REPLACEMENT OF CHLOROFLUOROCARBONS (CFC) IN METERED DOSE INHALATION PRODUCTS

Guideline Title	**Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products**
Legislative basis	**Council Regulation No 594/91 as amended, Directive 75/318/EEC as amended**
Date of first adoption	**December 1993**
Date of entry into force	**December 1993**
Status	**Last revised 1993**
Previous titles/other references	**None/ III/5378/93**
Additional Notes	**This guideline is intended to facilitate companies in compiling the dossier for submission for the replacement of a CFC propellant in an already authorised medicinal product. It identifies the considerations of quality, safety and efficacy which should be taken into account. The need for this guideline has been accentuated by the imminent lack of availability of existing replacements for CFC propellants for these important medicinal products.**

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1. INTRODUCTION

Chlorofluorocarbon (CFC) propellants are currently under discussion because of their deleterious effect on the ozone layer. CFCs and halons have a high resistance to biotic and abiotic decomposition and pass into the atmosphere undecomposed, and slowly ascend to the stratosphere. Current scientific knowledge on the possible destruction of the ozone layer, and the harmful effects that can thereby be anticipated, has been presented at recent international conferences.

There is an international consensus that significant reductions are necessary in both the production and the consumption of substances which deplete the ozone layer. Thus all member states and the Community have become parties to the Vienna convention for the protection of the ozone layer and the Montreal protocol on substances that deplete the ozone layer.

Council Regulation (EEC) No 594/91 as amended by Council Regulation (EEC) No 395/92 of 29 December 1992 prescribes a schedule for the phasing-out of substances that deplete the ozone layer. This includes schedules for the limitation and prohibition of the importation, exportation, production, and supply of chlorofluorocarbons and products containing them.

Many pharmaceutical products on the market contain CFCs as propellants and, in accordance with the regulations, companies will be reformulating their products to replace the CFC propellants with a suitable alternative. In the event that the replacement contains a new propellant (excipient) not previously authorised, the provisions of Directive 75/318/EEC as amended, apply.

This guideline has been prepared to facilitate companies in compiling the dossier for submission for the replacement of a CFC propellant in an already authorised medicinal product, and identifies the considerations of quality, safety and efficacy which should be taken into account. The need for this guideline has been accentuated by the imminent lack of availability of existing replacements for CFC propellants for these important medicinal products. It mainly addresses MDIs for the management of asthma and other chronic obstructive airway diseases. However, in principle it could be followed for inhalation products used for other therapeutic indications.

Appropriate expert reports should be submitted in support of the marketing authorisation, using the format given in the Notice to Applicants. At the request of the company the assessment of the product could be co-ordinated between member states.

Data are required to show that the new and the old products are at least therapeutically equivalent.

2. PHARMACEUTICAL REQUIREMENTS

2.1 New Propellant Specification

Documentation should be provided for the new propellant(s) taking as a basis the note for guidance on *Chemistry of Active Substances*. A suitable specification should be developed based on the quality of batches used in the toxicological tests.

2.2 Container and valves

Information should be provided if new containers and/or valves are used for the new formulated product.

2.3 Active substance

It is expected that the same active substance specification will be applied, particularly with regard to particle size specification. Any changes required because of reformulation should be justified and fully discussed in the pharmaceutical expert report.

Changes in the state of solvation (or desolvation) of the active substance should be investigated and the physical-chemical problems which arise if such a change is observed (e.g. crystal growth on storage) should be addressed.

2.4 Finished Product

The points listed below are not a comprehensive list of items to be addressed or specifications to be included. They include those issues which should be addressed in all cases and on which guidance may be required. This information should be given according to Part II A4 (Pharmaceutical development) and should be included in the stability protocol as outlined below. Sufficient canisters should be tested to give confidence in the results.

The following investigations on the finished product are intended to ensure whether the specifications of the already authorised product have to be changed or not. Any changes should be justified.

2.4.1 Moisture Content

The moisture content of the formulation should be evaluated and if necessary controlled because of its possible effect on stability and spray pattern.

2.4.2 Extractables

Data should be provided by the applicant demonstrating the extent of extraction of components into the formulation from the valve and container, monitored at least as long as the extraction reaches an equilibrium.

Information should also be provided on any processes used for the pre-extraction of materials from valve components prior to use. Such processes should be shown to produce the required end product consistently.

2.4.3 Priming Shots

The need for priming shots should be addressed: .

– before first use of the canisters

– after a time period typically allowed to elapse between doses as stated in the labelling

– after an extended period of non-use (3-5 days).

2.4.4 Amount Delivered

The amount of active substance delivered from the valves should be determined using the BP test for "content of active substance". This should be evaluated at the start (excluding priming shots if necessary) and at the end of the nominal (labelled) number of shots in the can.

2.4.5 Uniformity of Content

The uniformity of content per actuation ex valve or ex actuator should be reported and must be based on the assay of individual shots. If the canister contains a solution, the uniformity test can be performed as a weight determination of individual shots. The delivery should be assessed at the start and at the end of the nominal number of shots in the can.

The uniformity should also be assessed from the last nominal shot to exhaustion of the canister.

The following test is considered suitable:

Select 10 canisters from each of the valve up and down orientations of storage. Assay one shot from the start (excluding priming shot if necessary) and the end of the nominal (labelled) number of shots of each of the 10 containers.

The content of active of each shot should be < ± 25% of the mean.

If not more than 6 of 40 contents are > ± 25% of the mean but not more than ± 35%, test a further 10 canisters from each of the valve up and the valve down orientations.

Not more than 6 of 80 contents should be >+ 25% of the mean but not more than 35%.
The mean content of the shots as determined in this test should be within + 10% of the labelled claim.

2.4.6 Deposition of the emitted dose

The particle size distribution of the active substance in the aerosol should be evaluated by the determination of the deposition of the emitted dose using samples from the start and end of nominal shot content and to the point of exhaustion of the container.

Data from a multistage impinger is preferred showing calculation of respirable fraction, aerodynamic mass median diameter and geometric standard deviation. Additional data from the deposition of active substance using the twin impinger apparatus (B.P. App. XVII C Apparatus A) should be provided.

The amount retained by the actuator/mouthpiece should be evaluated. From the; data provided, it should be possible to draw up a mass balance sheet of the active substance. The use of other methods should be justified.

The finished product specification should contain suitable limits of the derived parameters based on the batch used in in-vivo trials.

Significant changes in these parameters over the shelf life of the product may need to be supported by in-vivo bioequivalence data.

2.4.7 Stability

Sufficient real-time data should be provided to assess product stability over the shelf life of the product. Data from at least two batches should be reported. In designing stability trials, the product should be stored in the valve-up and the valve-down orientations of storage at fixed conditions of temperature and humidity and cycling conditions. Data should be presented separately for both orientations.

The following information is required as discussed below:

– all items mentioned under 2.4.1-2.4.6. Data from each test need not be presented at each testing point but sufficient data should be generated in the protocol to give confidence in the stability of the product.

– information of content of active substance and decomposition products.

The characteristics of the formulation, the inner surface of the container and the leaching should be evaluated. Also the leakage of the contents from the container should be determined. If necessary suitable specifications should be established.

3. PRECLINICAL REQUIREMENTS

The safety of any new propellant shall have been suitably demonstrated as required by Directive 75/318/EEC as amended, where it refers to the development of new excipients.

The safety studies should have been carried out on batches of the excipient (propellant) that contained the impurities listed in the specification and at dose levels that allowed greater exposure of the test animals to these impurities than will occur in patients.

The contribution of animal model testing to the safety assessment of any individual active substance will be known from previous formulations. There thus remains the need to consider what preclinical studies could be appropriate to “bridge” the gap of knowledge between the databases for existing products and the potential new products containing a propellant plus other excipients.

In cases in which sufficient human safety data are available, preclinical studies may not be necessary.

Two aspects of safety are considered in this guideline - local effects and any possible systemic action that could differ from known data. The type of information required to give reassurance on safety and that can be usefully generated in animal models, is indicated. The design of studies to achieve this information may vary to accommodate the needs of individual active substances and formulations.

3.1 Local effects

It is possible that combining a known active substance with a new propellant system could produce interactions that result in an irritant or potentially hazardous formulation when applied to the respiratory system. Because a proportion of a dose intended for inhalation will also enter

the upper gastrointestinal tract, any new formulations should also be appropriately safe for ingestion. Separate oral studies will normally not be necessary.

Animal models may be useful to determine irritation effects or other undesirable consequences such as local retention resulting from inappropriate deposition characteristics. Data to reassure that these effects are unlikely in man could come from inhalation studies in an appropriate animal species. The design of such studies should allow examination of the local tissues involved to demonstrate the absence of significant treatment-related effects of the type described above resulting from inhalation and ingestion.

3.2 Systemic Activity

The testing of new inhalation products in clinical trials should have produced data on the relative absorption of the active substance in comparison with existing authorised products. The kinetic parameter values from plasma or other suitable assays, performed to show comparative systemic exposure, can be used to determine whether the existing safety margins are likely to be eroded. If not, then further animal studies would not be necessary. If so, the resulting safety factor may be reassessed on the basis of existing toxicological data to demonstrate, if possible, that an adequate margin remains. If the exposure has increased to such an extent that the validity of the pharmacology and toxicology (long term – repeated dose and effects on reproduction) has disappeared, it may be necessary to perform further animal studies to re-establish an appropriate reassurance.

3.3 Other Studies

At this time it is not envisaged that testing for mutagenic or carcinogenic potential for a combination of active substances and novel propellant excipients will be required, when each individual component in isolation has been shown not to have these potential effects.

Similarly, single dose studies and pharmacodynamic studies in animals are not considered to be necessary, except where they form a part of the testing for local adverse reactions or may be appropriate to test systemic effects.

Toxicokinetic data may be required to support additional toxicity studies.

4. CLINICAL REQUIREMENTS FOR INHALATION PRODUCTS

The major clinical requirement to be fulfilled is the need to ensure efficacy and safety of the reformulated product and to demonstrate that the change in formulation (e.g. due to change in excipients) has no adverse effect on the benefit-risk ratio to the patients in comparison with the existing CFC-containing products. Demonstration of pharmaceutical equivalence does not remove the need for demonstration of at least therapeutic equivalence.

For new non-CFC-containing products demonstrating equivalence with regard to efficacy can be done in the usual way, taking into account certain statistical considerations (see statistical consideration – 4.1.1). Depending on the active substance, most experience comes from clinical or pharmacodynamic trials. Appropriate examples will be considered in the next sections.

Clinical studies will be expected to establish safety in patients. For efficacy, however, in certain circumstances other studies or models may be appropriate, e.g. pharmacodynamic models,

pharmacokinetic studies, in vivo and/or in vitro deposition studies. These alternatives should be clinically validated.

With regard to safety, the usual issues which arise when an inhalation product is reformulated have to be addressed. In cases where a new unknown excipient is used, specific safety requirements should also be fulfilled. Data on the absorption, distribution, and retention of the new propellant in man following inhalation would be valuable in assessing the likely systemic burden of the propellant.

4.1 Efficacy of the new non-CFC-containing products

The CFC-containing products used in the management of asthma and other chronic obstructive airway diseases fall into two main classes, those with direct bronchodilator action, the $beta_2$ adrenergic agonists and the anticholinergic agents, and those described as disease modifying medicinal products, such as glucocorticosteroids (GCS), sodium cromoglycate (SCG) and nedocromil sodium (NS). The characteristics of these medicinal products and their modes of action necessitate widely different studies in the assessment of therapeutic equivalence/efficacy.

Any additional claim following reformulation must be fully supported.

For most orally administered medicinal products, therapeutic equivalence is shown by demonstrating bioequivalence. The measurement of systemic substance levels following inhalation is not only difficult for some products in the light of the small amounts of substance reaching the small airways and hence being absorbed and available for pharmacokinetic comparisons, but its relevance should be questioned when assessing the clinical efficacy of a substance which is delivered to the lung and where the desired clinical effect is brought about by local action.

Systemic substance levels are important in relation to safety. However, since a significant portion of the systemic level may be derived from non-lung deposition, such pharmacokinetic parameters are less appropriate for determining equivalence than are assessments of efficacy.

For some classes of products the applicant may be able to demonstrate that pharmacokinetic measures are relevant and appropriate to the assessment of both safety and efficacy (see section 4.1.4).

4.1.1 Statistical Considerations in the Assessment of Therapeutic Equivalence

The aim of a therapeutic equivalence trial is to demonstrate that the test product is of comparable efficacy to that of a standard therapy. Therapeutic equivalence is often regarded as a one-sided problem. This is in contrast to bioequivalence trials where it has to be demonstrated that there is no clinically relevant difference in either direction between the test product and the standard therapy.

Though the development of new medicinal products which have superior therapeutic effects is desirable, superiority of the test product to the standard therapy is not usually the primary concern in therapeutic equivalence trials. Therefore, the statistical analysis should primarily demonstrate that the test product is not inferior to the standard therapy by a clinically relevant amount. However, the statistical analysis of a study can in addition be designed to prove the test product to be superior to the standard therapy, after having confirmed that at least no relevant inferiority of the test product exists compared to the standard therapy.

Due attention should be given to formulate the null hypothesis and the alternative hypothesis correctly. Classical hypothesis testing is inappropriate in trials set up to assess therapeutic equivalence.

The determination of the minimally clinically relevant difference is critical, and should be argued on an individual basis. The argumentation should take specific clinical considerations into account. These should include the primary end-point, the statistical model, the indication, the efficacy of the reference product, and the natural course of the disease.

These considerations will in turn influence the sample size calculations which usually are based on the primary end-point, the minimally clinically relevant difference, the type I and the type 11 error levels, which all have to be fixed in the study protocol.

Although the arguments above are formulated from the classical (frequentist) viewpoint, the use of Bayesian or other well-argued approaches is acceptable.

4.1.2 Bronchodilators

For inhaled bronchodilators, demonstration of at least therapeutic equivalence can be obtained from pharmacodynamic, single dose, short term studies:

e.g. demonstration of equivalent dose and time-dependent increases in pulmonary function following single inhaled doses in patients with asthma.

It should be demonstrated in the protocol that the dose used in the trial is such that clinically relevant differences can be shown. Dose-ranging studies will be required if therapeutic equivalence is not shown.

Appropriate safety monitoring should be carried out, including some measure of systemic effect, e.g., heart rate, serum potassium and assessment of paradoxical bronchospasm (see also 4.2).

4.1.3 Glucocorticosteroids

The demonstration of clinical bioequivalence of inhaled glucocorticosteroids is difficult and at this stage in our knowledge the only definitive efficacy studies are the parallel group "head-to-head" direct clinical comparisons, preferably in steroid-naive patients, with demonstration of clinical efficacy based on assessments made by the patient at home, recorded on diary cards, and made at regular, say 2 weekly, intervals in the clinic. Assessments would include pulmonary function measurements, symptoms scores, inhaled bronchodilator requirements and rate of exacerbations, defining beforehand an adequate primary outcome-variable. Studies should address a particular disease severity/dose regimen. The duration of treatment would need to be a minimum period of 4 weeks; longer treatment periods might be advantageous.

Since improvement in patients who are stabilised on corticosteroids is unlikely, the use of such patients is discouraged. However, if patients on corticosteroids must be entered into a trial, the pre-entry criteria, the expected improvement and the size and duration of the trial should be justified.

Single dose allergen challenge studies are artificial compared with natural exposure. There is a body of evidence which would support the use of the late response as a clinical model for the evaluation of potential new therapeutic agents, for early dose-ranging in Phase II studies and for the investigation of basic mechanisms of allergic asthma. However, there is very little information on the reproducibility or dose-dependency of the late response and therefore its use in the demonstration of clinical bioequivalence is extremely limited and would not be appropriate.

Appropriate safety monitoring should be carried out, including some measure of systemic effect, e.g. assessment of hypothalamic pituitary adrenocortical function and assessment of paradoxical bronchospasm (see also 4.2).

4.1.4 Sodium Cromoglycate/Nedocromil Sodium

For sodium cromoglycate and nedocromil sodium an assessment of therapeutic equivalence can be obtained from a single dose pharmacodynamic study looking at the protection afforded against an exercise challenge or other SCG/NS sensitive challenge (for example cold air, metabisulphite, etc.) with appropriate justification of the model in respect of clinical efficacy. Such a study would compare the non-CFC containing product with the CFC-containing product in patients with known exercise-induced asthma or other induced asthmatic response.

Usual safety monitoring will be included in the study protocol (see 4.2).

4.2 Safety of the new non-CFC-containing Products

The safety profiles of the active substances as currently formulated are not in question. However, potential safety concerns do arise, both from the use of new excipients, including the new non-CFC-containing propellants, where safety in man following inhalation has not been investigated previously, and also from any possible interactions between these new excipients (including propellants) and the active substances, interactions which might enhance toxicity of the active substance. We should also be aware that the change in excipients (including propellants) might result in changes in product deposition patterns within the lung which might affect absorption and systemic safety.

Full animal toxicology will have been completed for each new excipient (see 3) but such data will not remove the need for clinical safety studies in man.

The aims of the safety program are twofold:

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 substance and an excipient mix which might result in changes in the safety of the medicinal product.

The safety of a new excipient mix need only be addressed once, but the assessment of interactions will be required for each substance combined with that new excipient mix (including new propellants). 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 product formulated in that excipient mix may be required.

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

4.2.1 Assessment of clinical safety of the new excipients (including propellants) in the formulated medicinal product

These studies will be large safety studies and are needed primarily to assess the safety of the new excipients (including the new propellants) in the formulated medicinal product.

Repeated dose comparative prospective studies will be required and the double-blind comparison has obvious advantages over the open design, resulting in a more definitive safety statement. The new non-CFC-containing product should be compared with the authorised CFC-containing product in a controlled randomised study over a treatment period of 3 months prior to marketing.

The trials should be set up in such a way that it is clear that the patients who complete them are representative of the whole patient population. The study design should be such as to encompass an assessment of the changeover from the original CFC-containing product to the new non-CFC-containing product.

Adverse event and haematological and biochemical monitoring should be undertaken in all safety studies, together with specific assessments, pertinent to the substance, to look for local and systemic effects which might not necessarily be recorded as, or manifest themselves as, adverse events. The designs should incorporate assessment of cough, wheezing and bronchospasm following inhalation and attempt to look at the incidence of this potentially dangerous/life threatening adverse effect. Proposals should be put forward to monitor the introduction of the new non CFC products in order to identify rare and unexpected adverse effects. A method such as the use of record linkage schemes should be considered, as these could provide a means for prospectively monitoring the new non CFC products against historical data relating to the products using CFC propellants.

(Careful observation of patients and a specific assessment of cough, wheezing and bronchospasm on first administration of the product during the first clinic visit, paying particular attention to the time to onset of any effect, could also be useful. Specific questioning and assessment of paradoxical bronchospasm would be appropriate in single dose studies and after the first dose of each limb in crossover studies.)

4.2.2 The assessment of clinical safety following re-formulation to assess any possible interactions between the substance and the new excipients

These studies will be of shorter duration and will be required for all inhaled products which have undergone re-formulation as described. These much shorter clinical safety studies are essentially looking at any possible interactions between the new excipients and the active substance, interactions which might result in changes in product safety.

Similar safety assessments, as described under 4.2.1 should be made but with specific emphasis on assessments to pick up acute toxicity, bronchospasm following inhalation and enhanced systemic activity. Monitoring should be focused on the known adverse event profiles of the CFC-containing product to assess change in these profiles as a consequence of the use of new excipients, together with attempting to identify new and unexpected effects.

Detailed safety studies are required; comparative efficacy assessments could be built into the designs as described in 4.1.3 above and might also include assessments of bronchial reactivity. In this way, efficacy and (short-term) safety can be assessed in the same study, with assessments based on clinical endpoints. Such studies might be one month comparative studies (CFC vs. non-CFC) of appropriate sample size. They would require careful statistical input to ensure adequate size and power to detect any clinically important differences between treatments in respect of safety.

4.3 Studies in children

The profile of the non-CFC-containing products following administration to children under 12 years must also be addressed.