European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 18 October 2007
Doc. Ref. CPMP/EWP/4151/00 Rev. 1

COMMITTEE ON MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

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)

DRAFT AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 October 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2008

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KEYWORDS	Guidance, orally inhaled products

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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 of orally inhaled formulations and variations/extensions to a marketing authorisation 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.

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 either abridged applications or variations/extensions to a marketing authorisation, used in the treatment and management of patients with asthma and/or COPD.

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.

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 medicinal products administered via:

- pressurised metered dose inhalers
- pressurised metered dose inhalers with spacer devices and holding chambers
- 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

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: Note for Guidance on 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 Note for guidance on the investigation of bioavailability and bioequivalence*

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

4. MAIN GUIDELINE TEXT

4.1 INHALATION DEVICES AND CLINICAL REQUIREMENTS

Propellant-containing 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 clinical documentation in respect of these devices are presented below.

4.1.1 Pressurised metered dose inhalers

Pressurised metered dose inhalers (pMDIs) contain different propellants and other excipients, and may use different valve 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 spacing devices remove the need for such co-ordination. Spacing devices are considered necessary for use with all pMDIs, and should always be used when a pMDI is used by a child. Appropriate data to support the use of a specific named spacing device 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 4.1.1.2).

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). Generation of extended safety data may be necessary. In respect of safety, local tolerability must be assessed and any evidence of increased bronchial hyperreactivity or paradoxical bronchospasm must be sought. It may be necessary to also assess any effect that the new propellant or excipient may have on mucociliary clearance.

4.1.1.1 Breath-operated inhalers

A minimal peak inspiratory flow rate (PIFR) is required to trigger a breath-operated inhaler (BOI) and if this minimal PIFR cannot be achieved by the patient, inhaler use will be unsuccessful. Therefore, the clinical programme has to include relevant data regarding the PIFR required to trigger the BOI and discussion of those patient groups who would normally be able to produce a sufficient PIFR to trigger the device and those patient groups who may have problems (for example patients with severe asthma, patients suffering from an acute attack of asthma, small children, etc). The relevant patient population must be adequately investigated and subsequently 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. However it must be demonstrated that the target populations can generate the same flow rates through the BOI and pMDI and therefore that all patients can trigger both devices successfully (see section 4.2).

For inhalers that can be breath-operated and hand-operated patients need an explanation in the package leaflet as to how to recognise an inadequate breath-operated inhalation and how and when to switch to a hand-operated inhalation procedure. The two modes of action should be compared using the parameters outlined below (see section 4.2) to determine whether there is a need for clinical data to support each method of inhalation.

4.1.1.2 Spacing devices and holding chambers

Spacing devices are usually expected to facilitate inhalation via a pMDI and decrease the amount of medicinal product deposited in the mouth and pharynx and subsequently swallowed. The use of a spacing device 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.

Any one specific spacing device may perform differently with different actives and similarly, any one specific active in a specific pMDI may perform differently if inhaled through different spacing devices. Therefore the ability to change from one spacing device to another or to use the same spacing device with different pMDIs cannot be assumed. The development of a pMDI should always include the testing of at least one specific named spacing device for use with the particular pMDI containing a particular active. This spacing device has to be appropriate for the intended patient population.

The behaviour of the spacing device 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 spacing device 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 spacing device before and during use.

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

If the product is to be administered with and without a spacing device, the use of the product alone as well as the use of the product with the device must be supported by appropriate *in vitro* or *in vitro* and clinical data (see sections 4.2 and 4.3 below). If these data are not in line with the criteria described in section 4.3, 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 spacing device on efficacy and safety.

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).

If the spacing device is to be replaced subsequently by an alternative spacing device *in vitro* characterisation of the new device may be sufficient to demonstrate comparability with the previous device; however depending on the active substance this may not be appropriate and further clinical development may be required (see sections 4.2 and 4.3, below).

The appropriately investigated spacing device(s) has to be specifically named in the SPC Section 4.2, the package leaflet, any product promotional material and possibly also on the product labelling.

4.1.2 Dry powder inhalers

In contrast to the pMDI 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.

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.

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 populations studied in the clinical programme. Extrapolation to patient populations other than those populations studied in the clinical programme is not then appropriate and marketing authorisations will be restricted appropriately. For all DPIs the patient population in whom the inhaler can be used should be carefully defined.

The use of a high flow rate dependent DPI as a reference product in a clinical study 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.

4.1.3 Solutions and suspensions for nebulisation

In specific circumstances (for example toddlers, the severely ill patient, the elderly, the disabled) inhalation of medicinal products *via* a nebuliser, either a jet nebuliser or an ultrasonic nebuliser, is a treatment option for patients with asthma and COPD. Generally nebulisers are sold separately from solutions and suspensions containing active substances for nebulisation and therefore these formulations are often inhaled via an available nebuliser rather than via the nebuliser used during the development of the medicinal products 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 nebulisers for both jet and ultrasonic nebuliser should be considered**.** The nebuliser system used should be described in the protocol in term 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 studied in the development programme should be described in the SPC, package leaflet and product literature and warnings should be included to state that the use of an alternative nebuliser system may alter the pulmonary deposition of active substance and dose adjustment may then become necessary.

Solutions for nebulisation with the same qualitative and quantitative composition as the authorised reference product may be waived of any clinical study, with justification; however *in vitro* equivalence must be demonstrated. For suspensions for nebulisation *in vitro* and clinical equivalence should be demonstrated.

In non-pressurised, pump activated liquid reservoir metered dose inhalers the speed of plume is decreased. In order to get a sufficient amount of active substance the patient has to inhale a specific volume of the aerosol. In patients with a limited inhalational capacity (for example, children) it has to be shown that the volume required to produce a clinical effect does not exceed the inhalational capacity of the patient.

4.1.4 Investigation of additional strengths

Dose linearity in respect of pulmonary deposition 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 cannot be demonstrated with the reference product, either the test product has to be adapted to the reference or therapeutic equivalence needs to be established with more than one strength of the product.

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

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

4.2 PHARMACEUTICAL PROPERTIES AND THE NEED FOR A CLINICAL PROGRAMME

4.2.1 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.

4.2.2 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, etc.)
- The pharmaceutical dosage form is identical
- The active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the solubility
- 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)
- Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product
- The inhaled volume needed to get sufficient amount of active substance should be similar
- The instructions for use of the inhalation device are the same
- The inhalation device has the same resistance to airflow (within +/- 15%)
- The delivered dose is the same (within +/- 15% of labelled claim)

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. 10^{th} percentile), median and maximum (e.g. 90^{th} percentile) achievable flow rate 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. 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 maximum allowable differences, a decision regarding equivalence can be made. The only exemption might be medicinal products for nebulisation (see also section 4.1.3).

If **any of** the above-mentioned criteria are not fulfilled or when equivalence cannot be demonstrated on the basis of the *in vitro* comparison, *in vivo* studies should be performed to substantiate equivalence.

4.3 CLINICAL DEVELOPMENT

4.3.1 Determination of pulmonary deposition

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

Different excipients, different devices or different pharmaceutical quality 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 4.2.2 above), one way to demonstrate equivalence in terms of local availability 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 can be performed in healthy volunteers.

Pulmonary deposition can be investigated by conducting imaging or pharmacokinetic 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, they can demonstrate linear dose-response relationships more easily, they measure total systemic exposure and can separate pulmonary from gastrointestinal absorption and they do not 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 concentrations are not measurable at clinical doses or are near the lower limit of quantification such that results may be highly variable.

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. Otherwise therapeutic equivalence must be demonstrated by means of appropriate clinical studies.

Pulmonary deposition (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.

4.3.1.1 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- or three-dimensional scintigraphic methods can be used. 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. 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. It has to be assured that the radio-labelling of the inhaled products has no influence on the deposition characteristics.

4.3.1.2 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 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. 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.

4.3.2 Pharmacodynamic studies

4.3.2.1 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, will almost always be required and becomes mandatory when equivalence is not shown *in vitro* and is not shown through investigation of pulmonary deposition.

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 kind of device (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 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 authorisation can be granted which will include all therapeutic indications as listed for the reference product.

4.3.2.2 Requirements for clinical studies in patients with asthma

Two different types of pharmacodynamic study provide acceptable methods for investigating therapeutic equivalence of inhaled drugs – studies of bronchodilatation and studies of bronchoprotection. Depending on therapeutic class 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 or bronchoprotection, the trial should be carried out in patients with asthma and who demonstrate reversibility of airway function, as assessed by measurement of forced expiratory volume in one second (FEV_1), of ≥15%, or ≥12% and a 200 ml improvement in FEV_1, 15 minutes after inhalation of an appropriate inhaled short-acting β_2 adrenergic agonist (SABA).

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 differences which might exist between the two products. Relative potency is considered a sensitive way of detecting differences between products and therefore is recommended. Demonstration of therapeutic equivalence on the y-axis could also be acceptable providing that the assay sensitivity is demonstrated indisputably. To enhance assay sensitivity it is recommended that the following be considered:

- Inclusion of less than optimally controlled symptomatic asthmatic patients (according to GINA Guidelines 2006) in studies of bronchodilatation.
- In general and unless otherwise justified, demonstration of assay sensitivity will require testing more that one dose of both the test and the reference products.
- Use of doses at the lower end of the recommended dose range (on the steep part of the dose-response curve).

Patients recruited to the study should be able to demonstrate a clinically relevant response to treatment.

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. The highest recommended dose has to be administered when assessing safety. However safety analyses should be included in the efficacy studies regardless of the dose being studied whenever possible. 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:** If the relative potency approach is used the 95% confidence interval for the primary endpoint must be contained entirely within 80 – 125 %.
- **Safety:** If possible bioequivalence in respect of systemic exposure should be demonstrated (the 90% confidence interval must be contained entirely within 80 – 125%). Otherwise equivalence in respect of relevant pharmacodynamic safety variables needs to be demonstrated. Also there should be no evidence that the test product is worse than the reference product in respect of changes in vital signs, biochemical parameters, frequency of adverse events.

4.3.2.2.1 Bronchodilatation studies

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.

4.3.2.2.2 Bronchoprotection studies

The bronchoprotective potency of a drug to provide protection against hyperresponsiveness 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 (for example choice of provocation, aerosol generation, nebuliser output, inhalation procedure, physical aspects, exclusion of diurnal variation, etc). It is recommended that the ATS Guideline be considered in this regard. Generally a double blind, double dummy, crossover study design 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. At least two dose levels should be studied.

The use of bronchial challenge as a means of assessing therapeutic equivalence will depend on the therapeutic class of the test product.

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

4.3.2.3.1 Bronchodilators

Inhaled bronchodilators fall into three categories - short-acting β_2 adrenoceptor agonists (SABAs), long-acting β_2 adrenoceptor agonists (LABAs) and anticholinergics.

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 therapeutic equivalence. In the bronchodilatation model an appropriate primary variable will be the FEV_1AUC; in the bronchial challenge study the primary variable will be either the $PC_{20}FEV_1$ or $PD_{20}FEV_1$ (see 4.3.2.2.2, above).

In these therapeutic equivalence studies the safety of SABAs should be investigated through bioequivalence based on pharmacokinetic data following administration of a single dose and also through documentation of adverse events and vital signs, assessment of any evidence of paradoxical bronchospasm and recording of laboratory parameters. If conclusions cannot be drawn from such investigations cumulative dose clinical studies may also be used in the assessment of safety.

Long-acting β_2 adrenoceptor agonists

Initial requirements in the assessment of therapeutic 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 (defined as a FEV_1 increase of 15%, or 12% and 200 ml, from baseline), the maximum response and the longer duration of effect of the LABA must be taken into consideration in the design of the study. In the bronchodilatation model the primary variable will be the FEV_1AUC; in the bronchial challenge study the primary variable will be either the $PC_{20}FEV_1$ or $PD_{20}FEV_1$.

An appropriate washout time between treatments has to be defined in any crossover design and justified in the protocol. Baseline measurements prior to each treatment period have to be documented to assess any possible carry-over effect.

The dose range should be explored in the single dose studies with assessment of low and high doses to enable demonstration of dose-response.

Safety of LABAs should be investigated through bioequivalence based on pharmacokinetic data and by measurement of biochemical parameters (including measurements of serum potassium and plasma glucose), recording of adverse events, vital signs and serial ECGs and measurement of the QTc interval, and assessment of any paradoxical bronchospasm. The safety profile must be defined for the maximum recommended dose regimen.

Anticholinergic drugs

The investigation of therapeutic equivalence in respect of 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 preferred provocation agent would be methacholine.

4.3.2.3.2 Inhaled glucocorticosteroids

The demonstration of therapeutic equivalence of inhaled glucocorticosteroids (ICS) is difficult. A successful therapeutic equivalence study requires demonstration of a significant dose-response relationship with the study of at least two doses of the test compared with, if possible, two doses of the reference product. There are certain circumstances when the use of excessive multiple actuations are required to achieve the required dose. This may result in unacceptable impact on the patient/volunteer (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 proportionality from the different strength products should be fully demonstrated.

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 doing so must be justified by the Applicant.

An alternative is the crossover study, a study design which has the advantages of the ability to study a much smaller population and the ability to detect within-subject variability; 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 may outweigh the advantages unless the impact of any carry-over effect can be controlled. Carry-over effects between treatment periods must be at least equal.

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 (see section 4.3.2.2.1). The population included should be as homogeneous 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. However the population should also be the target population.

The primary efficacy variable should be a pulmonary function measure and preferably FEV_1 measured regularly, if possible daily at home or at least every two weeks in the clinic. [Regular measurement of FEV_1 is a more sensitive measure of pulmonary function than peak expiratory flow rate (PEFR) which should be recorded daily at home as a secondary efficacy variable]. Electronic diary cards should be used if at all possible. Symptom scores, frequency of use of *reliever/rescue* medication and exacerbations should be recorded as secondary endpoints. Other efficacy variables which may be considered include PC_{20}, PD_{20}, expired nitric oxide (eNO), sputum eosinophils. Whatever primary efficacy variable is chosen should be justified based on its sensitivity to detect differences between

adjacent doses of the inhaled corticosteroid. The duration of treatment periods should be at least eight (if not twelve) weeks, any shorter treatment period should be justified.

Equivalent safety or an improved safety profile must be demonstrated. Appropriate safety monitoring within the therapeutic efficacy studies would include the recording of local adverse effects and any evidence of paradoxical bronchospasm and the assessment of systemic effects.

In addition, specific safety investigations must be carried out following inhalation of the maximum recommended daily dose of the ICS regularly over time in both adults and children. If possible systemic safety should be demonstrated through pharmacokinetic bioequivalence and measurement of pharmacodynamic parameters in adults and children.

The current view in respect of the measurement of systemic effects of ICSs is to assess the effect on the hypothalamic pituitary adrenocortical (HPA) axis in adults and on the HPA axis and/or on lower leg bone growth rate in children. Knemometry is validated, accurate and reproducible and has been used previously in the early assessment of systemic safety of ICSs in children.

In assessing the HPA axis in adult patients one option is the 24-hour urinary-free cortisol, if possible coupled with repeated measures of plasma cortisol over 24 hours. Such assessments should be made at least at the beginning and end of the eight- (or twelve-) week study.

A second and more robust alternative in adult patients, the repeated assessment of the change from baseline in 24-hour plasma cortisol as measured by AUC as the primary variable coupled with the change from baseline in 24-hour urinary-free cortisol as a secondary variable is an acceptable way to assess systemic effects of the ICSs.

A further alternative method of assessment of systemic effects on the HPA axis in adults, and an even more robust assessment and a more preferred assessment, is the study of a population of normal healthy volunteers with evaluation of HPA axis function using the ACTH (Synacthen) short stimulation test. Such a study would require treatment of healthy volunteers with a total daily dose of ICS at the upper limit of the proposed dose range over a treatment period of at least four weeks. The measurement of plasma cortisol over 24 hours at intervals during the study could be incorporated into this type of study.

Generally it is not felt to be appropriate to subject children to repeated venopuncture and therefore pharmacokinetic studies and the repeated measurement of plasma cortisol have not been used as first line methods to assess the systemic burden of ICSs in this young age group. However in the light of the very real need to ensure the systemic safety of these drugs in children and the acceptance that other methods to assess the systemic load are far from robust or even satisfactory, the use of an indwelling cannula to enable the collection of blood samples to measure both blood levels of the drug and any active metabolites and plasma cortisol at intervals over time should be considered. This approach may represent the best way of collecting reliable information on comparative systemic safety in children with asthma treated with ICSs. The ACTH short stimulation test is not recommended and should not be used for the assessment of the systemic effects of ICSs in children [Further discussion on the requirements for therapeutic equivalence studies in children will be addressed in appendix 1 (public consultation expected Q1 2008) – see section 4.6].

Whatever methods of assessing systemic effects of ICSs are used they should be fully discussed 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.

4.3.2.3.3 Combination products

For fixed combination products of known active substance therapeutic equivalence 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, 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 4.3.2.3.1 and 4.3.2.3.2, 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 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.

The assessment of the safety of combination products is as for the single actives and as described above in sections 4.3.2.3.1 and 4.3.2.3.2.

4.3.2.3.4 Sodium cromoglycate and nedocromil sodium

For sodium cromoglycate and nedocromil sodium therapeutic equivalence in terms of efficacy and safety can be obtained from bronchial challenge studies.

4.4 CLINICAL TRIALS AND CHANGE OF PHARMACEUTICAL SPECIFICATIONS

Pharmaceutical drug product specifications should be set based on pharmaceutical results of the batches used in the clinical studies. Any changes to these specifications (for example, fine particle dose) should also be based on data supported by clinical batches.

A widening of the specifications 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 original clinical programme.

4.5 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

See section 4.3.2.1, 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.

4.6 CHILDREN

See appendix 1 (public consultation expected Q1 2008).

4.7 SAFETY OF NEW EXCIPIENTS

The safety profiles of active drug substances as currently formulated are not in question. 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 mix in a formulated medicinal product

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

The assessment of 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 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 in that excipient mix may be required.

A change in excipient mix will necessitate further long-term safety assessment.

DEFINITIONS

Dose	Amount of drug administered at single occasion
Delivered/Emitted Dose	Dose released at the mouthpiece of the device
Linearity	In this context a function of f(x)=ax+b, with a=1 and b=0 is not necessary.
Metered Dose	Dose released from the valve
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
Spacing device	Also called a holding chamber
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 doses of 12 and 24 µg formoterol pMDI one and 2 puffs of the 12 µg strength or two puffs of both the 6 µg and 12 µg strength might be used.
Pulmonary Deposition	Amount of active substance deposited in the airways (mouth and throat excluded)