

---

# 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### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Wallace P. Adams (301) 594-5651 (CDER).

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
June 1999

---

X:\CDER\GUID\2070DFT.WPD  
5/27/99

# Guidance for Industry

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

Additional copies are available from:

Drug Information Branch (HFD-210)  
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)  
June 1999

*X:\CDERGUID\2070DFT.WPD  
May 27, 1999*

## Table of Contents

|       |  |    |
|-------|--|----|
| I     | INTRODUCTION .....   | 1  |
| II.   | BACKGROUND .....   | 2  |
| A.    | BIOAVAILABILITY AND BIOEQUIVALENCE DATA .....  | 2  |
| B.    | CMC TESTS AND IN VITRO BA TESTS (NONCOMPARATIVE) VERSUS<br>BE TESTS (COMPARATIVE) .....                  | 4  |
| III.  | FORMULATION AND CONTAINER AND CLOSURE SYSTEM .....   | 5  |
| A.    | FORMULATION .....  | 5  |
| B.    | CONTAINER AND CLOSURE SYSTEM .....   | 5  |
| IV.   | DOCUMENTATION OF BIOAVAILABILITY AND BIOEQUIVALENCE .....  | 6  |
| A.    | INDs/NDAs .....  | 6  |
| B.    | ANDAs .....  | 6  |
| C.    | POSTAPPROVAL CHANGE .....  | 8  |
| V.    | BIOAVAILABILITY AND BIOEQUIVALENCE: IN VITRO STUDIES .....   | 8  |
| A.    | BATCHES AND DRUG PRODUCT SAMPLE COLLECTION .....   | 8  |
| B.    | TESTS AND METRICS .....  | 9  |
| VI.   | BIOAVAILABILITY AND BIOEQUIVALENCE: CLINICAL STUDIES FOR LOCAL<br>DELIVERY .....                         | 16 |
| A.    | GENERAL INFORMATION .....  | 16 |
| B.    | BE CLINICAL STUDY ENDPOINTS .....  | 17 |
| C.    | CLINICAL STUDY BATCHES .....   | 17 |
| D.    | CLINICAL BE STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA .....   | 17 |
| VII.  | BIOAVAILABILITY AND BIOEQUIVALENCE: PK SYSTEMIC EXPOSURE<br>STUDIES .....                                | 19 |
| VIII. | BIOAVAILABILITY AND BIOEQUIVALENCE: PHARMACODYNAMIC OR<br>CLINICAL STUDIES FOR SYSTEMIC ABSORPTION ..... | 20 |
| A.    | GENERAL INFORMATION .....  | 20 |
| B.    | BE STUDY ENDPOINTS FOR CORTICOSTEROIDS .....   | 20 |
| C.    | CLINICAL STUDY BATCHES .....   | 21 |
| D.    | CLINICAL STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA .....  | 21 |
| IX.   | STATISTICAL ANALYSES .....   | 22 |

X:\CDER\GUID\2070DFT.WPD  
May 27, 1999

|     |   |    |
|-----|---|----|
| A.  | IN VITRO BA DATA .....  | 22 |
| B.  | IN VITRO BE DATA: NONPROFILE ANALYSES USING A CONFIDENCE<br>INTERVAL APPROACH ..... | 22 |
| C.  | IN VITRO BE DATA: SUPPORTIVE NONPROFILE AND PROFILE<br>ANALYSES .....               | 26 |
| D.  | IN VITRO BE DATA: PROFILE ANALYSES USING A CONFIDENCE<br>INTERVAL APPROACH .....    | 26 |
| E.  | IN VIVO BE DATA: CATEGORICAL ENDPOINTS .....  | 28 |
| X.  | MULTIPLE STRENGTHS .....  | 28 |
| A.  | SOLUTION FORMULATION NASAL SPRAYS .....   | 29 |
| B.  | SUSPENSION FORMULATION NASAL SPRAYS .....   | 29 |
| XI. | SMALLER CONTAINER SIZES .....   | 30 |
|     | REFERENCES .....  | 30 |

X:\CDERGUID\2070DFT.WPD  
May 27, 1999

*Draft - Not for Implementation*

**GUIDANCE FOR INDUSTRY<sup>1</sup>**

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

**I. INTRODUCTION**

This guidance is intended to provide recommendations to applicants who are planning product quality studies to measure bioavailability (BA) and/or establish (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). Product quality includes chemistry, manufacturing, and controls (CMC), microbiology, certain BA information, and BE information (i.e., information that pertains to the identity, strength, quality, purity, and potency of a drug product). Product quality BA and BE are reflective of potency, in that release of the drug substance from the drug product should be assessed and controlled to achieve a reproducibly potent product. BA studies can address many questions, but this guidance discusses studies that focus on product performance (i.e., release of drug substance from drug product). A BE study is normally used to compare a test product (T) to a precursor product (R) — the to-be-marketed product is compared to a pivotal clinical trial material; a generic product is compared to a reference listed drug.

Product quality approaches should be similar for all nasal aerosols and nasal sprays where the active ingredient/active moiety is intended for local action, regardless of drug or drug class. This guidance should be used with other, more general CMC and BA and BE guidances available from CDER (Internet, <http://www.fda.gov/cder/guidance/index.htm>). Product quality information is different from, yet complementary to, the clinical safety and efficacy information that supports approval of an NDA. For information about the type of safety and efficacy information that may be needed for a new active ingredient/active moiety intended for local action in the nose, or for a new product such as a nasal aerosol that may include an active ingredient/active moiety previously approved in a nasal spray, appropriate CDER review staff should be consulted.

---

<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. This guidance represents the Agency's current thinking on product quality information related to inhalation aerosols and metered dose spray pumps for nasal delivery. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

X:\CDERGUID\2070DFT.WPD  
May 27, 1999

# 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.