be available for use with all pMDIs, and should always be considered when a pMDI is used by a child (see section 4.1.3 below). Appropriate data to support the use of a specific named spacer with a pMDI containing a specific active substance or specific combination of active substances must be included in the dossier submitted in support of all applications for marketing authorisations for such products (see also section 4.1.3 below).

4.1.2 Breath-operated metered dose inhalers

A minimal peak inspiratory flow (PIF) is required to trigger a breath-operated inhaler (BOI) and if this minimal PIF cannot be achieved by the patient, inhaler use will be unsuccessful. Therefore, the clinical programme must include relevant data regarding the PIF required to trigger the BOI (these data may be generated using a placebo device) and discussion of those patient groups who would normally be able to produce a sufficient PIF to trigger the device and those patient groups who may have problems (for example patients with severe airflow obstruction, patients suffering from an acute attack of asthma, small children, etc).

The relevant patient population must be adequately investigated and subsequently clearly defined in order that the prescriber can be assured that the product is only prescribed to and used by suitable patient groups.

The reference product for a BOI can be the corresponding pMDI.

Some inhalers have two methods of actuation, hand-operated and breath-operated. Patients using these inhalers need explanations in the package leaflet as to how to recognise an inadequate hand-operated or breath-operated inhalation and as to when they may need to be switched from one method of actuation to the other. The two modes of action should be compared using the parameters outlined below (see section 5 below) to determine whether there is a need for clinical data to support each method of inhalation.

4.1.3 Spacers and holding chambers

Effective spacers facilitate inhalation via a non-breath-operated (standard) pMDI and decrease the amount of medicinal product deposited in the mouth and pharynx and subsequently swallowed. The use of a spacer is recommended for all patients in principle but particularly for those who find co-ordination of actuation of the pMDI with inspiration of breath difficult (for example children and the elderly) and for patients treated with inhaled glucocorticosteroids.

Spacers usually increase pulmonary deposition. However a specific spacer may perform differently with different active substances and similarly, a specific active substance in a specific pMDI may perform differently if inhaled through different spacers. The distribution and response to an active substance cannot be assumed to be equivalent if a different spacer is used or if a different pMDI is used with the same spacer. The development of a pMDI should always include the testing of at least one specific named spacer for use with the particular pMDI containing a particular active substance. This spacer has to be appropriate for the intended patient population.

The behaviour of the spacer will depend on the volume and material of the holding chamber, on the electrostatic properties of the internal surface of the chamber and on the way in which the device is used. Hence the *in vitro* testing should be carried out by preparing the spacer and setting up the apparatus in a clinically relevant manner which may influence the performance of the product, for example, inserting a time delay between actuation and inhalation to simulate tidal breathing (if the dose is not evacuated in one breath) and washing/preparation of the spacer before and during use according to the instructions of the manufacturer of the spacer.

When all data collected in the development programme are based on the product administered via a pMDI together with one or more specific, characterised spacers, the product can be authorised subsequently for use **only** if used with the specific named spacer(s).

If the product is to be administered with and without a spacer, the use of the product alone as well as the use of the product with a spacer must be supported by appropriate *in vitro* or *in vitro* and clinical data (see sections 5 and 6 below). If these data are not in line with the criteria described in section 5, below, clinical data covering the relevant patients groups (e.g. children, patients treated with inhaled glucocorticosteroids) will be required in order to investigate the impact of the spacer on efficacy and safety.

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.

If the spacer is to be replaced subsequently by an alternative spacer, appropriate *in vitro* or *in vitro* and clinical data (see sections 5 and 6 below) must be presented. It should be noted that using the Ph.Eur. methods without taking into account clinical relevant factors such as tidal breathing and time delays (see the third paragraph in this section, section 4.1.3, above) is not acceptable. If comparative *in vitro* determination using a validated method does not show equivalence (see section 5 below), clinical development will be required. Clinical development must include an assessment of systemic safety through investigation of equivalence based on pharmacokinetic data or pharmacodynamic data. The highest recommended dose has to be administered when assessing safety through pharmacodynamic equivalence (see section 6.2, below).

The appropriately investigated spacer(s) has to be specifically named in the SmPC Section 4.2 and in the package leaflet, and on occasions may need to be named also on the product labelling.

If a non-breath-operated (standard) pMDI is to be used in children it **must** 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 **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. The spacer has to be appropriate for the age groups of intended use.

4.2 Non-pressurised metered dose inhalers

Non-pressurised metered dose inhalers are portable, pump activated reservoir inhalation delivery devices containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s). In non-pressurised metered dose inhalers the speed of plume is decreased and therefore the inhalation manoeuvre takes longer than that for pMDIs (without using a spacer) and powder inhalers. In order deliver a sufficient amount of active substance the patient has to inhale a specific volume of the aerosol. In all patients, but especially those with a limited inhalational capacity (for example, children) it has to be shown that the volume required to produce the desired clinical effect does not exceed the inhalational capacity of the patient.

4.3 Solutions and suspensions for nebulisation

In specific circumstances (for example infants and young children, the severely ill patient, the elderly, the disabled) inhalation of medicinal products via a nebuliser system is a treatment option for patients with asthma and COPD. Currently jet, ultrasonic and vibrating mesh types of nebuliser systems are available. Generally nebuliser systems are sold separately from solutions and suspensions containing active substances for nebulisation and therefore these formulations are often inhaled via an available nebuliser system rather than via the nebuliser system used during the development of the medicinal product for nebulisation itself.

However the differences in delivered aerosol between nebuliser systems currently available are significant. Therefore a medicinal product formulated for nebulisation should be characterised using a specified and standardized nebuliser system(s). Representative nebuliser systems for jet, ultrasonic and vibrating mesh nebuliser systems should be considered**.** The nebuliser system used should be described in the protocol in terms of:

- Nebuliser type;
- Choice of driving gas;
- Driving gas pressure;
- Driving gas flow rate;
- Nebuliser fill volume;
- Time of nebulisation;
- Residual solute volume;
- Accessories.

The nebuliser system(s) studied in the development programme should be described in the SmPC and in the package leaflet. Warnings should be included in the informative texts (SmPC and package leaflet) to state that there is no information available in respect of pulmonary inhalation and deposition patterns across nebuliser systems that have not been studied in the development programme; the use of an alternative untested nebuliser system may alter the pulmonary deposition of the active substance, this in turn may alter the efficacy and safety of the product and dose adjustment may then become necessary. If a test product has been assessed with a range of nebuliser systems it should be clearly stated if any of these systems affect performance adversely compared with performance when administered with other nebuliser systems from the range studied.

When solutions for nebulisation have the same qualitative and quantitative composition as the reference product the requirement for clinical studies may be waived.

For suspensions for nebulisation therapeutic equivalence should be demonstrated through *in vivo* studies, unless justification is provided for the use of other types of studies to demonstrate equivalence.

4.4 Dry powder inhalers

In contrast to pressurized and non-pressurized MDIs dry powder inhalers (DPIs) often show a high flow dependency in their deposition characteristics. Therefore characterisation of flow rate dependency in the patient populations in whom the DPI is to be used must be presented (see also section 5.2 below).

The dossier submitted has to include sufficient *in vitro* data such that the flow deposition characteristics of the products within the range of clinically relevant pressure drops/flow limits can be described.

For a proposed DPI with a high flow rate dependency (the performance of the product is highly dependent on the flow rate during use) when compared with a reference product with a low flow rate dependency (the performance of the product is not greatly affected by the flow rate during use) marketing authorisation can only be granted for use in the patient populations studied. Extrapolation to patient populations other than those populations studied is not then appropriate and marketing authorisations will be restricted appropriately. For all DPIs the patient population in whom the inhaler can be used (i.e. patients who can generate a sufficient PIF to use the product) should be carefully defined.

The use of a high flow rate dependent DPI as a reference product may raise issues in respect of the conclusions which can be drawn regarding therapeutic equivalence unless deposition characteristics and inspiratory flow rates are standardised. Therefore, equivalence should be assessed across a range of inspiratory capacities (pressure drops/flow rates) which represent the patient population covered by the authorisation for the reference product.

4.5 Investigation of several product strengths

Dose linearity should be investigated *in vitro* for both the test and the reference product across all proposed strengths.

If dose linearity is demonstrated *in vitro* when different dose strengths of a known active substance are sought it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance. It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.

If linearity across all proposed product strengths is demonstrated with the test product but 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).

If an additional strength of a product is to be developed an acceptable benefit/risk balance for the product must be demonstrated.

The reference product should be the authorised innovator product if this product is still available. The choice of reference product should be justified.

4.6 New propellants and excipients

When a new propellant, excipient or excipient mix is introduced the possible impact on clinical efficacy and safety must be studied in addition to any toxicological and preclinical programme (see section 10 below). Generation of extended safety data may be necessary. Local tolerability must be assessed and evidence of increased bronchial irritability or paradoxical bronchospasm must be sought. It may be necessary to assess any effect that the new propellant or excipient may have on mucociliary clearance.

5. PHARMACEUTICAL PROPERTIES AND THE NEED FOR A CLINICAL PROGRAMME

5.1 New active substance

Products containing a new active substance are required to undergo a full development programme regardless of the type of device from which the new active substance is inhaled.

5.2 Known active substance

For abridged applications therapeutic equivalence to a reference medicinal product must be substantiated. In some cases, the use of only comparative *in vitro* data, obtained with an accepted method (e.g. multistage impactor/impinger), may be considered acceptable if the product satisfies **all** of the following criteria (compared with the reference product):

- The product contains the same active substance (i.e. same salt, ester, hydrate or solvate, etc.).
- The pharmaceutical dosage form is identical (e.g. pMDI, non-pressurised MDI, DPI, etc.).
- The active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behaviour.
- 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 be likely to affect the inhalation behaviour of the patient (e.g. particle size distribution affecting mouth/throat feel or "cold Freon" effect).
- Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product.
- The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%).
- 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.
- The inhalation device has the same resistance to airflow (within +/- 15%).
- The target delivered dose should be similar (within +/- 15%).

Data from the complete particle size distribution profile of individual stages of a validated multistage impactor/impinger method should be provided. Unless justified otherwise, comparative *in vitro* data on flow rate dependence 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. 10^{th} percentile), median and maximum (e.g. 90^{th} percentile) achievable flow rate in this patient population(s) should be investigated.

The efficacy and safety of the medicinal product will depend on the amount of active substance that reaches the lung and on the deposition site distribution. In addition, the safety will also be influenced by the rate and extent of systemic absorption from the gastrointestinal tract (i.e. the swallowed fraction). Therefore the *in vitro* comparison should be performed for the stages that represent the fine particle mass as well as the upper stages of the impactor/impinger which are relevant to the efficacy and safety of the medicinal product *in vivo*, unless otherwise justified.

The comparison should be performed per impactor stage or justified group of stages. At least 4 groups of stages are expected. Justification should be based on the expected deposition sites in the lungs. At least three consecutive batches of the test product and three batches of the reference product should be tested. The maximum allowable *in vitro* difference should be indicated and justified, e.g. +/- 15% may be justifiable. Per impactor stage or justified group of stages the 90% confidence intervals for the observed *in vitro* differences must be calculated. Based on the pre-established protocol and maximum allowable differences, a decision regarding equivalence can be made.

If the product does NOT satisfy ALL of these pharmaceutical criteria for equivalence, *in vivo* studies should be performed to substantiate equivalence.

6. CLINICAL DEVELOPMENT

6.1 Pulmonary deposition

Pulmonary deposition studies investigate the extent and pattern of pulmonary deposition of an inhaled active substance.

Different excipients, different devices or different aerosol performance characteristics of inhalation products containing the same active substance may have an important influence on pulmonary deposition resulting in a clinically relevant impact on efficacy and safety. If the product for which a new marketing authorisation is sought fails to show equivalence to the reference product based on *in vitro* data (see section 5.2 above), one way to demonstrate equivalent efficacy may be through a comparison of pulmonary deposition.

Pulmonary deposition studies are designed as double blind, crossover studies and should be carried out using a clinically relevant dose(s) and strength(s) of the product (which may be determined from the *in vitro* data). These studies should be performed in the intended patient population.

Pulmonary deposition can be investigated by conducting pharmacokinetic or imaging studies.

Pharmacokinetic studies may have some advantages, even though they provide data indirectly from plasma or urine: Pharmacokinetic studies are easier to perform, they are safer due to the lack of radiation, they avoid the risk of altering the formulation during radio-labelling and they can demonstrate linear dose-response relationships more easily.
In addition, pharmacokinetic studies measure total systemic exposure (for assessment of safety), and pulmonary absorption (for assessment of pulmonary deposition and efficacy) can be separated from gastrointestinal absorption. Pharmacokinetic studies may even take into account active substance removed by mucociliary clearance.

Limitations with pharmacokinetic studies include their inability to differentiate the distribution of drug within the different zones of the lung following inhalation and in some cases plasma/urinary concentrations are not measurable at clinical doses or are near the lower limit of quantification such that results may be highly variable.

In some cases equivalent pulmonary deposition demonstrated through pharmacokinetic studies in combination with safety data (for example, data from a systemic safety pharmacokinetic study, see section 6.1.1 below) might be considered as sufficient demonstration of therapeutic equivalence, if justified. However, in general, therapeutic equivalence must be demonstrated by means of appropriate pharmacodynamic and/or clinical studies.

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. If equivalent pulmonary deposition is shown through imaging studies this should be followed by appropriate pharmacokinetic studies or appropriate clinical studies to assess therapeutic efficacy. If imaging studies are used instead of pharmacokinetic studies to assess therapeutic efficacy the grounds on which the studies are being used must be fully justified.

In adults pulmonary deposition studies (whenever possible) and *in vitro* characterisation of the active drug, comparing the new product with a reference product, should be investigated prior to carrying out therapeutic equivalence studies.

In children pulmonary deposition studies 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 in children to warrant their use. Imaging studies in children are also not appropriate.

6.1.1 Pharmacokinetic studies

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). A pharmacokinetic study may be used for determination of pulmonary deposition but may also investigate systemic safety. In the investigation of systemic safety total systemic exposure has to be measured in the intended patient population and therefore the study must include the measurement of that amount of the active moiety absorbed through the lung and the gastrointestinal tract.

However it may be possible for substances with negligible gastrointestinal absorption that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.

In accordance with the standard accepted methods of assessment of bioequivalence the maximum concentration (C_{max}), the area under the curve (AUC) and the time to C_{max} (T_{max}) should be compared. Equivalent pulmonary deposition and equivalent systemic safety of two inhaled products may be concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25. However, in some circumstances, for example, for active substances with a narrow therapeutic window, the 90% CI may require tighter limits when assessing systemic safety. Conversely, for products with high variability it may be acceptable if certain conditions are satisfied to widen the acceptance range for C_{max} to 0.75 to 1.33 (see CHMP/EWP/QWP/1401/98 Rev.1 for further details).

If pharmacokinetic studies are carried out in children for the assessment of systemic safety the active substance should be measured in plasma.

6.1.2 Imaging studies

Regional quantification of the pulmonary deposition of two products can be carried out by measuring radioactivity in the different segments of the lung. Two-dimensional scintigraphic methods can be used. The whole lung percentage deposition of the drug should be measured as well as the proportion deposited in the central, intermediate and peripheral lung zone, oropharynx, mouthpiece, actuator and exhalation filter. Equivalent lung deposition of two drugs can be concluded if the 90% confidence interval of the radioactivity in each area is within a range of 0.8 to 1.25. It has to be assured that the radio-labelling of the inhaled products has only negligible influence on the deposition characteristics.

6.2 Pharmacodynamic studies

6.2.1 General considerations in the investigation of therapeutic equivalence

Therapeutic equivalence is defined as equivalent efficacy and safety when the new inhaled product for which a marketing authorisation is sought is compared with an appropriate reference product. Therapeutic equivalence demonstrated by means of appropriate clinical studies using well-validated study designs and comparing the test product with the reference product, becomes mandatory when equivalence is not shown *in vitro* according to the criteria provided in section 5.2 above and is not shown convincingly by investigation of pulmonary deposition and systemic safety as discussed in section 6.1 above.

Based on different inhalation techniques required for different inhalation devices it is recommended that the test and reference product should be inhaled from the same pharmaceutical dosage form (for example both the test and the reference product should be administered via a pMDI or both should be administered via a DPI) wherever possible, when assessing therapeutic equivalence.

If clinical studies are needed and the reference product has an authorised indication which includes both asthma and COPD, therapeutic equivalence studies may only be needed in one of the patient

populations in order to obtain a marketing authorisation. 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 *in vitro* data must be provided to demonstrate that the test and reference product produce comparable particle size distribution (see section 5.2 above) 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 authorisation can be granted which will include all therapeutic indications as listed for the reference product.

6.2.2 Requirements for clinical studies in patients with asthma

Two different types of pharmacodynamic study provide acceptable methods for investigating equivalence in respect of efficacy of inhaled drugs – studies of bronchodilatation/assessment of improved airway function and studies of bronchoprotection**.** One or other or both of these types of study may be used to satisfy the requirements of comparative efficacy.
Independent of the type of study, either bronchodilatation/improved airway function or bronchoprotection, the trial should be carried out in patients with asthma who demonstrate reversibility of airway function. **In adults** reversibility of airway function is assessed by measurement of forced expiratory volume in one second (FEV_1) with demonstration of ≥12% and ≥200 ml improvement in FEV_1 15 minutes after inhalation of an appropriate inhaled short-acting β_2-adrenoceptor agonist (SABA); **in children 6 years of age and older** reversibility of airway function is assessed by measurement of FEV_1 with demonstration of ≥12% improvement in FEV_1 15 minutes after inhalation of an appropriate inhaled short-acting β_2 adrenergic agonist; **in children 5 years of age and younger,** spirometry is feasible in children over 3 years, although either $FEV_{0.5}$ or $FEV_{0.75}$ may be a better measure than FEV_1 (the literature should be reviewed particularly with regard to criteria for accepting data, data reporting and repeatability), however the diagnosis of asthma is challenging in this younger age group and may need to be based on clinical judgment, assessment of symptoms and physical findings.

The study carried out must be sensitive enough to be able to discriminate between the two comparator products and to be able to pick up clinically relevant differences which might exist between the two products. Therefore, all patients recruited to a study should be able to demonstrate a clinically relevant response to treatment.

Relative potency – defined as the ratio of the potency of the test product to that of the reference product - is one way of summarising the relationship between the dose response curves of the test and reference products. Demonstration of equivalence for at least two dose levels on the pharmacodynamic endpoint is another approach that can be used. For either approach to be acceptable a minimum requirement is that the study has assay sensitivity. For a study to have assay sensitivity at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other. Therefore it is recommended that unless otherwise justified more than one dose of both the test and reference products are studied.

However, it is essential that doses on the steep part of the dose response curve are studied. If a dose too low on the dose response curve is chosen then demonstrating equivalence between two products is not convincing as this dose could be sub-therapeutic. Equally if a dose at the top of the dose response curve is included similar effects will be seen for doses much higher than that studied and hence demonstrating equivalence at this dose level would also not be convincing.

Equivalence in respect of safety should be demonstrated by investigation of equivalence based on pharmacokinetic data, relevant cardiovascular, biochemical and physiological parameters, and monitoring of adverse events. The highest recommended dose has to be administered when assessing safety through pharmacodynamic parameters. However safety assessments should also be included in the efficacy studies regardless of the dose being studied. The duration of a safety study depends on the therapeutic class of the test/active substance.

Two products will be considered as equivalent if the following criteria are completely fulfilled:

- **Efficacy:** The comparison between products has to be performed in two ways. One approach is to calculate the relative potency. A second approach is to compare the results for the clinical endpoint for the test and reference products at each dose level studied. The results using both approaches should be provided. In both cases the observed confidence intervals comparing test and reference products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. For both approaches the chosen equivalence margins should be pre-specified and appropriately justified. The acceptance criteria for relative potency should lie entirely within 0.67 to 1.5.
- **Safety:** Equivalence in respect of systemic exposure should be demonstrated through a pharmacokinetic safety study if possible (see section 6.1.1 above). Otherwise equivalence in respect of relevant pharmacodynamic safety variables needs to be demonstrated. 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.

6.2.2.1 Bronchodilatation studies/studies of improved airway function

Equivalent therapeutic efficacy can be investigated by measurement of the bronchodilating effect of the test and the reference product through appropriate primary and secondary endpoints. The duration of the study and the choice of primary and secondary endpoints are dependant on the therapeutic class of the test product. Overall sensitivity of the study can be increased by the inclusion of stable, but less than optimally controlled or only partially controlled patients with asthma. Less than optimally controlled asthma is defined according to pulmonary function, level of symptoms including nocturnal symptoms and nocturnal awakening, daily activity and/or daily requirement of *reliever* medication, at baseline (measured during a run-in period). The study design should incorporate at least two dose levels. Generally, a double blind, double dummy study design should almost always be possible.

6.2.2.2 Bronchoprotection studies

The bronchoprotective potency of a drug to provide protection against bronchial challenge can be assessed through bronchoprotection studies, either direct provocation for example with methacholine, histamine, acetylcholine or indirect provocation with adenosine monophosphate (AMP) or mannitol.
Bronchoprotection studies require a high degree of standardisation and patient selection (for example choice of provocation, aerosol generation, nebuliser output, inhalation procedure, physical aspects, exclusion of diurnal variation, at least 4-fold increase in PC_{20} FEV_1 after treatment etc). It is recommended that the ATS Guideline is considered in this regard. Generally a double blind, double dummy, study design, incorporating at least two dose levels is recommended. The primary outcome variable, the provocative concentration or provocative dose of the provocation agent which produces a 20% fall in FEV_1 ($PC_{20}FEV_1$ or $PD_{20}FEV_1$) must be measured at the time of the expected maximum effect of the drug.

6.2.3 Therapeutic class - specific considerations in the investigation of therapeutic equivalence

6.2.3.1 Bronchodilators

Inhaled bronchodilators fall into three categories - short-acting β_2 adrenoceptor agonists (SABAs), long-acting β_2 adrenoceptor agonists (LABAs) and anticholinergics. Clinical studies of bronchodilators can use a cross-over design. An appropriate washout between treatments has to be defined and justified in the protocol. Baseline measurements prior to each treatment period have to be documented in order that any possible carry-over effects can be assessed.

Short-acting β_2 adrenoceptor agonists
For the SABA either a single dose bronchodilatation study or a bronchial challenge study are acceptable study designs for the assessment of equivalence in respect of efficacy.

In adults appropriate primary variables in the bronchodilatation model are FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation) and change in FEV_1 (at an appropriate time point(s)); in the bronchial challenge study the primary variable is either $PC_{20}FEV_1$ or $PD_{20}FEV_1$ (see section 6.2.2.2, above).

In children aged 6 years and older appropriate primary variables in the bronchodilatation model are spirometric variables (e.g. change in FEV_1, or FEV_1/FVC (forced vital capacity) ratio (at an appropriate time point(s)) and/or FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation)); in pre-school children, spirometry is feasible in children aged 3 to 6 years, although either $FEV_{0.5}$ or $FEV_{0.75}$ may be a better measure than FEV_1 (the literature should be reviewed particularly with regard to criteria for accepting data, data reporting and repeatability), and specific airway resistance (sRaw), as measured by plethysmography or other validated methods, combined with clinical symptom scores can be used in children aged 2 to 6 years. Peak expiratory flow should be measured and recorded as a secondary efficacy variable only. In bronchoprotection studies methacholine challenge or exercise challenge for example, can be used in children 6 years of age and older, and cold dry air challenge or eucapnic hyperventilation can be used in the pre-school child. The primary variable is either PC_{20FEV1}methacholine or PD_{20FEV1}methacholine, or percentage change from baseline in sRaw (as measured by plethysmography); other validated endpoints can also be used. (See section 6.2.2.2, above and section 9, below).

In adults the safety of SABAs should be investigated through equivalence based on pharmacokinetic data (if this is possible and this will be dependent on the drug and the quality of the assay) following administration of a single dose (see section 6.1.1 above). If equivalent safety cannot be concluded from the pharmacokinetic study, safety data must be provided from a pharmacodynamic study(ies). The safety profile must then be investigated following administration of the maximum recommended dose. Recording of adverse events and assessment of any paradoxical bronchospasm, recording of vital signs and an ECG with measurement of the QTc interval, and measurement of laboratory parameters (including measurements of serum potassium and plasma glucose) will be required.

In children the safety of SABAs should be investigated through pharmacokinetic or pharmacodynamic studies, the latter following administration of the maximum recommended dose, as stated above for adults.

Long-acting β_2 adrenoceptor agonists
Requirements in the assessment of equivalence in respect of efficacy of LABAs are the single dose comparative studies of either bronchodilatation or bronchoprotection as for the SABAs. However the onset of action (the achievement of a clinically relevant benefit), the maximum response and the longer duration of effect of the LABA must be taken into consideration in the design of the study (see glossary for definitions).

In adults appropriate primary variables in the bronchodilatation model are FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation) and change in FEV_1 (at an appropriate time point(s)); in the bronchial challenge study the primary variable is either $PC_{20}FEV_1$ or $PD_{20}FEV_1$.

In children appropriate primary variables for both bronchodilatation studies and bronchoprotection studies are as described above for SABAs but with the exception of the primary variable in bronchodilatation studies in children 6 years and older, where FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation – any shorter time period must be fully justified) is the more appropriate primary variable of choice.

The dose range should be explored in single dose studies. Assessment of low and high doses to enable demonstration of dose response is required.

In adults the safety of LABAs should be investigated through equivalence based on pharmacokinetic data (if this is possible and this will be dependent on the drug and the quality of the assay) following administration of a single dose (see section 6.1.1 above). If equivalent safety cannot be concluded from the pharmacokinetic study, safety data must be provided from a pharmacodynamic study(ies). The safety profile must then be investigated following administration of the maximum recommended dose. Recording of adverse events and assessment of any paradoxical bronchospasm, recording of

vital signs and an ECG with measurement of the QTc interval, and measurement of laboratory parameters (including measurements of serum potassium and plasma glucose) will be required.

In children the safety of LABAs should be investigated through pharmacokinetic or pharmacodynamic studies, the latter following administration of the maximum recommended dose, as stated above for adults.

Anticholinergic drugs
The investigation of therapeutic equivalence in respect of short-acting and long-acting anticholinergic drugs is similar to that of SABAs and LABAs. However the differing characteristics of the β_2 agonists and the anticholinergic drugs have to be taken into account particularly in respect of onset of action and duration of effect. In any bronchial challenge study the provocation agent would be a cholinergic agonist. The safety of anticholinergic drugs has to be investigated in the usual way.

6.2.3.2 Inhaled glucocorticosteroids

The demonstration of equivalent efficacy of inhaled glucocorticosteroids (ICS) is difficult. A successful efficacy equivalence study requires demonstration of a significant dose response relationship with the study of at least two doses of the test compared with two doses of the reference product. It is important to recognise that the doses studied should be on the steep part of the dose response curve and convincing evidence of this will be required. There are certain circumstances when the use of excessive multiple actuations are needed to achieve the required dose. This may result in unacceptable impact on the patient (e.g. high powder loading of the excipient from a DPI). The use of a different higher strength product may be justified in such circumstances. Comprehensive *in vitro* dose comparability from the different strength products should be demonstrated (see section 4.5 above).

Currently the most well-used study design is the double blind, randomised, **parallel group** comparison of the test and the reference product; if the chosen study design differs from this, the reasons for this must be justified by the applicant.

An alternative is the double blind, randomised, **crossover** study, a study design which has the potential advantage of the ability to study a smaller population. However concerns regarding an unequal carry-over of corticosteroid effects within subjects between treatment periods and the potential difference in the baselines at the beginning of the two treatment periods must be considered. An appropriate washout period between treatments has to be defined and justified in the protocol to control the impact of any carry-over effect.
The use of this type of study should be justified and should be supported through published data.

There are two different pharmacodynamic models which can be considered in the investigation of equivalent therapeutic efficacy of ICSs.
One pharmacodynamic model to test therapeutic equivalence in terms of efficacy is the **bronchodilatation/assessment of improved airway function** model. In these studies, patients recruited should have demonstrable room for improvement in pulmonary function to respond differently to the two doses/strengths of the inhaled corticosteroid and should be symptomatic (see section 6.2.2.1 above). The population included should be responsive to inhaled corticosteroids and be as homogeneous a population as possible, to decrease variability and increase the power to detect a significant dose response relationship and obtain an estimate of the difference between formulations in respect of pulmonary function with a sufficiently narrow confidence interval.

In adults the primary efficacy variable should be a pulmonary function measure and preferably FEV_1 measured regularly, if possible daily measurements at home. Peak expiratory flow (PEF) should be measured and recorded daily at home as a secondary efficacy variable. If regular measurement of FEV_1 at home is not possible, morning PEF measured and recorded daily at home should be accepted as the primary efficacy variable. Measurements of FEV_1 at least every two weeks in the clinic should always be included as a secondary efficacy variable.

In children aged 6 years and older:

- The primary efficacy variable should also be a pulmonary function measure, FEV_1 measured and recorded daily at home if possible, under the supervision of a parent or carer is the primary variable of choice.

- If regular measurement of FEV_1 at home is not possible, morning PEF measured and recorded daily at home **may** be accepted as the primary efficacy variable, with measurements of FEV_1 at least every two weeks in the clinic as a secondary variable.

- If PEF is **not** the primary efficacy variable this parameter should always be measured and recorded daily at home as a secondary efficacy variable.

- FEV_1 measured at least every two weeks in the clinic should always be included as a secondary efficacy variable regardless of which primary variable (FEV_1 or PEF) is used.

- The use of PEF as a primary variable must always be justified.

In pre-school children:

- spirometry is feasible in children aged 3 to 6 years, although either $FEV_{0.5}$ or $FEV_{0.75}$ may be a better measure than FEV_1 (the literature should be reviewed particularly with regard to criteria for accepting data, data reporting and repeatability),

- sRaw measured by plethysmography or other validated methods, combined with clinical symptom scores, can be used in children aged 2 to 6 years).

Justification should always be provided to support the chosen efficacy variables.

The use of electronic diary cards (in both adults and children) is desirable and they should be used whenever possible.
The duration of treatment periods should be at least eight (if not twelve) weeks, any shorter treatment period should be justified.
The population studied should be representative of the target population.

Less experience exists with the model of **bronchoprotection**. This alternative method would compare inhaled corticosteroids following chronic dosing. **In adults** the primary efficacy variable is the change seen in the provocative concentration or provocative dose of, for example, adenosine monophosphate (AMP) which produces a 20% fall in FEV_1 (PC_{20FEV1}AMP or PD_{20FEV1}AMP). The study design should be shown to be dose sensitive and should incorporate at least two doses/strengths of the test and the reference product. Each dose level of the test and the reference product should be inhaled for at least 4 weeks, unless otherwise justified.

In children 6 years of age and older, methacholine challenge, for example, can be used to assess the change in airway hyperresponsiveness; the primary variable is the change seen in either $PC_{20}FEV_1$ or $PD_{20}FEV_1$ (see section 6.2.2.2, above and section 9, below). In the pre-school child cold dry air challenge or eucapnic hyperventilation can be used; the primary variable is the percentage change from baseline in sRaw (as measured by plethysmography). Other validated endpoints can also be used.

The population studied should be representative of the target population but with recruitment of patients with mild asthma and known bronchial hyperresponsiveness.
The use of this type of study should be justified and should be supported through published data.

Whatever primary efficacy variable is chosen should be validated and be justified based on its sensitivity to detect differences between doses of the ICS.
With both models, and in both adults and children, symptom scores, percentage of symptom-free days frequency of use of reliever/rescue medication and exacerbations should be recorded as secondary endpoints. Other efficacy variables which may be considered include expired nitric oxide (eNO) and

sputum eosinophils, validated quality of life (QoL) questionnaires and validated patient reported outcome measures (PROMs).

Equivalent safety must be demonstrated. Appropriate safety monitoring within the therapeutic efficacy studies should include the recording of local adverse effects and any evidence of paradoxical bronchospasm and the assessment of systemic effects.
Systemic safety should be demonstrated through pharmacokinetic equivalence in adults (if this is possible and this will be dependent on the drug and the quality of the assay). If safety cannot be assessed in this way, assessment of systemic safety following inhalation of the maximum recommended total daily dose regimen of the ICS, together with the assessment of a lower dose regimen, regularly over time, through measurement of pharmacodynamic parameters related to pharmacokinetic parameters will be required.

The current view in respect of the pharmacodynamic assessment of systemic effects of ICSs **in adults** is to assess the effect on the hypothalamic pituitary adrenocortical (HPA) axis. The preferred pharmacodynamic method of assessing the HPA axis is the repeated assessment of the change from baseline in 24-hour plasma cortisol as measured by AUC (as the primary variable) and C_{max}. The duration of treatment in such a study must be justified and must ensure that steady state has been reached in order that the potential systemic effects of the ICSs, both the test and the reference, can be assessed and compared. The study should be carried out in patients with asthma and all measurements should be carried out in a controlled, fully tested environment (and to achieve the latter patients should be studied as in-patients on those days when assessments are being carried out).

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.

In summary, systemic safety in children should be demonstrated by carrying out either

- two pharmacodynamic tests of safety – an assessment of the systemic effects of ICSs on the HPA axis **and** an assessment of growth (using a surrogate marker).
  or
- a pharmacokinetic assessment if possible and if justifiable.

The current view in respect of the pharmacodynamic assessment of systemic effects of ICSs in children is to assess the effect on the HPA axis and on lower leg bone growth rate as a surrogate marker for growth (see below and section 9).

In children the following tests of HPA axis function may be considered:

- Repeated assessment of the change from baseline in 12-hour plasma cortisol as measured by AUC (as the primary variable) and C_{max} is one method of assessing the HPA axis. The duration of treatment in such a study must be justified and must ensure that steady state has been reached in order that the potential systemic effects of the ICSs, both the test and the reference, can be assessed and compared. The study should be carried out in a population of children with asthma and **if possible** all measurements should be carried out in a controlled environment (and to achieve this, children should be studied as in-patients on those days when assessments are being carried out).

- The 24-hour urinary-free cortisol is a variable which could be used in the assessment of systemic effects of ICSs on the HPA axis although it is a much better test for the measurement of high urinary levels of cortisol than low levels. Difficulties are always encountered in the collection of urine samples, these are often incomplete such that the data are very difficult to interpret and subsequently may be of little value. Therefore such a test of HPA axis function is not considered to be the most appropriate test but if used, urine should be collected in a controlled environment. To achieve this, children should be studied as in-patients on those days when urine collections are being made.

However assessment of the HPA axis using spontaneous cortisol secretion may identify only those children with fairly profound abnormalities of the HPA axis that are evident in the unstressed state. More commonly, children treated with inhaled corticosteroids have normal cortisol profiles in the unstressed state but cannot mount an appropriate increase in serum cortisol during times of stress (ie infection, trauma etc). These children may not be identified by measurement of either plasma or urinary cortisols as described above. **Therefore it is important that the assessment of systemic safety in children should always include two different pharmacodynamic tests of safety – see above – and whichever tests are chosen should be justified.**

Growth should **not** be considered as the most appropriate **single** measure of the systemic effects of ICSs, **growth in a child may be normal but the HPA axis may be suppressed.** However **the following assessments of growth should be considered alongside the assessment of effects on the HPA axis when systemic safety is demonstrated through pharmacodynamic equivalence:**

- Ideally linear growth is measured by standard stadiometry over 12 months or longer; weight should be recorded.
- Knemometry is not a measure of linear growth but is a sensitive pharmacodynamic measure of systemic steroid exposure and will demonstrate an acute effect of inhaled corticosteroids on lower leg bone growth rate. Short-term changes seen in the lower leg bone growth rate over 4-8 weeks as measured by knemometry appear to correlate poorly with linear growth measurements and may overestimate any potential effects on growth, and extrapolation to possible effects on linear growth and final height are not appropriate. However knemometry is a sensitive technique and is useful as a surrogate marker of growth if the test product is being compared with a well-known reference product with a well-defined safety profile. Used in this way knemometry could be an indicator of equivalence. Knemometry is validated, accurate and reproducible but the duration of study, if less that 4 weeks, should be justified.

If pharmacokinetic studies are carried out in children for the assessment of systemic safety the active substance should be measured in plasma.

Whatever methods of assessing systemic effects of ICSs are used in either adults or children they should be discussed fully and justified in the dossier submitted. Advice from appropriate experts in the field might be useful to ensure that tests and assessments carried out are appropriate and are in line with current thinking.

6.2.3.3 Combination products

For fixed combination products of known active substances, **where the combination of specific active substances is not new and for which there are reference combination products**, therapeutic equivalence should be demonstrated for each/all of the component active substances of a fixed-dose combination product and study design will depend on the specific active substances in the combination. For example, efficacy and safety of the combination of an ICS and a LABA might be investigated in one study in which outcome measures capable of assessing both active components in the combination separately are included (co-primary variables in respect of efficacy will need to be defined, one for each component of the combination). The study design should include two doses of each combination product (the test and the reference combination product) in order to show a significant statistical dose response relationship.

Furthermore establishing therapeutic equivalence for combinations of ICSs and LABAs might be through separate studies assessing each separate active. The efficacy of the LABA component can be assessed following inhalation of a single dose through either measurement of bronchodilatation over at least 80% of the duration of action or bronchial challenge studies; the efficacy of the ICS component will be through the study of multiple dose inhalations over time – see sections 6.2.3.1 and 6.2.3.2, above.

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 reference to CPMP/EWP/240/95Rev.1 for further details. The ICS alone treatment group could receive the same dose of corticosteroid as in the combination product or alternatively receive a higher dose. A full dossier will be required.

The assessment of the safety of combination products is as for the single active substances and as described above in sections 6.2.3.1 and 6.2.3.2.

In children the development of combination products should be as described above and in previous sections (see sections 6.2.3.1 and 6.2.3.2 above) unless otherwise justified.

Co-packaged combinations (combination packs)
Co-packaged combinations (combination packs) are special entities in inhalation therapy. Combination packs are only acceptable in very exceptional circumstances, taking into account the required justifications set out in the *CPMP/EWP/240/95 Rev.1: Guideline on the Clinical Development of Fixed Combination Medicinal Products.* A co-packaged combination can be justified through improvement of the benefit/risk assessment due to addition or potentiation of therapeutic action of the active substances compared with the single active substance. In the case of accepted and well-established combination therapy, a co-packaged combination can be justified through increased compliance and adherence to therapy when compared with the same therapy administered as separate active substances each administered via separate devices. However the clinical relevance of this improved compliance has to be adequately investigated and proven in the claimed population. Applicants are strongly advised to consult with the relevant national competent authority/EMEA prior to submission regarding the acceptability of the proposed combination pack.

7. CLINICAL TRIALS AND CHANGE OF PHARMACEUTICAL SPECIFICATIONS

Drug product specifications should be set based on pharmaceutical data from the batches used in the clinical studies. Any changes to these specifications (for example, fine particle dose) should also be based on data from clinical batches.

A widening of the specification limits which are clinically relevant cannot be supported at a later date, when therapeutic equivalence has been demonstrated following the completion of appropriate clinical studies, without possibly affecting the conclusions drawn from the clinical programme.

8. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

See section 6.2.1, above.
If clinical studies are carried out in patients with COPD the study proposals discussed above may not be appropriate. The *CPMP Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) CPMP/EWP/562/98* should be considered.

9. CHILDREN AND ADOLESCENTS

It is considered that in the development of orally inhaled products for use in children and adolescents where therapeutic equivalence between two inhaled products must be demonstrated, pharmacokinetic and pharmacodynamic and/or clinical studies are likely to be required. Such studies may be required

across the entire age range of childhood, and may need to be performed separately for each sub-group - less than 2 years, 2 – 5 years and 6-12 years. The clinical development may also include studies in adolescents. Justification will be required for which age groups are studied and which are not.

Data generated in adult populations should not be ignored in the development in children. However there are 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. Therefore 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.

The airway in the younger child differs from the airway in the adult and the amount of the dose of an inhaled drug reaching the lower airway in an infant and in a young child will differ from the amount which would reach the lower airway in an adult. The child displays different breathing patterns and has differing tidal volumes, airway geometry, etc. compared with adults. Resistance and inspiratory flow differ between the older child/adolescent and the younger child.

The characteristics of the delivery device may be such that the device is more difficult for a child to use than it is for an adult and therefore the child is less able to use the device correctly, or the child may use the device differently from an adult. Such differences in the handling of the product by a child may result in a changed risk/benefit relationship in the child compared with that seen in the adult. Examples include the following:

- A pMDI used by a young child is unlikely to be as effective as when used by an adult due to the difficulty the child may have with the device in terms of achieving the same level of co-ordination and with resultant therapeutic failure.

- It is known that the use of a spacer together with a pMDI may increase the amount of the inhaled dose of the drug deposited in the lung by up to 200% depending on the characteristics of the spacer and the child's age and inhaler technique. (Also see section 4.1.3, above and the final paragraph in this section, below).

  When comparing two products administered via pMDIs equivalence may be demonstrated when the pMDI is used without a spacer but not demonstrated when the pMDI is used with a spacer.

- The internal resistance of the DPI may be such that a child will find the inhaler more difficult to use than would an adult. Therefore when comparing two DPIs which may be equivalent in adults, equivalence may not be demonstrated in children who inhale with a lower PIF.

The risk of, and the concerns about, adverse effects differ across different age groups. Children and young adults are more susceptible to the systemic adverse effects and particularly the life-threatening effects of ICSs than older adults. Therefore when comparing two products, which have been shown to be equivalent in adults with regard to systemic safety, differences in the susceptibility to systemic adverse effects in children become relevant. Conversely, local adverse effects are much less common in children than in adults. Differences which might exist between the test and the reference product which may be clinically irrelevant in adults may be clinically relevant in children.

Therefore if the new product is to be used in children and a claim of therapeutic equivalence is to be made assurance that both efficacy and safety in this young age group is appropriate is required. 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 improved compared with that of the reference medicinal product, particularly in respect of systemic safety at the top of the proposed dose range.

If an indication for use in children is sought the following scenarios may arise resulting in differing clinical requirements:

1. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 5.2, above)

   and

   i) the inhalation device of the test product is identical to that of the reference product which is approved in the intended paediatric population

   or

   ii) the pharmaceutical dosage form of the test product is a pMDI with the **same** spacer as recommended for use with the reference product when administered via a pMDI and which is approved in the intended paediatric population

   clinical studies in children **will not** be required.

2. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 5.2, above)

   but

   the inhalation device of the test product is **not** identical to that of the reference product; however the reference product is approved in the intended paediatric population and the inhalation device of the test product is approved in the intended paediatric population containing another active substance,

   clinical studies in children **may not** be required (**providing** 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 – see sections 4.4 and 5.2, above). If there are differences in flow rate dependency between the test and reference products, therapeutic equivalence in children has to be demonstrated through appropriate studies (see section 6.2 above).

3. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 5.2, above)

   but

   i) the inhalation device of the test product is **not** identical to that of the reference product which is approved in the intended paediatric population

   and

   ii) the inhalation device of the test product is approved for use in adults but is **not** approved in the intended paediatric population (it is a new device for use in children),

   as an absolute minimum clinical requirement a handling study in this young age group will be required to ensure that, for example, the child is able to generate the minimal PIF to trigger the inhalation device (see section 4, above). Such a study **must** be supported by comparative *in vitro* data to demonstrate that the test and reference product produce comparable particle size distribution through the flow rate and pressure drop range and air volume which are clinically applicable to children (see sections 4.4 and 5.2, above). If there are differences in flow rate dependency between the test and reference products, therapeutic equivalence in children has to be demonstrated through appropriate studies (see section 6.2 above).

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If none of the above apply **clinical development of the product in children will be required.** Demonstration of therapeutic equivalence in respect of both efficacy and safety will be required. Equivalent efficacy must be demonstrated through appropriate pharmacodynamic and/or clinical

efficacy studies (either bronchodilatation studies, studies to assess improved airway function or bronchoprotection studies, see section 6.2, above). Clinically validated and relevant age-dependent efficacy variables (both primary and secondary as necessary) 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.

Equivalent safety must also be demonstrated. Systemic safety should be demonstrated through pharmacokinetic equivalence if this is possible and if justifiable or through pharmacodynamic equivalence, see section 6.2, above. The use of pharmacokinetic data will be dependent on the drug and the quality of the assay and 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. In pharmacodynamic assessments inhalation of the maximum recommended total daily dose regimen, together with the assessment of a lower dose regimen, over an appropriate time period dependent on the active substance (see section 6.2, above) will be required

It is essential to demonstrate that the study has assay sensitivity and the ability to confirm that the test and the reference products are therapeutically equivalent.

If differing age groups of children are included within a single clinical study stratification by age group should be carried out within the stud**y.**

For further discussion on the clinical development of orally inhaled formulations in respect of the demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma in children see sections 6.1 and 6.2, above. It should be noted that if therapeutic equivalence is to be demonstrated on a clinical endpoint the equivalence margins should not simply be extrapolated from those used in adults. The justification of the chosen margins should take into account the age of the subjects and the severity of their asthma.

Adolescents
For adolescents aged between 12 and 17 years, interpolation from data generated in studies in adults may be possible if specific studies have been carried out in children less than 12 years of age. 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 studied. Stratification into a 12 to 17 years age group and 18 years and above is not necessarily required; however data generated (both efficacy and safety data) from the two age groups should be documented and analysed separately, if possible.
If studies have not been carried out in children (less that 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population (see sections 6.1 and 6.2, above).

Spacers and Holding Chambers
See section 4.1.3, above.

10. SAFETY OF NEW EXCIPIENTS

The safety profiles of currently used excipients do not raise questions regarding the safety of currently authorised products. However, potential safety concerns do arise, both from the use of new excipients where safety in man following inhalation has not been investigated previously, and also from any possible interactions between these new excipients and the active drug substances, interactions that might enhance toxicity of the active drug substance. A change in excipients might result in changes in drug deposition patterns within the lung which might affect absorption and systemic safety. Full animal toxicology will have been completed for each new excipient but such data will not remove the need for clinical safety studies in man.
The aims of a safety programme in this situation are two fold:

i) to determine the safety of a new excipient in a formulated medicinal product

ii) to assess interactions which may occur between an active drug substance and a new excipient or a new excipient mix which might result in changes in the safety of the medicinal product.

The assessment of a new excipient or a new excipient mix need only be addressed once, but the assessment of interactions will be required for each drug substance combined with that new excipient or new excipient mix. Obviously if changes in absorption or systemic safety are seen in these interaction studies, these changes will need to be quantified and long-term safety assessments of the active drug formulated with that new excipient or new excipient mix may be required.
A change in excipient or the excipient mix will necessitate further long-term safety assessment.

DEFINITIONS

Assay sensitivity	Ability of a clinical trial to distinguish an effective treatment from a less effective treatment or ineffective treatment.
Breath-operated inhalers	Breath-triggered metered dose inhalers for which a patient needs to generate a minimum (trigger-point) airflow value in order for the inhaler to release the aerosol.
Delivered/Emitted dose	Delivered dose is the quantity of drug substance that is available to the user, ex-device, on a per dose basis (i.e. released at the mouthpiece of the device).
Dose/Single dose	Amount of drug administered on a single occasion.
Duration of effect	For example – the time at which FEV_1 has returned towards baseline by at least 85 – 90% from the peak effect.
Linearity	Property of the function of the type f(x)=ax+b, where a and b are numerical constants.
Maximum response	For example - at least a 12% or 15% maximum change in FEV_1.
Metered dose	Metered dose is the quantity of active drug substance contained in the delivery device metering chamber.
Onset of action	For example - an increase in FEV_1 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 FEV_1 is at least 15%.
Reference product	An authorised product against which therapeutic equivalence is claimed.
Relative potency	The relative potency of the test product to the reference product is defined as the dose of the test product that produces the same biological response as one unit of the dose of the reference product (i.e. comparative outcomes for different doses).
Spacer	A spacer may also be referred to as a spacing device and is also known as a valved holding chamber. It aids inhalation.
Strength/dose	Strength is what is metered in the device for a single inhalation manoeuvre whereas a single dose may contain for example 2 puffs of a pMDI or 4 puffs of a pMDI. So, for example, for doses of 12µg and 24µg formoterol pMDI one and 2 puffs of the 12µg strength or two puffs of both the 6µg and 12µg strength might be used.
Single dose study	Single administration of each of the dose levels to be tested.
Product strength	Product strength may be either the delivered dose or the metered dose.
Pulmonary deposition	Amount of active substance deposited in the airways (mouth and throat excluded).

Therapeutic equivalence	Efficacy and safety profile of the test and reference products are sufficiently comparable so that a clinically relevant difference between products can be reliably excluded.

LIST OF ABBREVIATIONS

AUC	Area Under the Curve
BOI	Breath-Operated Inhaler
CFC	Chlorofluorocarbon
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for Proprietary Medicinal Products
DPI	Dry Powder Inhaler
EC	European Commission
ECG	Electrocardiogram
eNO	Expired Nitric Oxide
EWP	Efficacy Working Party
FEV_1	Forced Expiratory Volume in one second
GINA	Global Initiative for Asthma
HPA axis	Hypothalamic Pituitary Adrenocortical Axis
ICH	International Conference on Harmonisation
ICS	Inhaled Glucocorticosteroid
LABA	Long-Acting β_2Adrenoceptor Agonist
OIP	Orally Inhaled Product
$PC_{20}FEV_1$	Provocative Concentration of the Provocation Agent which produces a 20% fall in FEV_1
$PD_{20}FEV_1$	Provocative Dose of the Provocation Agent which produces a 20% fall in FEV_1
PEF	Peak Expiratory Flow
PIF	Peak Inspiratory Flow
PD	Pharmacodynamic
PK	Pharmacokinetic
pMDI	Non-breath-operated (standard) Pressurised Metered Dose Inhaler
PMS Study	Post Marketing Surveillance Study
PROM	Patient Reported Outcome Measure
QoL	Quality of Life
QTc	Time Corrected QT Interval in the ECG
QWP	Quality Working Party
SABA	Short-Acting β_2 Adrenoceptor Agonist

SmPC	Summary of Product Characteristics
sRaw	Specific Airway Resistance