MATTERS RELATING TO THE REPLACEMENT OF CFC'S IN MEDICINAL PRODUCTS

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Additional Notes	**This guideline sets out certain administrative and regulatory questions which relate to CFC replacement in medicinal products as required by Council Regulation 594/91 as amended.**

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1. INTRODUCTION

Council Regulation (EEC) No 594/91 as amended by Council Regulation (EEC) 3952/92 prescribes a schedule for the phasing out of substances that deplete the ozone layer. This includes a phasing out of chlorofluorocarbon (CFC) production and consumption by 31 December 1994.

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.

The CPMP has prepared a guideline on the replacement of CFCs in medicinal products which identifies the considerations of quality, safety and efficacy to be taken into account by companies when preparing the dossiers for submission for the replacement of a CFC propellant in an already authorised medicinal product.

In order to help prospective applicants further, the CPMP has defined below its position on certain administrative and regulatory questions which relate to CFC replacement in medicinal products.

2. REPLACEMENT PROPELLANTS

Non-ozone depleting alternative propellants are being developed to replace CFCs in medicinal products. The CPMP has identified the issues raised by their development as being a matter of Community interest. Accordingly, a co-ordinated review of the pharmacy and toxicology of a putative replacement propellant may be requested. Following such a review, advice on the suitability of such an alternative propellant for use in medicinal products will be given by the CPMP to Member States.

In accordance with the requirements of Directive 75/318/EEC as amended, as with all excipients, the first time that an applicant requests marketing authorisation for a (reformulated) medicinal product containing a new propellant, documentation on the toxicology and pharmacokinetics of the latter must be supplied (in addition to those issues of quality, safety and efficacy which must be taken into account). In the event that the CPMP has already formulated an opinion on the acceptability of the propellant then documentation on the toxicology and pharmacokinetics of the latter need not be provided, unless in the view of the competent authority the specifications of the propellant in the application are so different from the first propellant that there are serious concerns about the safe use of the propellant in the (reformulated) product.

For subsequent applications containing the same new propellant, documentation on the specific toxicology and pharmacokinetics of the propellant is not required. As is usual, it will be adequate to refer to the presence of the excipient in an authorised medicinal product, unless in the view of the competent authority the specifications of the excipient in the second application are so different from the first excipient that there are serious concerns about the safe use of the excipient in the second application.

3. CATEGORISATION OF AN APPLICATION FOR AUTHORISATION FOR A REFORMULATED MEDICINAL PRODUCT IN WHICH A CFC IS REPLACED BY AN ALTERNATIVE PROPELLANT

If the reformulation involves a replacement of propellant only such an application would be classified as a variation (type II).

If, however, reformulation resulted in changes such as a different content per actuation or dosing schedule or a quantitative change in the active substance(s) or a change in the bioavailability, then the application would be classified as an extension abridged applications .

4. DOSSIER REQUIREMENTS

First applications

For each medicinal product containing a known active substance reformulated with new propellant(s), the first applicant should follow the note for guidance on *Replacement of CFCs in MDI Product*s.

Second applications

A second applicant for a product containing the same active substance(s) and the same propellant(s) as an already approved product should submit a Part I (which includes a pharmaceutical expert report, a preclinical expert report which refers in particular to any potential for local irritability, and a clinical expert report), and a Part II. The dossier should also include an assessment of therapeutic equivalence to the first product **or** to a previously authorised CFC containing medicinal product.

5. EXEMPTIONS FOR ESSENTIAL USE

Council Regulation (EEC) 594/91 on substances that deplete the ozone layer, as amended, sets out a procedure to determine any essential uses of chlorofluorocarbons which may be permitted in the Community after 31 December 1994 and until 31 December l999 and any quantities of CFCs which may be produced by each producer for this purpose.

A list of essential uses for CFCs, which has been agreed by the Management Committee of the Regulation, has been submitted to the Technical and Economic Committee of the United Nations Environmental Program (UNEP).

The list includes metered dose inhalation products for use in the treatment of asthma and other chronic obstructive airways diseases. Consequently, such products have a preliminary exemption from the Regulation on Ozone Depleting Substances from 31.12.94 until 31.12.95. The nomination for their exemption for the period 1.1.96 to 31.12.96 will be considered by the Technical and Economic Committee of UNEP in mid 1994. Thereafter, extensions of the exemption period will be considered on a regular basis within the allowed time-frame.

In accordance with the Regulation, manufacturers of all other medicinal products containing CFCs (i.e. all those medicinal products which are not included in the list of essential uses for

CFCs) will no longer be able to obtain CFCs from producers after 31 December 1994. Similarly, the importation of CFCs from third countries shall cease on 31 December 1994 at the latest.

6. REPLACING PRODUCTS WHICH HAVE ESSENTIAL USE STATUS

For variations, when marketing authorisation has been granted for a reformulated product containing an alternative propellant, stocks of the previous CFC-containing formulation should be phased-out from the market in accordance with a time table which has been agreed with the competent authority or authorities.

For abridged applications, in the interests of consumer protection and for pharmacovigilance purposes, when marketing authorisation has been granted for a reformulated product containing an alternative propellant, the new product should be clearly identifiable e.g. brand name, label, colour etc. and distinguishable from the previous CFC containing formulation.

7. AUTHORISATIONS AND RENEWALS DURING THE EXEMPTION PERIOD FOR CFC-CONTAINING PRODUCTS WHICH HAVE ESSENTIAL USE STATUS

In accordance with Article 4.6 of Directive 65/65/EEC as amended, after 1.1.95, all applications for authorisation for medicinal products (including renewals) shall be accompanied by "if applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented to the environment."

This will apply to applications for CFC containing products. The applicant should also justify the inclusion in the formulation of an excipient whose production and consumption is being phased out.

When the period of exemption expires, CFCs will no longer be supplied. All medicinal products containing CFCs which are covered by the essential use exemption should therefore be reformulated to exclude the CFCs.

8. REPLACEMENT PROPELLANTS AND THE ENVIRONMENT

The alternative propellants proposed for use in medicinal products in the place of CFCs have negligible ozone depleting potential. However, they are greenhouse gases and as such their use in metered dose inhalers may have an adverse impact on the environment.

Environmental regulations are not currently an issue for hydrofluorocarbons. But, as part of their long term strategy, applicants are encouraged to develop and promote formulations which take into account both the therapeutic needs of the patient and environmental considerations.