CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

September 19, 1994.

POINTS TO CONSIDER:

CLINICAL DEVELOPMENT PROGRAMS FOR MDI AND DPI DRUG PRODUCTS

This document represents a summary of current Division of Oncology and Pulmonary Drug Products recommendations for clinical development of new inhalation drug products and changes in formulation and/or device of existing approved inhalation drug products (i.e., "switches"). This document specifically addresses metered dose inhaler (MDI) and dry powder inhaler (DPI) devices.

These recommendations are intended as general outlines of the types of studies which the Division feels should be conducted and do not represent official Agency policy. Sponsors are strongly encouraged to discuss details of study design as well as specific issues related to individual drug products with the Division prior to conducting clinical trials. Particular attention must be paid to the choice of placebo, rescue therapy, active controls and blinding procedures for clinical trials involving inhalation drug products in order to maximize the information obtained and the interpretability of the studies.

The recommendations on page 2 of this document relate to a new inhalation drug product (i.e., a drug product not previously administered by the inhalation route as an MDI or DPI). The remainder of the document provides recommendations for changes in formulation and/or device of an existing approved inhalation drug product.

General inquiries regarding the contents of this document or specific inquiries regarding individual drug products should be addressed to:

Ms. Cathie Schumaker
Supervisory Consumer Safety Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology and Pulmonary Drug Products
HFD-150, 5600 Fishers Lane
Rockville, MD 20857

301-827-1055

- **Recommendations for Clinical Trials for a New Inhalation Drug Product, e.g. a new MDI.**
  Goal: To demonstrate the safety and effectiveness of the product.

ADULT PROGRAM

I. Dose Ranging Study
   1. Single and/or repetitive dose (as appropriate).
   2. Placebo and active control.
   3. Sufficient number and range of doses to clearly define the dose-response curve.

II. Long term Safety and Efficacy Studies
   1. Two double-blind, randomized, placebo and active controlled twelve week (minimum) safety and efficacy studies in the population intended for marketing.
   2. Long-term safety study of at least 200 patients for one year. (May be accomplished by open-label extension of twelve week studies.)

III. Additional Indications Require Studies as Appropriate, e.g.;
   1. Exercise-induced bronchospasm (EIB) for a bronchodilator: two single-dose, placebo and active control studies.
   2. Prednisone-substitution for an inhaled corticosteroid: two repetitive dose, placebo-controlled studies.

PEDIATRIC PROGRAM[1]

I. Dose Ranging Study
   1. Single and/or repetitive dose (as appropriate).
   2. Placebo and active control.
   3. Sufficient number and range of doses to clearly define the dose response-curve.

II. Long Term Safety and Efficacy Study
   1. One double-blind, randomized, placebo and active controlled twelve week (minimum) safety and efficacy study in the population intended for marketing.

III. Additional Indications Require Studies as Appropriate, e.g.;

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[1] If adult program pursued first, otherwise same as adult program listed above.

1. Exercise-induced bronchospasm (EIB) for a bronchodilator: one single-dose, placebo and active control study.

- **Recommendations for CFC-Replacement Clinical Trials in Bronchodilator Aerosols.**
  Goal: To demonstrate comparable safety and effectiveness between the non-CFC and CFC products.

ADULT PROGRAM

I. Safety and Tolerability Study
   1. Small number of healthy subjects.
   2. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.
   3. Multiple dose levels of each active formulation.
   4. Single and repetitive dosing.

II. Dose Ranging Study
   1. Single dose, separate day.
   2. Crossover design.
   3. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.
   4. At least two dose levels of each formulation.

III. Long Term Safety and Efficacy Studies
   1. One double-blind, randomized, 12 week (minimum) safety and efficacy study in population intended for marketing.
      a. Arms:
         i. CFC active formulation.
         ii. Non-CFC active formulation at dose(s) selected from dose ranging study.
         iii. Non-CFC placebo formulation.
      b. Rescue for CFC active formulation should be CFC active formulation.
      c. Rescue for non-CFC active formulation and non-CFC placebo formulation should be non-CFC active formulation.
      d. Rescue for any non-approved bronchodilator should be albuterol.
   2. Long term safety study of at least 200 patients for one year. (May be

accomplished by open-label extension of 12 week study.)

bronchodilators cont'd...

IV. Exercise-Induced Bronchospasm Challenge Study
   1. Single dose.
   2. Crossover design.
   3. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.

V. Switch Study (OPTIONAL)[2]
   1. Double blind (half of patients switch to non-CFC formulation).
   2. Safety and efficacy, including PFTs, should be assessed for at least 8 weeks after the switch.
   3. Patient groups may include children.

PEDIATRIC PROGRAM[3]

I. Repetitive Dose Safety and Tolerability Study
   1. Should follow demonstration of safety in adult patients.
   2. Small number of patients.

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[2] This study is designed to mimic the effect of replacement of the CFC formulation with the non-CFC formulation of the drug product in the relevant patient population. The study is recommended but not required.

[3] Applicable only if pediatric indication is approved for the CFC formulation.

- **Recommendations for CFC-Replacement Clinical Trials in Non-bronchodilator, Non-steroid Aerosols, e.g. cromolyn.**
  Goal: To demonstrate comparable safety and effectiveness between the non-CFC and CFC products.

ADULT PROGRAM

I. Safety and Tolerability Study
   1. Small number of healthy subjects.
   2. Multiple dose levels of each active formulation.
   3. Single and repetitive dosing.
   4. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.

II. Dose Ranging Study (Either of these studies is acceptable)
   1. Challenge studies (e.g. exercise).
      a. Single dose.
      b. Crossover design.
      c. Arms:
         i. CFC active formulation.
         ii. Non-CFC active formulation
         iii. Non-CFC placebo formulation.
      d. At least 2 dose levels of each active formulation.
   2. Four Week Safety and Efficacy Study
      a. Arms:
         i. CFC active formulation.
         ii. Non-CFC active formulation.
         iii. Non-CFC placebo formulation.
      b At least 2 dose levels of each active formulation.

III. Long Term Safety and Efficacy Studies
   1. One double-blind, randomized, 12 week (minimum) safety and efficacy study in population intended for marketing.
      a. Arms:
         i. CFC active formulation.
         ii. Non-CFC active formulation at dose(s) selected from dose ranging study.
         iii. Non-CFC placebo formulation.
   2. Long term safety study of at least 200 patients for one year. (May be accomplished by open-label extension of 12 week study.)

non-bronchodilator, non-steroid cont'd...

IV. Exercise Induced Bronchospasm Challenge Study
   1. Single dose.
   2. Crossover design.
   3. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.

V. Switch Study[4]
   1. Double blind (half of patients switch to non-CFC formulation).
   2. Safety and efficacy, including PFTs, should be assessed for at least 8 weeks after the switch.
   3. Patient groups may include children.

PEDIATRIC PROGRAM[5]

I. Repetitive Dose Safety and Tolerability Study.
   1. Should follow demonstration of safety in adult patients.
   2. Small number of patients.

[4] This study is designed to mimic the effect of replacement of the CFC formulation with the non-CFC formulation of the drug product in the relevant patient population. The study is recommended but not required.

[5] Applicable only if pediatric indication is approved for the CFC formulation.

- **Recommendations for CFC-replacement Clinical Trials in Inhaled Corticosteroid Aerosols.**
  Goal: To demonstrate comparable safety and effectiveness between the non-CFC and CFC products.

ADULT PROGRAM

I. Safety, Tolerability and Bioavailability Study
   1. Small number of healthy subjects.
   2. Single and repetitive dosing.
   3. Arms:
      a. CFC active formulation at the highest approved dose.
      b. Non-CFC active formulation at escalating doses.
      c. Non-CFC placebo formulation.
   4. Assessments should include comparative pharmacokinetics of the CFC and non-CFC active formulations at the highest doses.

II. Dose Ranging, Safety and Efficacy Study.
   1. Double-blind, randomized, twelve-week (minimum) study.
   2. Arms:
      a. CFC active formulation.
      b. Non-CFC active formulation.
      c. Non-CFC placebo formulation.
   3. At least two dose levels of each active formulation.
   4. Low to intermediate doses of the active formulations should be studied (High doses are not required in this study).
   5. Efficacy assessments:
      a. Include single dose response and response to repetitive dosing.
      b. Single dose efficacy end-point(s) must be clinically-relevant, e.g. FEV_1, PEFR, bronchoprotective effect following allergen challenge, etc.
      c. Assessment of response to repetitive dosing (over 12 weeks) should include on-going measurements (e.g. diary symptom scores, AM and PM PEFRs, etc) and interval assessments (e.g. weekly or bi-weekly methacholine challenge, PFTs, etc).
      d. Sponsor should provide data validating the sensitivity and clinical relevance of the efficacy model such as adequate, published or unpublished data, pilot study data, etc.
   6. Safety assessments:
      a. Safety parameters should include HPA-axis suppression (ACTH stimulation tests and 24-hr urinary cortisol recommended), pharmacokinetics of the inhaled drug, effects on bone metabolism, etc. assessed at intervals throughout the study.

...inhaled corticosteroids cont'd.

7. Long term safety study of at least 200 patients for one year including assessment of systemic effects of corticosteroids.
    a. Doses of the study drug should be selected to cover a broad range including low, intermediate and high dose levels.

IV. Switch Study (OPTIONAL)[6]
1. Double blind (half of patients switch to non-CFC formulation).
2. Safety and efficacy, including PFTs and systemic corticosteroid effects, should be assessed for at least 8 weeks after the switch.

PEDIATRIC PROGRAM[7]

I. Dose Ranging, Safety and Efficacy Study (similar to study in adults)
1. Should follow demonstration of safety/tolerability in adults.
2. Double-blind, randomized, twelve-week study.
3. Arms:
    i. CFC active formulation.
    ii. Non-CFC active formulation.
    iii. Non-CFC placebo formulation.
4. At least two dose levels of each active formulation.
5. Low to intermediate doses of the active formulations should be studied (High doses are not required in this study).
6. Safety end-points should include objective assessment of corticosteroid systemic effects at regular intervals during the study (i.e.adrenal suppression, growth suppression, etc.).
7. Long term safety study of at least 200 pediatric patients for one year including assessment of systemic effects of corticosteroids.
    a. Doses of the study drug should be selected to cover a broad range including low, intermediate and high dose levels.

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[6] This study is designed to mimic the effect of replacement of the CFC formulation with the non-CFC formulation of the drug product in the relevant patient population. The study is recommended but not required.

[7] Applicable only if pediatric indication is approved for the CFC formulation.

- **Recommendations for Clinical Trials for New Formulation/New Device of an approved drug, e.g. a switch from an approved MDI to DPI of the same drug.**
  Goal: To demonstrate comparable safety and effectiveness of the DPI to the MDI.

ADULT PROGRAM

I. Dose Ranging Study.
   1. Single and/or repetitive dose (as appropriate).
   2. Arms:
      a. Original formulation/device (e.g., MDI).
      b. New formulation/device (e.g., DPI).
      c. New formulation/device placebo.
   3. At least 2 dose levels of the original formulation/device (e.g., MDI) and of the new formulation/device (e.g., DPI).
   4. Comparability of dose-response of the two products should be shown.

II. Long Term Safety and Efficacy Studies
   1. Double-blind, randomized, twelve week (minimum) study.
      a. Arms:
         i. Original formulation/device (e.g., MDI).
         ii. New formulation/device (e.g., DPI) at dose(s) selected from dose ranging study.
         iii. New formulation/device placebo.
   2. Long term safety study of at least 200 patients for one year. (May be accomplished by open label extension of twelve week study.)

III.. Additional Indications Require Studies as Appropriate, e.g.;
   1. EIB for a bronchodilator: 1 single dose, placebo and active (original formulation/device) controlled study.

PEDIATRIC PROGRAM

I. Dose Ranging Study (similar to adult program)

II. Long Term Safety and Efficacy Studies (similar to adult program)

III. Additional Indications Require Studies as Appropriate (similar to adult program)

- **Recommendations for Clinical Trials for Same Formulation but Different Device, e.g. switch from one approved DPI device to another DPI device with an identical formulation.**
  Goal: To demonstrate comparable safety and effectiveness of the new device to the original device.

ADULT PROGRAM

I. Dose Ranging Study.
   1. Single and/or repetitive dose (as appropriate).
   2. Arms:
      a. Original device.
      b. New device.
      c. New device placebo.
   3. At least 2 dose levels of each active product.
   4. Comparability of the dose-response of the two products should be shown.

II. Short Term Safety and Efficacy Study
   1. Double-blind, randomized study for the life of the new device or four weeks, whichever is longer.
   2. Arms:
      a. Original device.
      b. New device at dose selected from dose ranging study.
      c. New device placebo.

III. Additional Indication(s)

If comparability is shown between the original device and the new device for the main indication (e.g. asthma) and data for an additional indication (e.g. EIB) is available for the original device, no further studies are needed for the additional indication for the new device.

PEDIATRIC PROGRAM

If the dose and in vitro characteristics (e.g. design, flow rates, resistance, etc.) are similar between the original device and the new device and the new device has been shown to have comparable safety and efficacy to the original device in adults, no pediatric studies are needed. If the new device is significantly different from the original device, the pediatric program should include the same studies as listed above for adults.

"The long term safety data required in the Points to Consider (Sept 19, 1994) document may now be obtained through EITHER of the following options:

1. Two hundred patients followed for one year.

2. Three hundred patients followed for six months AND one hundred patients for one year.

In either case, the data should be available at the time of submisson of the NDA, or, at the latest, at the time of the four-month safety update."