

---

# Guidance for Industry

## Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

### ***DRAFT GUIDANCE***

*This guidance document is being distributed for comment purposes only.*

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the Federal Register notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the Federal Register.

For questions on the content of the draft document contact Wallace Adams, 301-594-5618.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**Biopharmaceutics  
April 2003**

# Guidance for Industry

## Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

*Additional copies are available from:*

*Division of Drug Information (HFD-240)  
Center for Drug Evaluation and Research (CDER)  
5600 Fishers Lane,  
Rockville, MD 20857 (Tel) 301-827-4573  
Internet at <http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**Biopharmaceutics**

**April  
2003**

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
<b>A.</b>	<b>BA and BE Data .....</b>	<b>3</b>
	1. <i>Local Delivery BA/BE Concepts.....</i>	3
	2. <i>Systemic Exposure and Systemic Absorption BA/BE Concepts.....</i>	4
<b>B.</b>	<b>CMC and In Vitro BA Tests (Noncomparative) Versus BE Tests (Comparative) .....</b>	<b>5</b>
<b>III.</b>	<b>FORMULATION AND CONTAINER AND CLOSURE SYSTEM.....</b>	<b>5</b>
<b>A.</b>	<b>Formulation.....</b>	<b>5</b>
<b>B.</b>	<b>Container and Closure System.....</b>	<b>6</b>
<b>IV.</b>	<b>DOCUMENTATION OF BA AND BE .....</b>	<b>6</b>
<b>A.</b>	<b>NDAs .....</b>	<b>6</b>
<b>B.</b>	<b>ANDAs .....</b>	<b>6</b>
	1. <i>Solution Formulations.....</i>	7
	2. <i>Suspension Formulations with PK Systemic Exposure Data.....</i>	7
	3. <i>Suspension Formulations without PK Systemic Exposure Data.....</i>	7
<b>C.</b>	<b>Postapproval Change .....</b>	<b>8</b>
<b>V.</b>	<b>IN VITRO STUDIES .....</b>	<b>8</b>
<b>A.</b>	<b>Batches and Drug Product Sample Collection.....</b>	<b>8</b>
	1. <i>NDAs.....</i>	8
	2. <i>ANDAs.....</i>	9
<b>B.</b>	<b>Tests and Metrics .....</b>	<b>9</b>
	1. <i>Single Actuation Content (SAC) Through Container Life.....</i>	11
	2. <i>Droplet Size Distribution by Laser Diffraction.....</i>	12
	a. <i>Nasal sprays.....</i>	12
	b. <i>Nasal aerosols.....</i>	13
	3. <i>Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor... 14</i>	14
	a. <i>Nasal sprays: Drug in Small Particles/Droplets.....</i>	14
	b. <i>Nasal aerosols: Particle/Droplet Size Distribution.....</i>	15
	4. <i>Drug Particle Size Distribution by Microscopy.....</i>	15
	5. <i>Spray Pattern.....</i>	16
	a. <i>For nonimpaction systems.....</i>	17
	b. <i>For impaction systems.....</i>	17
	c. <i>For both nonimpaction and impaction systems.....</i>	18
	6. <i>Plume Geometry.....</i>	18
	7. <i>Priming and Repriming.....</i>	20
<b>VI.</b>	<b>CLINICAL STUDIES FOR LOCAL DELIVERY .....</b>	<b>20</b>
<b>A.</b>	<b>General Information .....</b>	<b>20</b>
	1. <i>NDAs.....</i>	20
	2. <i>ANDAs.....</i>	21
<b>B.</b>	<b>Clinical Study Batches.....</b>	<b>21</b>

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

C.	Clinical BE Study Design and Subject Inclusion Criteria.....	22
D.	Clinical BE Study Endpoints .....	23
VII.	PK STUDIES FOR SYSTEMIC EXPOSURE .....	24
A.	General Information .....	24
B.	Study Batches.....	25
C.	Study Design and Subject Inclusion Criteria .....	25
D.	Study Measures .....	26
VIII.	PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION.....	26
A.	General Information .....	26
B.	Clinical Study Batches.....	27
C.	Clinical BE Study Designs and Subject Inclusion Criteria .....	27
D.	Clinical BE Study Endpoints for Corticosteroids .....	28
IX.	NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING .....	29
X.	MULTIPLE STRENGTHS.....	29
A.	Solution Formulation Nasal Sprays.....	30
B.	Suspension Formulation Nasal Sprays.....	30
XI.	SMALLER CONTAINER SIZES .....	31
	REFERENCES.....	31
	TABLE 1 .....	32

*Note: The following stand alone documents will be provided when completed.*

**APPENDIX A: DECISION TREE FOR PRODUCT QUALITY STUDIES**

**APPENDIX B: STATISTICS FOR IN VITRO BA DATA**

**APPENDIX C: NONPROFILE IN VITRO BE DATA — USING PBE STATISTICS**

**APPENDIX D: NONPROFILE IN VITRO BE DATA — USING PBE STATISTICS**

**APPENDIX E: STATISTICS FOR IN VITRO PROFILE COMPARISONS**

**APPENDIX F: STATISTICS FOR ALLERGIC RHINITIS STUDIES**

**APPENDIX G: STATISTICS FOR SYSTEMIC EXPOSURE AND ABSORPTION**

## **Guidance for Industry<sup>1</sup>**

### **Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### **I. INTRODUCTION**

This guidance is intended to provide recommendations to applicants who are planning product quality studies to measure bioavailability (BA) and/or establish bioequivalence (BE) in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for locally acting drugs in nasal aerosols (metered-dose inhalers (MDIs)) and nasal sprays (metered-dose spray pumps). This guidance addresses BA and BE studies of prescription corticosteroids, antihistamines, anticholinergic drug products, and the over-the-counter (OTC) mast-cell stabilizer cromolyn sodium. Applicability of the guidance to other classes of intranasal drugs that may be developed in the future should be discussed with the appropriate CDER review division.

This guidance does not cover studies of nasal sprays included in an applicable OTC monograph<sup>2</sup> or studies of (1) metered-dose products intended to deliver drug systemically via the nasal route or (2) drugs in nasal nonmetered dose atomizer (squeeze) bottles that require premarket approval.

The first draft of this guidance was issued in June 1999 for comment. Because of changes made as a result of comments received to the docket, internal discussions, and deliberations of the Advisory Committee for Pharmaceutical Science, we have decided to issue the guidance once again in draft. A series of attachments are being developed and will be posted with this draft

---

<sup>1</sup> This guidance has been prepared by the Oral Inhalation and Nasal Drug Products Technical Committee, Locally Acting Drug Products Steering Committee, Biopharmaceutics Coordinating Committee, with contributions from the Inhalation Drug Products Working Group, the Chemistry, Manufacturing, and Controls Coordinating Committee, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> 21 CFR 341. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.