DECISION

No. 3/09.03.2007

on approval of Guidelines on replacement of chlorofluorocarbons in metered dose inhalation medicinal products

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 485/09.05.2005, modified and completed through Minister of Health Orders No. 159/22.02.2006, No. 1599/12.12.2006 and No. 395/27.02.2007, reunited on summons of the National Medicines Agency President in the ordinary meeting of 09.03.2007, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Article 1. – The Guideline on replacement of chlorofluorocarbons in metered dose inhalation medicinal products, according to the Annex, which is integral part of this decision, is approved.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on replacement of chlorofluorocarbons in metered dose inhalation medicinal products

CHAPTER I
Introduction

This Guideline represents a translation into Romanian and an adaptation of the CPMP Guideline III/5378/93, "Replacement of Chlorofluorocarbons (CFC) in metered dose inhalation medicinal products" from 1993. While during this period significant developments of the monographs on the inhalation preparations mentioned in the European Pharmacopoeia have taken place, certain provisions of the European Guidelines have become anachronic in relation with actual standards, therefore, where applicable, provisions of this Pharmacopoeia were referred to. These were adopted within Romania through the Xth edition of the Romanian Pharmacopoeia, 2004.

Chlorofluorocarbon (CFC) propellants have been taken into consideration at the end of the 80s and the beginning of the 90s 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 international conferences organised during that period.

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 Warsaw 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 3093/94/EC on substances that deplete the ozone layer have introduced a schedule in order to gradually remove these substances. This includes schedules for the limitation and prohibition of the importation, exportation, production and supply of chlorofluorocarbons and products containing them.

Many pharmaceutical medicinal products on the market contain CFCs as propellants and, in accordance with the regulations, companies will be reformulating these medicinal 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 2001/83/EC as amended, apply.

The European Guideline on the "Replacement of Chlorofluorocarbons in metered dose inhalation products" 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 medicinal 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 medicinal product could be co-ordinated between member states.

Data are required to show that the new (CFC excepted) and the old medicinal products are at least therapeutically equivalent.

CHAPTER II
Pharmaceutical requirements

II.1. **New Propellant Specification**

Art. 1. - Documentation should be provided for the new propellant(s) taking as a basis the note for guidance 3AQ5a/1987 on *Chemistry of Active Substances*; a suitable specification should be developed based on the quality of batches used in the toxicological tests.

II. 2. **Container and valves**

Art. 2. - Information should be provided if new containers and/or valves are used for the new formulated product.

II.3. **Active substance**

Art. 3.- (1) It is expected that the same active substance specification will be applied, particularly with regard to particle size specification.

(2) Any changes required because of reformulation should be justified and fully discussed in the pharmaceutical expert report.

Art. 4. - 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.

II.4. **Finished medicinal product**

Art. 5. - (1) 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 scientific guidance may be required.

(2) This information should be given according to point 3.2.2.2. "Pharmaceutical development" from the Minister of Public Health Order No. 906/2006 on approval of norms and analytic, pharmaco-toxicologic and clinical protocols on the testing of medicinal products and should be included in the stability protocol as outlined below.

(3) Inhalation medicinal products should correspond to provisions in the monograph called „Inhalation preparations" from the edition in force of the European Pharmacopoeia.

(4) The use of other methods should be justified.

(5) Specifications of the finished medicinal product should contain adequate limits of the parameters derived based on the batch used on *in vivo* studies.

(6) It may occur that some significant changes of these parameters during the availability period of the medicinal product should require the support of *in vivo* bioequivalence.

(7) The purpose of tests mentioned in the European Pharmacopoeia, as well as the tests below, which should be carried out on the finite medicinal product, is verification

whether specifications of already authorised medicinal products must be modified or not; any change should be justified.

II.4.1. **Water content**

Art. 6. - The water content of the formulation should be evaluated and if necessary controlled because of its possible effect on stability and spray pattern.

II.4.2. **Container and valves**

Art. 7. - (1) The applicant should provide data 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.

(2) 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 finite product consistently.

II.4.3. **Priming shots**

Art. 8. - The need for priming shots should be addressed:

a) Before first use of the recipients;

b) after a time period typically allowed to elapse between doses as stated in the labelling;

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

II.4.4. **Stability**

Art. 9. - (1) Sufficient real-time data should be provided to assess product stability over the shelf life of the medicinal product.

(2) Data from at least two batches should be reported.

(3) In designing stability trials, the medicinal 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.

(4) Data should be presented separately for both orientations.

Art. 10. – The following information should be provided:

a) all items mentioned under II.4., (data from each test need not be presented at each testing point); yet, sufficient data should be generated in the protocol to give confidence in the stability of the medicinal product;

b) information of content of active substance and decomposition products.

Art. 11. - (1) The characteristics of the formulation, the internal surface of the recipient and the extraction of the content must be evaluated.

(2) Likewise, the loss of content from the recipient, due to non-tightness.

(3) If necessary, adequate specifications should be established.

CHAPTER III
Preclinical requirements

Art. 12. - The safety of any new propellant shall have been suitably demonstrated as required by Directive 2001/83/EC as amended, where it refers to the development of new excipients.

Art. 13. - 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.

Art. 14. - (1) The contribution of animal model testing to the safety assessment of any individual active substance will be known from previous formulations.

(2) There thus remains the need to consider what preclinical trials could be appropriate to bridge the gap of knowledge between the databases for existing medicinal products and the potential new medicinal products containing a propellant plus other excipients.

Art. 15. - In cases in which sufficient human safety data are available, preclinical trials may not be necessary.

Art. 16. - (1) Two aspects of safety are considered in this guideline - local effects and any possible systemic action that could differ from known data.

(2) The type of information required to give reassurance on safety and that can be usefully generated in animal models, is indicated.

(3) The design of studies to achieve this information may vary to accommodate the needs of individual active substances and formulations.

III.1. **Local effects**

Art. 17. - (1) 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.

(2) 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.

(3) Separate oral studies will normally not be necessary.

Art. 18. - (1) Animal models may be useful to determine irritation effects or other undesirable consequences such as local retention resulting from inappropriate deposition characteristics.

(2) Data to reassure that these effects are unlikely in man could come from inhalation studies in an appropriate animal species.

(3) 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.

III.2. **Systemic activity**

Art. 19. - (1) The testing of new inhalation medicinal products in clinical trials should have produced data on the relative absorption of the active substance in comparison with existing authorised medicinal products.

(2) 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.

(3) If not, then further animal studies would not be necessary.

(4) 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.

(5) 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.

III.3. **Other studies**

Art. 20. - (1) 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.

(2) 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.

Art. 21. - Toxicokinetic data may be required to support additional toxicity studies.

CHAPTER IV
Clinical requirements for inhalation medicinal products

Art. 22. - (1) The major clinical requirement to be fulfilled is the need to ensure efficacy and safety of the reformulated medicinal 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.

(2) Demonstration of pharmaceutical equivalence does not remove the need for demonstration of at least therapeutic equivalence.

Art. 23. - (1) For new non-CFC-containing medicinal products, demonstrating equivalence with regard to efficacy can be done in the usual way, taking into account certain statistical considerations (see IV.1.1).

(2) Depending on the active substance, most experience comes from clinical or pharmacodynamic trials.

(3) Appropriate examples will be considered in the next sections.

Art. 24. - (1) Clinical trials will be expected to establish safety in patients.

(2) 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.

(3) These alternatives should be clinically validated.

Art. 25. - (1) As far as the safety is concerned, the usual issues which arise when an inhalation medicinal product is reformulated have to be addressed.

(2) In cases where a new unknown excipient is used, specific safety requirements should also be fulfilled.

(3) 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.

V.1. **Efficacy of the new non-CFC-containing medicinal products**

Art. 26. - (1) The CFC-containing medicinal products used in the therapeutic management of asthma and other chronic obstructive airway diseases fall into two main classes, those with direct bronchodilator action, the beta2 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).

(2) The characteristics of these medicinal products and their modes of action necessitate widely different studies in the assessment of therapeutic equivalence/efficacy.

(3) Any additional claim following reformulation must be fully supported.

Art. 27. - (1) For most orally administered medicinal products, therapeutic equivalence is shown by demonstrating bioequivalence.

(2) The measurement of systemic substance levels following inhalation is not only difficult for some medicinal 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.

Art. 28. - (1) Systemic substance levels are important in relation to safety.

(2) 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 the efficacy assessments.

Art. 29. - For some classes of medicinal 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 IV.1.4).

IV.1.1. **Statistical considerations in the assessment of therapeutic equivalence**

Art. 30. - (1) The purpose of a therapeutic equivalence trial is to demonstrate that the test medicinal product is of comparable efficacy to that of a standard therapy.

(2) Therapeutic equivalence is often regarded as a one-sided problem.

(3) 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 medicinal product and the standard therapy.

Art. 31. - (1) Though the development of new medicinal products which have superior therapeutic effects is desirable, superiority of the test medicinal product to the standard therapy is not usually the primary concern in therapeutic equivalence trials.

(2) Therefore, the statistical analysis should primarily demonstrate that the test product is not inferior to the standard therapy by a clinically relevant amount.

(3) However, the statistical analysis of a study can in addition be designed to prove the test medicinal product to be superior to the standard therapy, after having confirmed that at least no relevant inferiority of the test medicinal product exists compared to the standard therapy.

Art. 32. - (1) Due attention should be given in order to formulate the null hypothesis and the alternative hypothesis correctly.

(2) Classical hypothesis testing is inappropriate in trials set up to assess therapeutic equivalence.

Art. 33. - (1) The determination of the minimally clinically relevant difference is critical, and should be argued on an individual basis.

(2) The argumentation should take specific clinical considerations into account.

(3) These should include the primary end-point, the statistical model, the indication, the efficacy of the reference medicinal product, and the natural course of the disease.

Art. 34. - These considerations will in turn influence the sample size calculations which are usually based on the primary end-point, the minimally clinically relevant difference, the type I and II error levels, which all have to be fixed in the study protocol.

Art. 35. - Although the arguments above are formulated from the classical (frequentist) viewpoint, the use of Bayesian or other well-argued approaches is acceptable.

IV.1.2. **Bronchodilators**

Art. 36. - 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.

Art. 37. - (1) It should be demonstrated in the protocol that the dose used in the trial is such that clinically relevant differences can be shown.

(2) Dose-ranging studies will be required if therapeutic equivalence is not shown.

Art. 38. - 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).

IV.1.3. **Glucocorticosteroids**

Art. 39. - (1) 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.

(2) Assessments would include pulmonary function measurements, symptoms scores, inhaled bronchodilator requirement and rate of exacerbations, defining beforehand an adequate primary outcome-variable.

(3) Studies should address a particular disease severity/dose regimen.

(4) The duration of treatment would need to be a minimum period of 4 weeks; longer treatment periods might be more advantageous.

Art. 46. - (1) Since improvement in patients who are stabilised on corticosteroids is unlikely, the use of such patients is discouraged.

(2) 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.

Art. 40. - (1) Single dose allergen challenge studies are artificial compared with natural exposure.

(2) 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.

(3) 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.

Art. 41. - 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 IV.2.).

IV.1.4. **Sodium Cromoglycate/Nedocromil Sodium**

Art. 42. - (1) 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.

(2) Such a study would compare the non-CFC containing medicinal product with the CFC-containing product in patients with known exercise-induced asthma or other induced asthmatic response.

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

IV.2. **Safety of the new non-CFC-containing medicinal products**

Art. 43. - (1) The safety profiles of the active substances as currently formulated are not in question.

(2) 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.

(3) 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.

Art. 44. - Complete animal toxicology will have been completed for each new excipient, but such data will not remove the need for clinical safety studies in man.

Art. 45. - The aims of the safety program are twofold:

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

b) to assess interactions which may occur between an active substance and an excipient mix which would lead to modifications in the medicinal product's safety;

Art. 46. - (1) 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).

(2) 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.

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

IV.2.1. **Assessment of clinical safety of the new excipients (including propellants) in the formulated medicinal product**

Art. 47. - 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.

Art. 48. - (1) 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.

(2) The new non-CFC-containing medicinal product should be compared with the authorised CFC-containing medicinal product in a controlled randomised study over a treatment period of 3 months prior to marketing.

Art. 49. - (1) The trials should be set up in such a way that it is clear that the patients who complete them are representative of the entire patient population.

(2) The study design should be such as to encompass an assessment of the changeover from the original CFC-containing medicinal product to the new non-CFC-containing medicinal product.

Art. 50. - (1) 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.

(2) 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.

(3) Proposals should be put forward to monitor the introduction of the new non CFC medicinal products in order to identify rare and unexpected adverse effects.

(4) 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 medicinal products against historical data relating to the medicinal products using CFC propellants.

Art. 51. - (1) Careful observation of patients and a specific assessment of cough, wheezing and bronchospasm on first administration of the medicinal product during the first clinic visit, paying particular attention to the time to onset of any effect, could also be useful.

(2) Specific questions and assessment of paradoxical bronchospasm would be appropriate in single dose studies and after the first dose of each limb in crossover studies.

IV.2.2. **The assessment of clinical safety following re-formulation to assess any possible interactions between the substance and the new excipients**

Art. 52. - (1) These studies will be of shorter duration and will be required for all inhalation medicinal products which have undergone re-formulation as previously described.

(2) 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 the medicinal product safety.

Art. 53. - (1) Similar safety assessments, as described under IV.2.1 should be made but with specific emphasis on assessments to pick up acute toxicity, bronchospasm following inhalation and enhanced systemic activity.

(2) Monitoring should be focused on the known adverse event profiles of the CFC-containing medicinal product to assess change in these profiles as a consequence of the use of new excipients, together with the attempt of identifying new and unexpected effects.

Art. 54. - (1) Detailed safety studies are required; comparative efficacy assessments could be built into the designs as described in IV.1.3 above and might also include assessments of bronchial reactivity.

(2) In this way, efficacy and (short-term) safety can be assessed in the same study, with assessments based on clinical endpoints.

(3) Such studies might be one month comparative studies (CFC vs. non-CFC) of appropriate sample size.

(4) They would require careful statistical input to ensure adequate size and power to detect any clinically important differences between treatments in respect of safety.

IV.3. **Studies in children**

Art. 55. - The profile of the non-CFC-containing medicinal products following administration to children under 12 years must also be addressed.