The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

CPMP/180/95

GUIDELINE FOR PMS STUDIES FOR METERED DOSE INHALERS WITH NEW PROPELLANTS

I INTRODUCTION

The change over to reformulated MDIs presents an unusual public health situation. Millions of patients will be exposed to the new propellants for the first time over a relatively short period. The safety of the propellants will have been established by extensive formal pre-clinical and clinical studies and separate regulatory review. However, it is desirable to confirm this by post-marketing surveillance (PMS) as new propellant/excipient systems are introduced, and before CFC-based inhalers finally become unavailable. In this regard, there are already limitations on the availability of CFCs to the pharmaceutical industry for the manufacture of MDIs.

There are a number of factors influencing the choice of study designs for PMS. Because of the difference in active drug, formulation, time of launch, and type of product (branded vs. generic; new products; replacement products), it is not possible for all reformulated products to be studied using the same study design.

It is likely that preferred options for PMS study designs will be observational cohort studies or large randomised Phase IV clinical trials. Whichever is chosen, a multinational approach should facilitate collection of the maximum amount of data in the shortest possible time. This will obviously depend on the time of introduction in each country.

II PRODUCTS TO BE STUDIED

It is proposed that a study could include one product or a range of products with the same propellant. One PMS study on a reference product may be sufficient to assure the safety of a given propellant which is used in a range of products.

III STUDY DESIGN

PMS studies would be either observational cohort studies, within-patient switching studies, or randomised, parallel group comparative trials, according to the desired objectives. Blinding may be considered. There should be adequate methodology for identifying the products used. Control groups will be necessary and will normally use the CFC product. Consideration should be given to including smaller numbers of patients in the control group compared to the treatment group.

It is desirable that for patients in CFC control groups, no "new propellant" products should be prescribed. It must be recognised that, as time progresses, it will become more difficult to identify CFC control groups, and therefore other control groups may eventually become appropriate. The ability to perform studies depends on the continued availability of CFC based products for use in control groups.

Treatment allocation may be defined by general prescribing or study design.

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IV PATIENT TYPES AND NUMBERS

The types of patient populations participating in PMS studies for MDIs with new propellants should reflect the indications and contra-indications for the products as stated in SmPCs. Patient inclusion should come as close as practical to the real prescribing situation.

When defining patient types and numbers, the following will be taken into account:

1. Existing CFC patients and new patients can be included.
2. Completion of the study should be achievable in a reasonable time period.
3. Patient numbers and data generated by the study should be sufficient to test hypotheses or to give the desired precision for the incidence of "an event".
4. Concurrent participation in more than one PMS study should be disallowed. Sequential participation, in line with the availability of different non-CFC inhalers, may be permissible.

V TREATMENT PERIOD

The treatment period will normally be between three and six months. In certain cases, for example when testing specific hypotheses, the duration may be shorter or longer.

VI CONCOMITANT MEDICATIONS

Patients will be allowed to continue with concomitant therapies as per the product data sheet. In most cases, it would be impractical to expect that other CFC or non-CFC products could be avoided, as these will be co-prescribed as required by individual patients.

VII REPORTING PARAMETERS

Data will be collected at the beginning and end of the study, and at interim visits to the doctor prompted by serious adverse events. Information will be collected on serious adverse events as defined in the EU pharmacovigilance guidelines. Interim and final study reports, and also individual reports for serious suspected reactions will be formatted and submitted in accordance with European regulatory requirements. Follow-up information will be provided as appropriate.

The following minimum information will be collected:

- Basic demography: age, sex
- indication
- Product under study and concomitant medications
- Date treatment started and stopped
- Serious adverse events

VIII POSSIBILITIES FOR POOLING RESULTS

The pooling of data may be possible and is desirable in order to enlarge safety databases. Pooling results will only be appropriate where products contain the same propellant. Such pooling should follow established methods e.g. meta-analysis.