Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Sciences

April 26, 2000
CDER Advisory Committee Conference Room 1066
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Members Present
Vincent H.L. Lee, Ph.D., Chair
James Li, M.D., Ph.D.
Stanley J. Szefler, M.D.

Consumer Representative
Gloria L. Anderson, Ph.D.

FDA
Eric B. Sheinin, Ph.D.
Guirag Poochikian, Ph.D.
Wallace P. Adams, Ph.D.
Yi Tsong, Ph.D.
Venkata R.S. Uppoor, Ph.D.

Executive Secretary
Nancy Chamberlin, Pharm.D.

Invited Guests
Richard C. Ahrens, M.D.
Michael Baaske,Ph.D.
Charan R. Behl, Ph.D.
Richard N. Dalby, Ph.D.
Hartmut Derendorf, Ph.D.
William Gore, Ph.D.
Lester I. Harrison, Ph.D.
Walter W. Hauck, Ph.D.
Sylvie Laganiere, Ph.D.
Nikhil J. Parekh
Sam C. K. Shum, Ph.D.
Thomas R. MacGregor, Ph.D.

These summary minutes for the April 26, 2000 meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Sciences were approved on November 5, 2000.

I certify that I attended the April 26, 2000 Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee of the Advisory Committee for Pharmaceutical Sciences and that these minutes accurately reflect what transpired.

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Nancy Chamberlin, Pharm.D.
Executive Secretary

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Vincent H. L. Lee, Ph.D.
Chair

On April 26, 2000, the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science met in an open session at the CDER Advisory committee Conference Room 1066, 5630 Fishers Lane, Rockville, Maryland. There were approximately 180 people in attendance.

At 8: 30 a.m., the meeting was called to order by Vincent H. L. Lee, Ph.D., Chair. This was followed by the conflict of interest statement, read by Nancy Chamberlin, PharmD., Executive Secretary, and the introduction of meeting participants.

Eric Sheinin, Ph.D., introduced the topics and presented FDA's objectives for the meeting. He outlined the responsibilities for the subcommittee as follows:

- Address and discuss questions related to the content uniformity of orally inhaled and nasal drug products

- Address and discuss questions related to in vitro and in vivo bioavailability and bioequivalence testing for OINDPs

- Present findings to the Advisory Committee for Pharmaceutical Science

Chemistry, Manufacturing and Controls: Content Uniformity

Guirag Poochikian, Ph.D., presented the FDA's current requirements for dose content uniformity (DCU) testing and summarized the public comments received for DCU specifications since publication of the draft guidances.

Walter W. Hauck, Ph.D., presented work in progress on Alternative Statistical Approaches for Measuring DCU. He recommended that FDA fully specify their criteria, not the acceptance rules.

Questions to the Committee

A. *Should there be a single content uniformity standard for all orally inhaled and nasal drug products (OINDPs)?*

Subcommittee Comments

- Consensus that more data are needed before this question can be answered
- A single content uniformity standard would be desirable
- Because of the different devices and different drug moieties, multiple standards may be the best approach
- Existing products that may not meet present standards might be grandfathered for as long as they are on the market
- Content uniformity must be considered in the context of in vitro and in vivo assessments
- It may be desirable to reconvene after data become available

B. *Should the FDA continue development of the proposed statistical approach to evaluating content uniformity?*

Subcommittee Comments

- Yes
- Data from existing products would enable the parametric statistical approach to move forward
- A number of statistical approaches are available in addition to that presented by Dr. Hauck
- One approach would be to use the properties of reference product to help determine criteria
- With the proposed statistical approach, the agency sets the allowable consumer risk, and the producer determines its own risk

Bioavailability (BA) and Bioequivalence (BE)

Wallace P. Adams, Ph. D., presented current FDA BA/BE background and issues related to the guidances for BA and BE Studies for Nasal Aerosols and Nasal Sprays for Local Action and for Orally Inhaled MDIs, DPIs and Inhalation Solutions for Local Action.

In Vitro BA and BE Testing

Yi Tsong, Ph.D., presented the FDA view on work in progress on an equivalence approach for Profile Analysis of Cascade Impactor Data: measures from in-vitro studies ("chi-square" approach). Then Andrew R. Clark, Ph.D., presented an alternative view on Profile Analysis of Cascade Impactor Data. David Ganderton, Ph.D., presented information on In Vitro Tests for Performance and Comparability of DPIs.

Questions to the Committee:

A. Profile Analysis

1. *Should all stages, including the inlet (throat) of the cascade impactor (CI) be considered in a comparison of test and reference products?*

   Subcommittee Comments

   - Yes. The data are used comparatively to support bioequivalence. The relationship of drug deposition on specific stages to safety and efficacy is not known, therefore, all stages and inlet should be considered.

2. *Should a statistical approach rather than a qualitative comparison be used for profile comparisons? If yes, does the chi-square comparative profile approach seem appropriate?*

   Subcommittee Comments

   - A statistical approach is preferred because it allows quantitation

- The chi-square approach is still in progress – it is premature to comment at this time

B. In Vitro Tests for DPIs: Comparability

1. Prior to doing in vivo studies to establish equivalence of a test DPI product, a firm would need to design its product to have the best likelihood of being found equivalent in these in vivo studies.

   a. *What design features of the device and formulation and what parameters should be considered in determining pharmaceutical equivalence?*

      Subcommittee Comments
      - Operating characteristics of equivalent devices should be as similar as possible
      - Match airflow resistance and flow-rate dependence of drug delivery
      - Devices must be functionally similar
      - It would be helpful to know what flow rates patients actually generate with the test and reference devices

   b. *What comparative in vitro tests should be conducted to help support bioequivalence?*

      Subcommittee Comments
      - Peak flow rate at particular pressure drops
      - Rate of rise in flow in cascade impactor
      - Variability of the devices at multiple flow rates
      - Goalposts for the in vitro tests should be clinically relevant

In Vivo BA and BE

Izabela Roman, M.D., Ph.D., presented the advantages and disadvantages of the three proposed models for *Clinical Studies for Local Delivery of Nasal Aerosols and S*prays in the draft guidance. Dr. Roman indicated that the Day(s) in the Park Study and the Environmental Exposure Unit Study designs are useful for determining onset of action, but are not useful for bioequivalence studies for drugs which require more than one or two days to reach maximum effect. Because of the longer duration of action, the traditional study design allows observation of steady-state efficacy and long-term safety.

Richard Ahrens, M.D., presented *Clinical Studies to Assess Inhaled Corticosteroid Bioequivalence*. He noted that there is need for a study design that has sensitivity to dose-response, thus is capable of demonstrating in vivo bioequivalence for inhaled corticosteroids. Dr. Ahrens described a proposed crossover study design in which carryover is controlled by starting each treatment period with a regimen of oral steroids. He believes that this study design will enable the bioequivalence study to be conducted in many fewer patients than with a parallel study design.

Venkata R. S. Uppoor, Ph.D., presented *Pharmacokinetic Studies for Oral Inhalation Aerosols and Nasal Sprays – Current FDA Practices*.

Lester I. Harrison, Ph.D. presented *Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies for Systemic Exposure of Locally Acting Drugs – Industry View* and stressed the need for caution until predictability is demonstrated. Then Hartmut Derendorf, Ph.D, presented the Academic View on *Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies for Systemic Exposure of Locally Acting Drugs,* describing how to assess bioequivalence from local and systemic exposure and stated that goalposts need to be defined.

Questions to the Committee

A. Clinical Studies for Local Delivery of Nasal Aerosols and Sprays

1. Three study designs have been proposed in the draft guidance for drugs intended to have local action: traditional treatment study; day(s) in the park study, and environmental exposure unit study. These study designs are based on seasonal allergic rhinitis (SAR).

   Is it feasible to demonstrate a dose-response for locally acting nasal drugs? If not, what other approaches can be relied upon to establish equivalent local delivery?

   Subcommittee Comments

   - Yes, but requires hundreds of subjects
   - Crossover approach is a problem for seasonal allergy due to shortness of the allergy season
   - If a clinical study is nondiscriminating to dose, rather than relying only on in vitro studies, a scintigraphy study could be considered. However for a multi-phase product (i.e., suspension), it is difficult to make a labeled product that duplicates the marketed product
   - In vitro tests may be so discriminating, but irrelevant, that they would keep an equivalent product from the market
   - A key requirement of a bioequivalence test is the ability to show differences. Setting an appropriate goalpost can deal with a very discriminating test
   - Plasma drug pharmacokinetics could reflect equivalent deposition, dissolution from the nasal suspension formulation, and local concentration. The study may need to involve charcoal block.
   - No consensus was reached for this question.

2. *Can bioequivalence established based on SAR assure bioequivalence for other indications such as recurrence of nasal polyps, or other non-SAR conditions?*

   Subcommittee Comments

   - More data needed
   - No known correlation between SAR and non-SAR

B. Clinical Studies for Local Delivery of Orally Inhaled Corticosteroids (ICS)

1. A number of approaches have been proposed to assess bioequivalence of ICS (e.g., clinical trials, bronchoprovocation tests, steroid reduction model, trials with surrogate measures such as exhaled nitric oxide (eNO), etc).

   Are any of these study designs proven to offer better discrimination in terms of dose-response sensitivity?

   Subcommittee Comments

   - Perform the bioequivalence study at lower doses to avoid plateau of response
   - Of questionable value:
     a. eNO is not yet acceptable as a surrogate marker
     b. Beta-agonist reversibility is a potential marker of response
     c. FEV1 and peak flow changes are small
     d. Changes with methacholine or histamine challenge cannot be differentiated
   - Select the right patients based on entrance criteria

2. *What other in vivo approaches (e.g., surrogate markers) might be sufficiently sensitive and validated to establish in vivo BA and BE for inhaled corticosteroids?*

   Subcommittee Comments

   - eNO is not accepted yet as a surrogate marker

C. PK or PD Studies for Systemic Exposure of Locally Acting Drugs
Are there situations where in vitro data plus systemic PK and systemic PD data can be relied on to assure local drug delivery for either nasal or inhaled drugs?

Subcommittee Comments

- The participants did not have situations that responded to the question
- For orally inhaled products, the in vitro and pharmacokinetic assessments are important but not sufficient. Clinical studies for local delivery are needed.
- The clinical trial could be a bridging study rather than a full-scale study
- When the nasal dose is increased to increase plasma drug levels for quantitation, the dose should remain within the therapeutic dose range

Open Public Hearing Session:

Abdul Zahir, Ph.D., Clay-Park Labs, Inc., presented *Data related to BE testing of Nasal Sprays,and Comments on the BE Studies of Nasal Sprays for Systemic Action*. Harry Dugger, Ph.D., Flemington Pharmaceutical, discussed the *Uniqueness of Lingual Spray Delivery* and

factors to consider if attempting to apply the nasal spray guidance to lingual spray products.

The AAPS Inhalation Technology Focus Group(ITFG)/ International Pharmaceutical Aerosol Consortium (IPAC) Collaboration Technical Teams representatives presented information on the various teams. R. Harris Cummings, Ph.D., Magellan Laboratories, presented the *Overview of the ITFG/IPAC Collaboration*. Stephen J. Farr, Ph.D., Aradigm Corporation, presented on the *Work of the BA/BE Team*. Bo Olsson, Ph.D., AstraZeneca, presented on the *Work of the Specifications Team (Dose Content Uniformity/ Particle Size Distribution).* Carole Evans, Ph.D., Magellan Laboratories, presented on the *Work of the Tests and Methods Team*. Gordon Hansen, Boehringer Ingelheim, presented on the *Work of the Supplier Quality Control Team*. Kaushik J. Dave, R.Ph., M.R.P.S., Ph.D., Schering-Plough Research Institute, presented on the *Work of the Leachables and Extractables Team*. Then Cynthia Flynn, Ph.D., Aventis presented the concluding presentation on ITFG/IPAC Collaboration.

Kenneth B. Neugebauer, Solvay Fluorides, Inc., presented some concerns about CMC Issues.

Eric J. Schenkel, M.D., Valley Clinical Research Center, presented information on the *Growth Effects of Nasal Steroids in Children and Differences among the Steroid Preparations.*

The meeting adjourned on April 26, 2000 at 5:15 p.m.

Prepared by:

Nancy Chamberlin, PharmD.
Executive Secretary
Orally Inhaled and Nasal Drug Products Subcommittee of the
Advisory Committee for Pharmaceutical Sciences