M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 6, 2001

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Inhalation Products

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Inhalation Products

Presented for: 3rd World Meeting on Pharmaceutics, Biopharmaceutics, Pharmaceutical Technology

Date Presented: April 3, 2000

Presented by: Wallace P. Adams, Ph.D.

Number of Pages: 25

Melissa Lamb

Attachment

90S-0308

M698

Inhalation Products

Symposium:
Bioequivalence of Special Dosage Forms

3rd World Meeting on Pharmaceutics, Biopharmaceutics,
Pharmaceutical Technology

Berlin, Germany
3 April 2000

Wallace P. Adams, Ph.D.
Office of Pharmaceutical Science
CDER/FDA

BIOEQUIVALENCE (BE)

- Comparable bioavailability of a drug product to a pharmaceutically equivalent reference product when studied under similar experimental conditions
- Two pharmaceutical equivalents are considered BE if they exhibit comparable:
  - rate and extent of absorption, or
  - other appropriate nonpharmacokinetic parameter(s) representative of drug delivery to the site of action

R Patnaik, LJ Lesko, K Chan, RL Williams, Europ J Drug Metab Pharmacokinet 1996;21:159-64

Pharmaceutical Equivalents

- Drug products that contain the identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standards
- 21 CFR 320.1 Definitions

METHODS FOR DOCUMENTATION OF BE

- In vivo studies in humans comparing drug or active metabolite in an accessible biologic fluid
- In vivo studies in humans comparing a pharmacodynamic endpoint
- Comparative clinical trials to demonstrate bioequivalence
- Comparative in vitro studies

THE DRUG PRODUCT
Aerosols (MDIs) and Sprays

- Inhalation aerosols, nasal aerosols, and nasal sprays are each a combination of **formulation** and **device**
- Change to either formulation or device may alter delivery of drug to sites of action
- A test (T) product that differs from the reference (R) product in formulation or device may not be BE to R

Many of the following slides are based on the draft* Guidance for Industry:

BA and BE Studies for Nasal Aerosols and Nasal Sprays for Local Action, June 1999

***The draft is distributed for comment purposes only, and not for implementation**

LOCALLY ACTING NASAL AEROSOLS AND NASAL SPRAYS: BE RECOMMENDATIONS (AN OVERVIEW)

- Qualitative sameness
- Quantitative sameness
- Comparable in vitro performance
- Comparable in vivo performance for efficacy
  - **not requested for solution formulation nasal aerosols and nasal sprays**
- Comparable in vivo performance for systemic absorption
  - **not requested for solution formulation nasal aerosols and nasal sprays**

BE RECOMMENDATIONS: Formulation Equivalence

- Qualitative sameness (Q_1)
  - identical active and inactive ingredients as in the RLD
- Quantitative sameness (Q_2)
  - inactive ingredients within ± 5% of the concentrations in the RLD

BE RECOMMENDATIONS: The Device

- Likelihood of equivalence is:
  - greatest when T uses the same brand and model (particularly the metering valve or pump and actuator) as used in R.
  - if not feasible, valve or pump, and actuator designs should be as close as possible in all critical dimensions (e.g., metering chamber volume, actuator orifice diameter)

BE Studies for Nasal Aerosols and Nasal Sprays

Local Delivery Study Recommendations

- **Demonstration of dose-response relationship**
  - Doses may differ by 2- or 4-fold
  - Lower dose may be below the labeled dose
- **Clinical study endpoints**
  - Based on symptoms associated with seasonal allergic rhinitis (SAR)
  - Incorporation of safety assessments

BE Studies for Nasal Aerosols and Nasal Sprays

Local Delivery Study Recommendations

- **Clinical Study Designs**
  - Randomized, double-blind, placebo-controlled parallel group studies
- **Study Type**
  - Treatment, not prophylactic
- **Subjects**
  - History of seasonal allergic rhinitis (SAR)
  - Positive skin test for specific allergens
- **Exposure**
  - Single dose (antihistamines) or short term multiple dose (corticosteroids) regimens

BE Studies for Nasal Aerosols and Nasal Sprays

Local Delivery Study Recommendations

- **Traditional Treatment Study**
  - Single-blind placebo lead-in period (1-14 days)
  - Two-week treatment duration
  - Safety measure (lab tests, adverse events reporting, other)
- **Day(s) in the Park Study**
  - Baseline evaluation for allergic rhinitis symptoms
  - Park exposure for a specified period over 1-2 days
  - Adverse events reporting
- **EEU study**
  - Controlled indoor environment
  - EEU exposure to establish baseline allergic rhinitis symptoms
  - EEU exposure for specified periods over 1-2 days
  - Adverse events reporting

BE Studies for Nasal Aerosols and Nasal Sprays

Systemic Exposure Recommendations*

- **PK Study Design**
  - Randomized, two-way crossover
  - Single or multiple dose
  - Replicate or nonreplicate design
- **Subjects**
  - Generally healthy (non-SAR) volunteers
- **BE Metrics**
  - AUC and C_{max}
- *Systemic absorption (PD or clinical) study is recommended when PK study is not feasible

PD BE Studies for Albuterol Inhalation Aerosol (MDI)

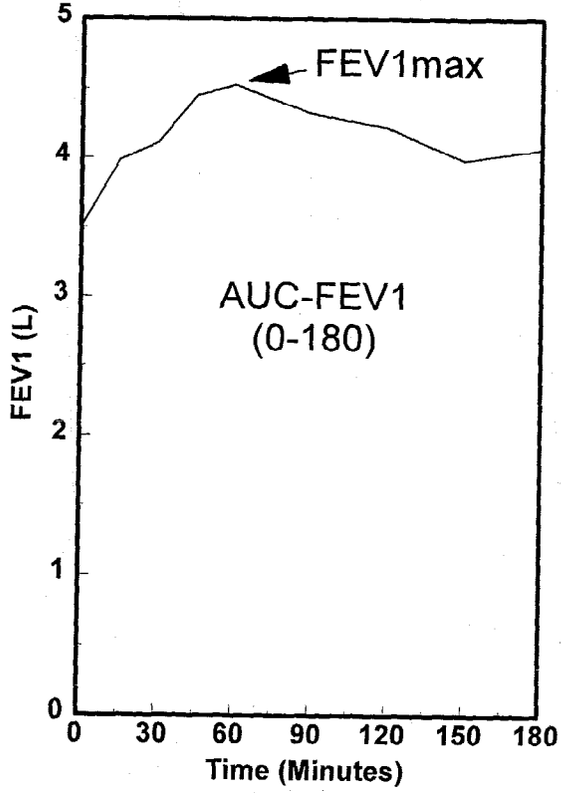
Local delivery study recommendations

- **PD Endpoints**
  - **Based on the ability of albuterol to dilate airways**
    - Forced expiratory volume in one second **(FEV1)**
  - **Based on the ability of albuterol to protect airways from bronchospasm induced by challenge agents**
    - Provocative dose or concentration of the agent required to reduce the FEV_1 by 20% (PD_{20} or PC_{20})

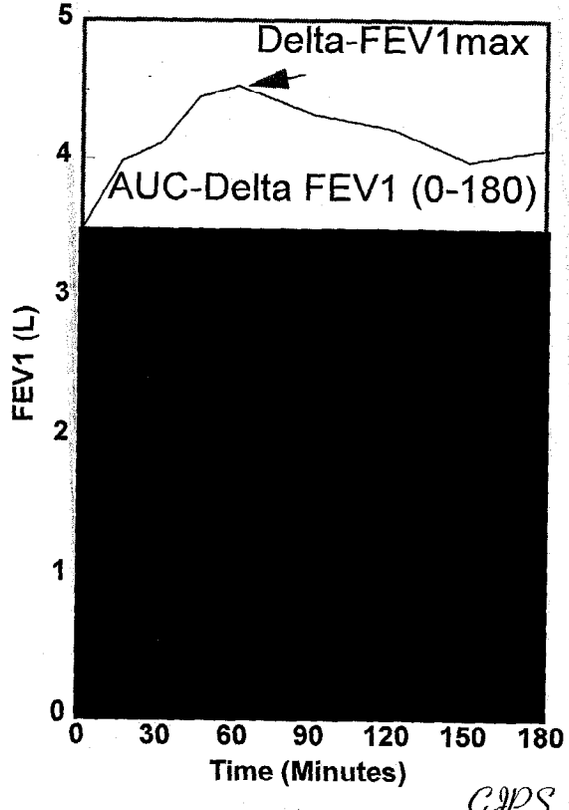
PD BE Studies for Albuterol MDI

Local delivery study recommendations

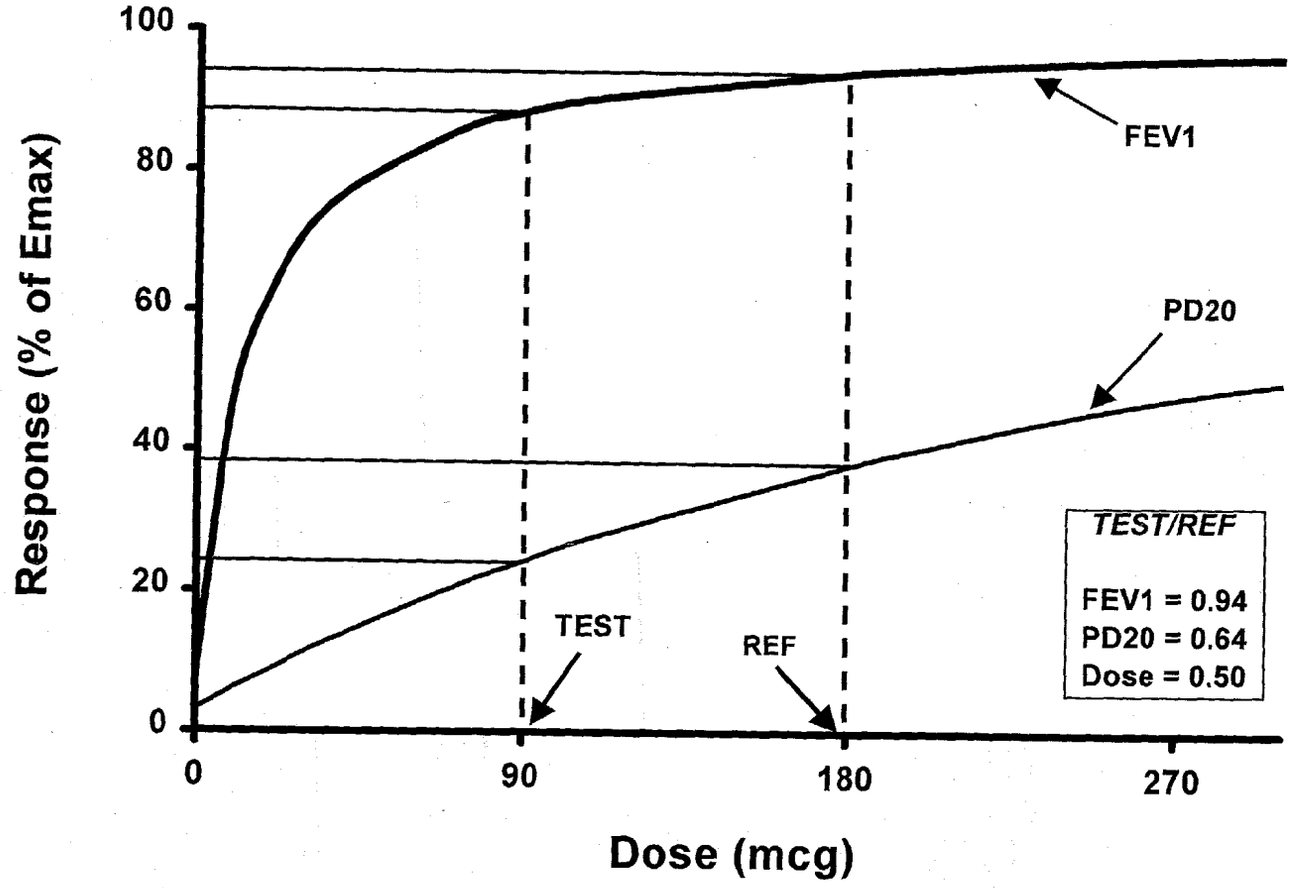
- **BE Metrics based on FEV_1**



Time (Min)	FEV1 (L)	Delta-FEV1 (L)
0	3.52	0.00
15	3.98	0.46
30	4.11	0.59
45	4.45	0.93
60	4.53	1.01
90	4.32	0.80
120	4.11	0.59
150	3.98	0.46
180	4.07	0.55



Relative Bioavailability
Based on *Response Scale* and *Dose Scale*
(Pharmacodynamic Studies)

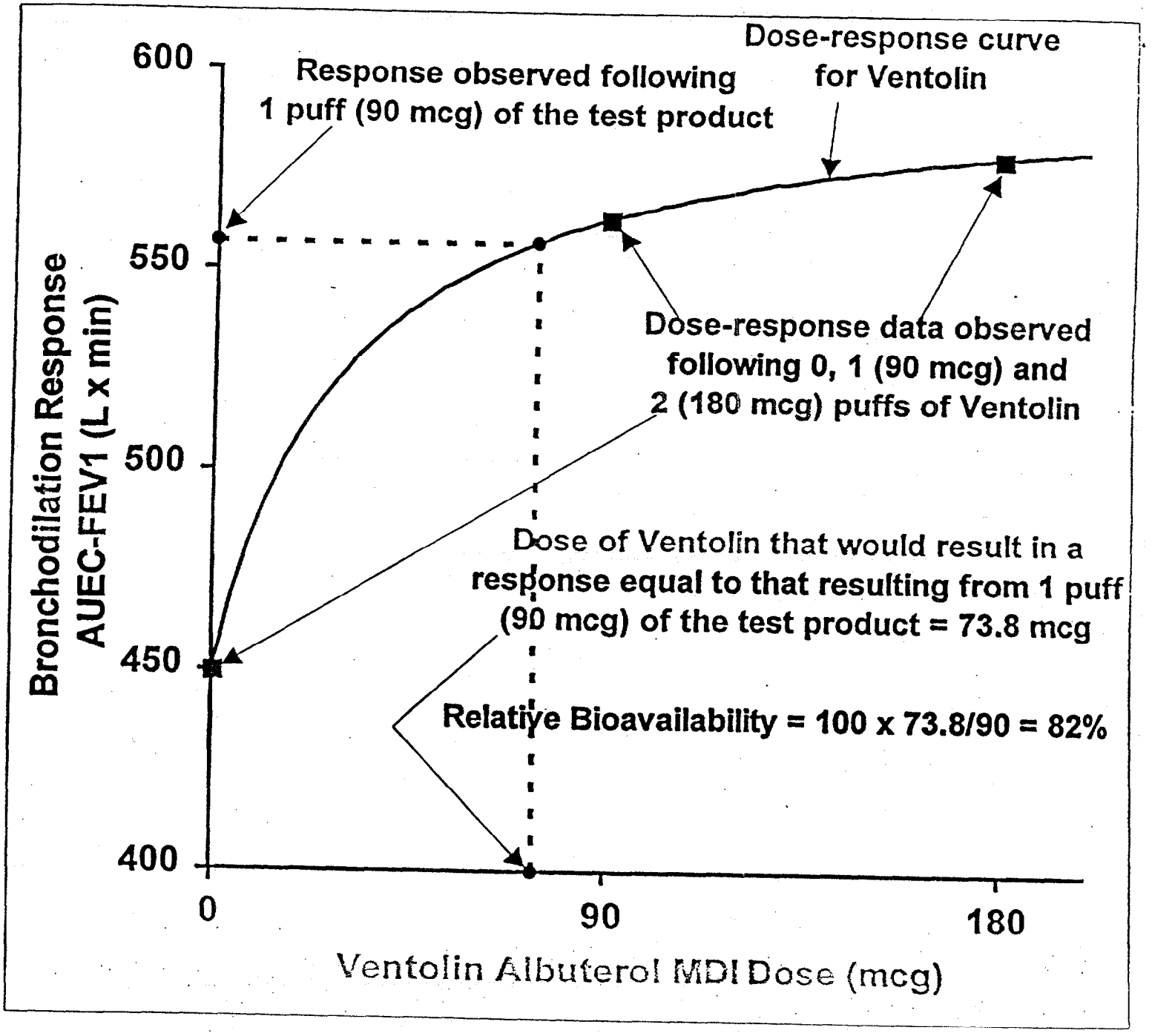


PD BE Studies for Albuterol MDI
Local delivery study recommendations

- **Study Design**
  - Randomized, crossover studies
- **Treatments**
  - Minimum
    - T1 T2, R1 R2
  - Preferred
    - T1 T2 T3, R1 R2 R3

T = Test Product, R = Reference Product
1, 2 & 3 = Dose (Number of actuations)

Application of the Dose Scale Approach to Albuterol MDI's (hypothetical example)



N R Gillespie, Ph.D.
ACPS/PADAC
16 Aug 1996

Dose Scale Analysis Method

Relative bioavailability is estimated by fitting the following E_{max} model to the pooled dose-response data of test and reference products:

$$y = E_0 + \frac{E_{max} * Dose * F^{i}}{ED_{50} + Dose * F^{i}}$$

Where:

y =response, Dose = Administered dose, i = Treatment indicator (0 = Ref, 1 = Test), E_0 = Baseline response, E_{max} = Fitted maximum drug effect, ED_{50} = dose corresponding to 50% of E_{max}, F = relative bioavailability

A 90% confidence interval for F is estimated by a bootstrap procedure.

Each bootstrap estimation includes calculation of F by fitting the above model to a "sample data set" of the observed dose-response data, generated by repetitive sampling with replacement.

BE Studies for Inhalation Aerosols
Systemic Exposure/Systemic Absorption Study Recommendations

- **Current recommendation for Albuterol MDI**
  - **study design**
    - cumulative dose/single day design
    - doses given 30 min apart
    - total actuations: 12
  - **pharmacodynamic endpoints**
    - BP, 12 lead ECG, serum glucose, serum potassium
- **PK study design under consideration**

IN VITRO BE:
Number of Batches and Units

- 3 batches of T and 3 batches of R
- ≥30 units of T
  - ≥10 units from each of the three batches
- ≥30 units of R
  - ≥10 units from each of the three batches
- For solution formulation T nasal sprays
  - ≥10 units from each of three sublots of solution
  - product prepared from three different batches of the same device may be used

BE RECOMMENDATIONS: Comparable in vitro performance

- Dose content uniformity through container life
  - on primed cans
- Droplet and particle size distribution
  - two methods (minimum), based on different measurement principles
  - multistage cascade impaction
  - laser diffraction or other

BE RECOMMENDATIONS: Comparable in vitro performance (Continued)

- Spray pattern
- Plume geometry
- Priming and repriming
  - number of actuations to prime
  - prime loss rate
- Tailoff characteristics
  - to exhaustion

IN VITRO BE:
Statistical Comparisons under Consideration

- Profile comparisons
  - For cascade impactor data
  - Based on chi-square differences, or
  - Other possible statistics
- Nonprofile comparisons
  - For dose content uniformity through container life and other in vitro tests
  - Based on population BE criterion

PROPOSED BE CRITERION FOR CU:
In Vitro Population BE Criterion and BE Limit

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_R^2} \leq \theta$$

μ_T, μ_R = T and R means (log scale)

$\sigma_R^2 = \sigma_{CR}^2 + \sigma_{LR}^2$

$\sigma_T^2 = \sigma_{CT}^2 + \sigma_{LT}^2$

σ_{CT}, σ_{CR} = between canister T and R standard deviations (log scale); includes between-batch variances

σ_{LT}, σ_{LR} = within T and R canister between life stage standard deviatio

θ = in vitro BE (upper) limit

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