

# SCHERING CORPORATION

5251 '99 SEP 23 MD 109  
2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033



September 22, 1999

TELEPHONE: (908) 298-4000

Dockets Management Branch  
HFA-305, Room 1061  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852

**SUBJECT: RESPONSE TO DOCKET NO. 99D-1738**

Dear Sir/Madam:

Enclosed herein are our comments to the "Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action."

Schering Corporation has addressed bioequivalence requirements for Beclomethasone Dipropionate Nasal spray products with FDA, beginning in December of 1996 (SP to Dr. Janet Woodcock) and additionally with Mr. Douglas Sporn ( Office of Generic Drugs ) in March of 1997. Although we find many of our previous comments addressed in this "Draft Guidance" and generally are in agreement, please take note of the following comments :

Solution Products Reliance on In-Vitro Methods- Page 3

Schering-Plough agrees that the most critical factors for delivery to the upper respiratory tract are release of drug substance from the product and delivery to the mucosa. While in-vitro methods seem appropriate to characterize the delivery of drug substance from the product, there is, according to Schering-Plough's knowledge, no adequate evidence suggesting that in-vitro methods can predict clinical performance. A number of the *in-vitro* assessments which are suggested to replace clinical trials for solution products have been developed for oral inhalation and will according to Schering-Plough's assessment not be able to adequately characterize products intended for nasal delivery. Schering Plough believes that the results of clinical studies are indispensable element of establishing therapeutic equivalence between two formulations.

99D-1738

C 8

Relatively little is known about the delivery of pharmaceuticals to the mucosa of the upper respiratory tract. Methods to characterize deposition without major alterations of the product and enabling three-dimensional imaging of drug deposition in relation to anatomical structures are in development, but substantial further progress is necessary before a more thorough understanding of nasal delivery is possible. At the same time, relevant indications include diseases with major alterations of the anatomical structures such as polyposis and claims on effects, which are probably related to delivery to the sinuses and the internal entrance of the Eustachian tube. Based on the somewhat limited knowledge about nasal delivery and facing different indications and claims there is no agreement about an appropriate target for particle size distribution.

The methodology currently used for the characterization of particle size distribution is in Schering-Plough's view insufficient to establish therapeutic equivalence between two solution products:

- The multistage cascade impactor (CI) and the multistage liquid impinger (MSLI) are optimized for products intended for oral inhalation. This includes the dimensions of the test inlet serving as "throat", the flow rate and the particle size spectrum covered. The concept of the test inlet has to be fundamentally different for nasal products, the relevant flow rate is lower for nasal products and the method should allow an adequate coverage and precision to assess particles larger than 10 micron.
- In line with the Draft Guideline, laser diffraction and light microscopy may only provide supportive evidence for the characterization of particle size distribution; both have major limitations, which are widely acknowledged.

*Suspension Formulations with PK Systemic Exposure Data – Page 7*

Schering-Plough agrees with the Draft Guideline that a pharmacokinetic approach for the establishment of comparable safety is only valid, if the nasal administration results in sufficiently high plasma or blood concentrations to produce meaningful AUC-data. In Schering's experience, potential issues with some commonly used drugs are:

- tissue concentrations may be substantially higher than blood or plasma concentrations and small changes in blood or plasma concentrations may reflect relatively large changes in individual tissues which are relevant to safety.

- If the mean concentration or a substantial number of individual concentrations are below or close to the limit of quantitation, the sensitivity of a pharmacokinetic comparison may become undesirably low .

In our view, major active metabolites have to exhibit comparable blood concentrations as well. This should be at least the case for compounds for which a metabolite is more active than the parent compound. Corresponding changes are suggested for Section VII, Bioavailability and Bioequivalence, PK Systemic Exposure Studies to address the characterization of major active metabolites.

*Suspension Formulations without PK Systemic Exposure Data – Page 7*

The Draft Guideline states that for products intended for local action, which produce blood or plasma levels too low for adequate measurement, a BE study with a clinical endpoint to establish equivalent local delivery to nasal sites and a study with a pharmacodynamic or clinical endpoint to establish systemic absorption are recommended.

Our suggestion is to add 'sensitive' before 'pharmacodynamic or clinical endpoint to establish systemic absorption.... This addition would be in line with the paragraph "BE Study Endpoints for Corticosteroids" on page 20.

*Clinical BE study Designs and Subject Inclusion Criteria –Page 18*

The Draft Guidance proposes that the three study designs outlined in the draft will cover all indications. In our opinion there should be individual justification that other indications of the originator product may not be associated with substantially different drug delivery issues.

*Bioavailability and Bioequivalence: PK Systemic Exposure Studies – Page 20*

If several actuations from the drug in each nostril are needed, the increase in bioavailability across doses may or may not be dose proportional, in particular, if a relatively large volume is administered which may partially trickle out of the nasal cavity either into the throat or out of the nares. In our view it is debatable, whether this approach (without evidence supporting dose proportionality) will result in a reliable and sensitive estimate of systemic exposure.

*BE Study Endpoints for Corticosteroids – Page 20*

As discussed in the 1998 Advisory Board Meeting with respect to New Chemical Entities and New Formulations, assessments of HPA-axis function may be less sensitive than the assessment of growth. This appears to be particularly relevant if the product labeling includes pediatric use and if an effect on growth has been shown for the originator product or if the effect on growth is unknown. In the interest of a similar safety standard for originator and generic products a growth study, preferably intermediate term (one-year) stadiometry data, should be provided for corticosteroids indicated for the use in children. In our view, this should apply always if the originator product is indicated for the use in children, since a labeling restriction for the generic product may be impractical and growth data are a sensitive indicator for systemic effects in the absence of other data such as bone densitometry.

Sincerely,



Joseph F. Lamendola, Ph.D.  
Vice President  
U.S. Regulatory Affairs

Attach the Airborne Express Shippers Label within the dotted lines.

**AIRBORNE EXPRESS**

F SCHERING LABORATORIES  
R RES AFFAIRS  
O 2000 GALLOPING HILL RD  
M KENILWORTH NJ 07033  
USA  
9075/0017H 708-740-5433

4026492 315

Origin  
ECC

These No.'s  
MUST match  
Shipment No.  
4026492-315



Service

DOCKETS MANAGEMENT BRANCH  
(HFA)305 FDA  
5630 FISHERS LANE, RM 1061  
ROCKVILLE MD 20857  
USA  
DOCKETS MANAGEMENT BRANCH

Please place special services sticker here if necessary

IF DESTINATION IS OUTSIDE OF THE UNITED STATES, THESE COMMODITIES, TECHNOLOGY OR SOFTWARE WERE EXPORTED FROM THE UNITED STATES IN ACCORDANCE WITH THE EXPORT ADMINISTRATION REGULATIONS. DIVERSION CONTRARY TO U.S. LAW PROHIBITED.

Seq. No. E

Weight I-E  
Billing Ref.  
Bill To

Remember: Airborne Express cannot deliver without your airbill attached here.

### United States Shipping



1. Complete applicable white sections of the U.S. Airbill. Sign and date the Airbill at the Sender's Signature line. Please press hard.
2. Peel off protective covering from back of Airbill.
3. Affix Airbill to envelope within dotted lines shown.
4. When using a Drop Box - follow special instructions on the Drop Box.

### International Shipping



Includes Canada & Puerto Rico  
Must be typed

1. Complete applicable white sections of the International Express Airbill. Sign and date the Airbill at the Sender's Signature line.
2. Place Airbill in plastic sleeve.
3. Peel off bottom portion from back of plastic sleeve. Do not seal top portion of the plastic sleeve to the envelope.
4. Affix bottom portion to envelope within the dotted lines shown. Airborne driver must sign Airbill before sealing

### Limitation on Contents

The maximum acceptable contents of a Letter Express is forty (40) 8-1/2 x 11 pages. If the gross weight of the contents, envelope and airbill exceeds 1/2 pound, the next higher rate will apply. Contents must be of a size and shape which fit the envelope and allow it to be securely sealed without damage. Cash or cash equivalent should not be shipped. Items of high intrinsic value should not be shipped in Letter Express packaging.

### Limitations of Liability

Liability of Airborne Express is limited on Letter Express to \$100.00 U.S.D., unless a higher value is declared for carriage on our airbill. The maximum declared value on the Letter Express is \$500.00 U.S.D. Airborne Express shall not be liable in any event for special, incidental or consequential damages, including but not limited to loss of profits or income. Services are provided as defined in the current Airborne Express Service Guide (subject to change without notice). Copies are available upon request.