Oral Inhalation and Nasal Drug Products
Expert Panel Planning Meeting
November 8, 1999
Parklawn Conference Room J

## I. Welcome and Purpose of Meeting

Dr. Williams welcomed the group and asked for an introduction of attendees (roster attached). He explained that the purpose of this meeting was to discuss both the substance and the process of the proposed Oral Inhalation and Nasal Drug Products (OINDP) Expert Panel, saying that OPS uses Expert Panels for information sharing with stakeholders. OPS Expert Panels are carefully crafted to include a wide spectrum of input from academia, industry, and other interested bodies. He explained that the role of this Expert Panel is fact-finding and analysis and to link with the Advisory Committee for Pharmaceutical Science, the Pulmonary Drugs Advisory Committee, and the Regulatory Policy Staff. The Expert Panel may reach consensus if desired, or it can present individual views. Its function is purely advisory, as the Agency, by law, cannot delegate its decision-making powers.

This panel will look at science, technical, compendial, and research issues relevant to the OINDP product quality guidances:

**CMC**

1) *Draft Guidance for Industry: Metered Dose Inhaler and Dry Powder Inhaler (DPI) Drug Products* (October 1998)

2) *Draft Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* (May 1999)

**BA/BE**

1) *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (June 1999)

2) *Guidance for Indusry: Bioavailability and Bioequivalence Studies for Orally inhaled Metered Dose Inhalers, Dry Powder inhalers and Inhalation Solutions for Local Action* (under development)

Although the Expert Panel does not have FDA members, Expert Panel discussions on scientific and technical issues can include FDA representatives.

David Mazzo (PhRMA) endorsed timely finalization/implementation of the guidances. Jim Jamieson (IPAC) stated the timeframe for the Expert Panel should not be restricted to 2-3

meetings. Dr. Williams concluded by saying that he hopes for a lively scientific and technical discussion, and that he anticipates the Expert Panel being formed and meeting monthly for a few months. The Agency need not necessarily delay publication of the final guidances, since the guidance process is an ongoing one, with future revisions possible if additional data becomes available for consideration.

## II. CMC Draft Guidances

Dr. Poochikian discussed the two draft CMC guidances intended to cover all inhalation products. He pointed out that they are not regulations, but are purely advisory to industry.

He presented the guidance philosophy, scope, and rationale for assurance of drug product quality. He explained that the draft CMC guidances were based on agency experience with the complex delivery systems and container closure systems associated with OINDP. Goals for the guidances are to provide for consistency and expedite the review process.

In summary, Dr. Poochikian stated that drug product approval means approval of attributes and manufacturing process including process controls, release testing, and stability.

CMC issues of importance to the group were summarized as follows:

- Extractables/Leachables
- Nebulizers/Testing of partial doses
- IND process/Considerations for pivotal clinical trials
- Stability protocols/Key tests for product performance
- Specifications: Content uniformity/Particle size distribution/Impurities and degradants
- Drug delivery
- Excipients
- Tests/Not redundant

Industry representatives commented that CMC stakeholders have sharp differences of opinion on technical and scientific issues, and want the differences to be narrowed. Also, What is important, vs. What is nice to have needs to be clarified, and forming an OINDP Expert Panel provides a unique opportunity to pull together experts for a science and data-driven process to look at CMC and BA/BE issues and gain consensus. Roger Williams added that an Expert Panel could help resolve the issue of relevant tests and reasonable tests.

## III. BCC Issues for Guidances

Dr. Larry Lesko introduced the Biopharmaceutics Coordinating Committee Issues and served as moderator.

Dr. Adams gave a brief status of the *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. He stated that 14 responses from industry were received at the Docket.

The *Guidance for Indusry: Bioavailability and Bioequivalence Studies for Orally inhaled Metered Dose Inhalers, Dry Powder inhalers and Inhalation Solutions for Local Action* is still under development.

Dr. Adams explained that the bioavailability measurement is for product quality BA only and that pharmacokinetic studies are inadequate to fully document bioequivalence establishment. He summarized the General BE Approach as pharmaceutical inequivalence, in vitro BE data, and in vivo BE data.

BA/BE issues of importance to the group were summarized as follows:

- Need for absolute BA
- Feasibility of pharmacokinetic studies - what does this mean? PK can provide more than safety (absorption, bioavailability)
- Study population: healthy volunteers vs. patients - distinguish BA vs. BE
- BE criteria - option of scaling/clarity of specific statistical criteria/systemic vs. local BE
- Issue of dose - meaning of high dose
- Safety - Cmax only vs. complete AUC
- Source of variability in BE testing - role of deposition studies?
  - (When detection is difficult - PK)
  - (Solution vs. Suspension)
- Scientific appropriateness of in vitro tests for BE testing (in vivo tests)
  - Example - Spray pattern and plume geometry
- Powder-based systems - in vitro tests - appropriate?

## IV. Product Quality Research Institute (PQRI)

Dr. Hussain provided a description of PQRI and its research capabilities, which include collection of current data, as well as the generation of new data through research. The purpose of PQRI is to provide a continuing scientific base for regulatory policy. It is being organized into technical committees and working groups, and the Biopharmaceutics Technical Committee already formed, includes the area of OINDP.

Key Issues:

- Do we need OINDP research?
- How do we move into PQRI?

**V. Expert Panel Plans**

Walter Hauck emphasized that systemically active drugs should be off the table for the Expert Panel.

Dr. Sam Shum, representing AAPS, was selected to serve as the chair of the Expert Panel. The group decided to form two subcommittees, CMC and BA/BE. IPAC agreed to host subcommittee sessions in December in order to develop topics of concern in more detail.

Jim Jamieson (IPAC) indicated the AAPS/IPAC Focus Group on Inhalation Technology will make its work available to the OINDP Expert Panel. The OINDP Expert Panel will build consensus based on new information vs. current practice.

It was agreed the OINDP Expert Panel would meet towards the end of January 2000.

**VI. Adjournment**

## Oral Inhalation and Nasal Drug Products Expert Panel Planning Meeting Attendees:

**Academia**
Dr. Hartmut Derendorf
Dr. Richard N. Dalby
Dr. Walter Hauck

**USP**
Dr. Margareth Marques

**AAPS**
Dr. Charan Behl
Dr. Sam Shum

**IPAC**
Mr. Jim Jamieson
Dr. Lester Harrison

**GPIA/NAPM/NPA**
Dr. Michael Baaske

Dr. Sylvie Laganiere

**CHPA**
Mr. Kenneth Warner

**PhRMA**
Dr. David Mazzo
Dr. Thomas MacGregor

**FDA**
Dr. Roger Williams
Dr. Martin Himmel
Dr. Guirag Poochikian
Dr. Allen Rudman
Dr. Vinod Shah
Dr. Dale Conner
Dr. Ajaz Hussain
Dr. Tom Layloff
Dr. Yi Tsong
Dr. Eric Sheinin
Dr. Yuan-yuan Chiu
Dr. Charles Hoiberg
Dr. Frank Holcombe
Dr. Larry Lesko
Douglas Sporn
Larry Ouderkirk
Dr. Wallace Adams
Leanne Cusumano
Dr. Craig Bertha
Dr. Mark Vogel
June Cory
David Morley