Orally Inhaled and Nasal Drug Products (OINDP)

Subcommittee Report

Background Information

Advisory Committee for Pharmaceutical Science Meeting

November 15, 2000

Rockville, MD

This background information document includes the following information:

1. Titles of three draft guidances for orally inhaled and nasal drug products.

2. Meetings held since issuance of the three draft guidances.

3. April 26, 2000, OINDP Subcommittee meeting participants

4. Agenda for the April 26, 2000, OINDP Subcommittee meeting.

5. Questions asked of the OINDP Subcommittee.

   The main focus of the April 26 meeting was to obtain responses from the Subcommittee on a series of questions that would be useful in refining the draft guidances, with particular emphasis on bioavailability and bioequivalence guidances for locally acting nasal and orally inhaled drugs.

Orally Inhaled And Nasal Drug Products (OINDP)

Draft Guidances

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation
(October 1998)

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products: Chemistry, Manufacturing, and Controls Documentation
(May 1999)

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
(June 1999)

Meetings

AAPS Workshop on Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery (Co-Sponsored with FDA and USP), 3-4 June 1999

OINDP Expert Panel Planning Meeting, 8 November 1999

Meeting of the OINDP Subcommittee of ACPS, 26 April 2000

OINDP Subcommittee Meeting of April 26, 2000

PARTICIPANTS

Vincent H.L. Lee, Ph. D., Chairperson
Nancy Chamberlin, Executive Secretary

MEMBERS

Richard Ahrens, M.D.
James Li, M.D., Ph.D.
Stanley j. Szefler, M.D.

CONSUMER REPRESENTATIVE

Gloria L. Anderson, Ph.D.

INVITED GUESTS

Michael Baaske, Ph. D.
Charan 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.
Thomas R. MacGregor, Ph. D.
Nikhil J. Parekh, Ph. D.
Sam C. K. Shum, Ph. D.

FDA

Wallace P. Adams, Ph.D.
Guirag Poochikian, Ph. D.
Eric Sheinin, Ph. D.

ORALLY INHALED AND NASAL DRUG PRODUCTS SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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

AGENDA

8:30	Call to Order/Chairman's Remarks	Vincent H. L. Lee, Ph.D.
8:40	Introduction and Objectives	Eric Sheinin, Ph.D.
	Chemistry, Manufacturing and Controls: Content Uniformity	
8:55	Current FDA Practices for NDAs	Guirag Poochikian, Ph.D.
9:10	Alternative Statistical Approaches	Walter W. Hauck, Ph.D.
9:30	Subcommittee Discussion	
10:00	**Break**	
	Bioavailability (BA) and Bioequivalence (BE)	
10:15	Current FDA BA/BE Background and Issues	Wallace P. Adams, Ph. D.
	In Vitro BA and BE Testing	
10:30	Profile Analysis of Cascade Impactor Data: Proposed FDA Approach	Yi Tsong, Ph.D.
11:00	Profile Analysis of Cascade Impactor Data: An Alternative View	Andrew R. Clark, Ph.D.
11:30	DPIs: In Vitro Tests for Performance and Comparability	David Ganderton, Ph.D.
12:00	Subcommittee Discussion	
12:30	**Lunch**	
1:30	Open Public Hearing	

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

AAPS inhalation Technology Focus Group (ITFG) / International Pharmaceutical Aerosol Consortium (IPAC) Collaboration Technical Teams:

	Overview of the ITFG/IPAC Collaboration	R. Harris Cummings, Ph.D. Magellan Laboratories
	Presentation on the Work of the BA/BE Team	Stephen J. Farr, Ph. D. Aradigm Corporation
	Presentation on the Work of the Specifications Team (Dose Content Uniformity/Particle Size Distribution)	Bo Olsson, Ph. D. Astra Zeneca
	Presentation on the Work of the Tests and Methods Team	Carole Evans, Ph. D. Magellan Laboratories
	Presentation on the Work of the Leachables and Extractables Team	Dave Kaushik, R.Ph., M.R.P.S., Ph.D. Schering-Plough Research Institute
	Concluding Presentation on ITFG/IPAC Collaboration	Cynthia Flynn, Ph.D. Aventis
	CMC Issues	Kenneth B. Neugebauer Solvay Fluorides, Inc.
	Growth Effects of Nasal Steroids in Children And Differences Among the Steroid Preparations	Eric J. Schenkel, M.D. Valley Clinical Research Center

In Vivo BA and BE

2:30	Clinical Studies for Local Delivery of Nasal Aerosols and Sprays	Izabela Roman, M.D., Ph.D.
2:50	Clinical Studies for Local Delivery of Orally Inhaled Corticosteroids	Richard C. Ahrens, M.D.
3:10	**Break**	
3:25	Subcommittee Discussion	

3:50	PK and PD Studies for Systemic Exposure of Locally Acting Drugs	
3:50	Current FDA PK Practices	Venkata R. S. Uppoor, Ph.D.
4:00	Industry View	Lester I. Harrison, Ph.D.
4:20	Academic View	Hartmut Derendorf, Ph.D.
4:40	Subcommittee Discussion	

Adjourn

OINDP SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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QUESTIONS

CMC - CONTENT UNIFORMITY

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

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

IN VITRO BA AND BE TESTING

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?*

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?*

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?*

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

IN VIVO BA AND BE TESTING

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?

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

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?

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?*

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?