IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

NASAL INNOVATION FORUM

NAVIGATING REGULATORY BRIDGING STRATEGIES FOR NASAL PRODUCT DEVELOPMENT

Rachel Ward, PhD

Director, Emerging Enterprise

Kymanox®

Nasal Spray Products

Regulatory Pathways Drug-Device Combinations

How are Nasal Spray Products Regulated?

Nasal Spray Products are frequently **drug-biologic-device combination products**

DRUG CONSTITUENT
Disease Modifying Agent

+

DEVICE CONSTITUENT
Delivery Device

=

DRUG –LED COMBINATION PRODUCT

Regulatory Approval Pathways

Two pathways leveraging previously approved products to streamline development

ANDA
Generics

505(b)(2)
Hybrid Pathway

Regulatory pathway is determined by similarity [sameness] to comparator product

Abbreviated New Drug Application (ANDA)

Establishing Sameness & Bioequivalence

What is an ANDA?

An application submitted and approved under **section 505(j)** of the FD&C Act for a drug product that is a **duplicate** of a previously approved drug product.

KEY FOUNDATION
Relies on FDA's finding that the previously approved drug product (the **Reference Listed Drug (RLD))** is safe and effective.

www.fda.gov

Primary Requirement

Bioequivalence to the RLD must be established

Sameness Requirement

Test product must be the same as RLD with respect to:

- ✓ Active ingredient(s)
- ✓ Conditions of Use
- ✓ Dosage form
- ✓ Route of Administration
- ✓ Strength
- ✓ Labeling (with permissible differences)

KEY LIMITATION

Cannot be submitted if clinical investigations are necessary to establish safety & effectiveness.

NO UNIQUE CLINICAL CLAIMS

505(b)(2) Pathway: Streamlined Development

Leveraging Prior Data via Scientific Bridging

What is a 505(b)(2) Application?

A **New Drug Application (NDA)** that contains full reports of investigations of safety & effectiveness, where at least some of the information required for approval comes from **studies not conducted by or for the applicant**, and for which the applicant has not obtained a right of reference of use.

Sources of Data

1) Agency's finding of safety and/or effectiveness for a listed drug
2) Published literature

SCIENTIFIC BRIDGE

Reliance on data is done via establishing a **scientific bridge** to a Listed Drug (LD) or subject of study in published literature

LD Selection

- ✓ Potential LD is chosen from list of RLD's in the FDA's **Orange Book.**
- ✓ If discontinued, may still serve as LD if there was Federal Register determination that product was not discontinued for safety effectiveness reasons.
- ✓ If LD not commercially available for testing, an **equivalent Reference Standard (RS)** may be used.

Scientific Bridging Applications

Types and Purposes

What is "Bridging"?

Bridging refers to the process of establishing the **scientific relevance** of information developed in an earlier phase of the development program or another development program to support the combination product for which an applicant is seeking approval.

01

LD BRIDGE

Establishing a **scientific bridge to a LD** to rely on the Agency's findings of safety and effectiveness *(505(b)(2) pathway)*

02

BRIDGING DURING PRODUCT DEVELOPMENT

Leveraging information from early studies to support the to-be-marketed product

Examples

505(b)(2) Pathway

- ✓ Similar formulation/API with a **bespoke device**
- ✓ **New route of administration**

Sponsor Owned Data

- ✓ Bridging early-stage clinical studies to final **to-be-marketed formulations**

Clinical Bridging Approach

FDA Guidance Framework for Identifying Gaps to Inform a Bridging & Leveraging Approach

01 — Identify Differences & Assess Impact

Identify all differences between *Combination Products A* and *B*, and consider the potential effect of the individual and aggregate differences on the **safety and effectiveness profile.**

Examples: Changes in AE profile, Changes in dose accuracy, Changes in manufacturing process that impact drug quality

02 — Inventory Existing Information

Identify existing information for *Combination Product B* and compare it to the **safety and effectiveness submission requirements** necessary for approval.

03 — Establish Bridging Strategy

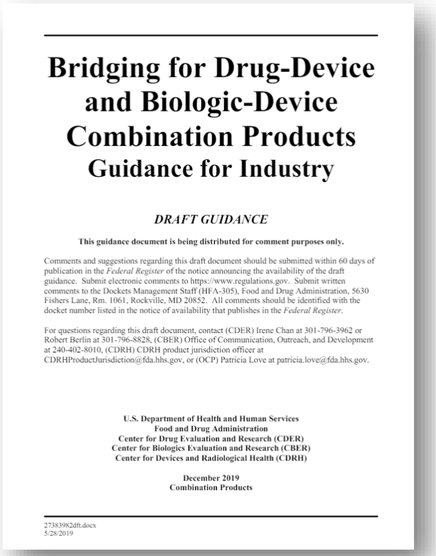
Identify and explain **how and why** existing information on *Combination Product A* can be bridged and leveraged to support approval of *Combination Product B*, accounting for considerations from Steps 1 and 2.

04 — Address Remaining Gaps

Focus on any **information gaps remaining** from Steps 2 and 3, and consider whether other existing information, outside of that directly gathered for *Combination Products A* or *B*, can be reviewed and used to address these gaps under proposed regulatory pathway.

05 — Final Gap Analysis

Compare findings from Steps 2 through 4 and identify the **remaining gaps in information** that need to be addressed in the product application.



Bridging for Drug-Device and Biologic-Device Combination Products
Guidance for Industry

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 in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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 (CDER) Irene Chan at 301-796-3962 or Robert Berlin at 301-796-8828, (CBER) Office of Communication, Outreach, and Development at 240-402-8010, (CDRH) CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov, or (OCP) Patricia Love at patricia.love@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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Combination Products

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[Combination Product Clinical Bridging Guidance (fda.gov)]

Establishing a Scientific Bridge

Methods for Development Testing

What are the key distinctions from ANDAs?

- ✓ **Products that rely on an LD do NOT have to Bioequivalent (BE) to the LD**
- ✓ **Scientific bridge DOES need to be established to determine what from the LD label can be utilized**

BRIDGE ESTABLISHMENT METHODS

Scientific bridges are most often established via **comparative Pharmacokinetic (PK) bridging studies**

21 CRF 320.24: In vivo and/or in vitro methods can be used to establish BE, and these methods can also be utilized to establish a scientific bridge:

- ✓ In vitro-in vivo correlation (IVIVC)
- ✓ Pharmacokinetic and/or Pharmacodynamic (PD) studies

BA GUIDANCE

BA ≥ LD

Rely on LD Efficacy

BA ≤ LD

Rely on LD Safety

KEY PK PARAMETERS

C_{max} : Maximum plasma concentration

AUC_{0-inf} : Total drug exposure over time

BENEFITS & APPLICATIONS

Clinical Program Reduction

Single PK bridging study may replace clinical safety/efficacy data

Label Leveraging

Reduced testing by leveraging from LD label

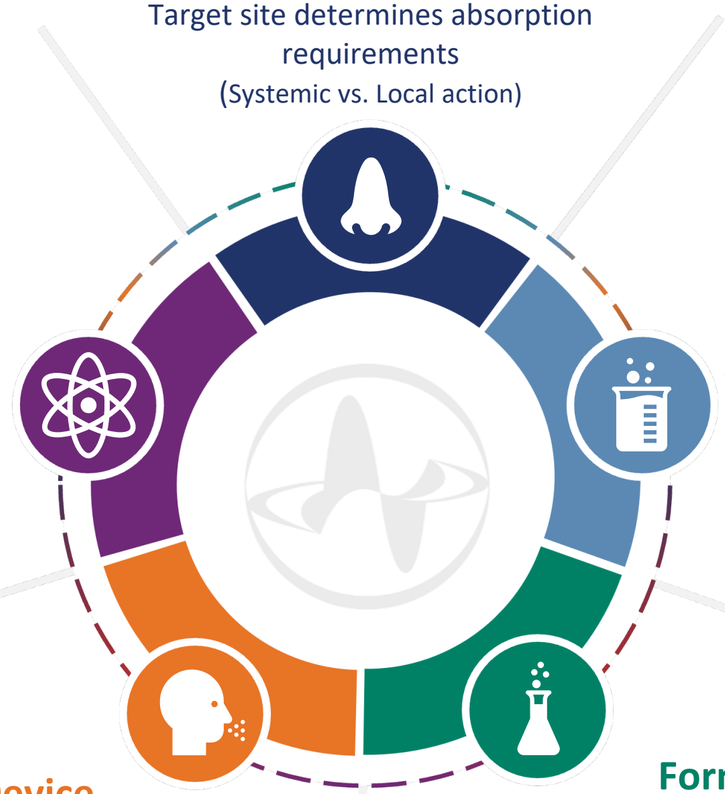
Key Variables Influencing Bioavailability

Development Goal

Optimize which variables can be kept the **same/similar** as other products while **not impacting** the unique claims.

Location of Action
Target site determines absorption requirements
(Systemic vs. Local action)

API CHARACTERISTICS
API characteristics that impact drug delivery
- ✓ **Size/molecular weight**
- ✓ **Lipopilicity**



Dose Volume
Volume of drug product delivered per administration affecting local concentration and absorption kinetics

Delivery Device
Device characteristics that impact drug delivery
- ✓ Spray administration angle
- ✓ Plume geometry

Formulation
API Characteristics & Formulation Design
- ✓ **Drug Product:** Particle diameter, excipients
- ✓ **Physical Attributes:** Viscosity, liquid vs. spray dried

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Key Variables Influencing Bioavailability

API Characteristics

Size of API

Impact of molecular weight on intranasal bioavailability

LOW-MOLECULAR WEIGHT	HIGH-MOLECULAR WEIGHT
✓ Relatively high bioavailability	✓ Low bioavailability
✓ Low variability	✓ High variability

Compared with injections

Clinical Example: Zanamivir (Antiviral)

Molecular Weight: 332 Da Log P: -3.2 (very hydrophilic)

Intranasal Bioavailability: ~11%

Intranasal	Intravenous
Cmax: 3% of IV	Cmax: 100%
Tmax: 1.8 h	Tmax: 0.3 h

(Cass et al., 1999)

Lipophilicity

Hydrophilic vs. Lipophilic drug absorption characteristics

HYDROPHILIC (low log P)	LIPOPHILIC
✓ Poor membrane permeation	✓ Better membrane interaction
✓ Lower bioavailability	✓ Still limited by nasal barriers
✓ Delayed absorption	

Clinical Example: Sumatriptan (Migraine)

Molecular Weight: 295 Da Log P: 0.9 (more lipophilic)

Intranasal Bioavailability: ~16%

Intranasal	Intravenous
BA: ~16%	BA: ~100%
Tmax: 1.5 h	Tmax: 0.17 h

(Cass et al., 1999)

Key Variables Influencing Bioavailability

Formulation

Formulation changes can drastically improve the bioavailability of nasally-delivered products.

Classic Example: Morphine

The Challenge

IN bioavailability of morphine in **aqueous solution** is low due to:

- ✓ Low lipophilicity
- ✓ Absorption mainly in small intestine after swallowing

Baseline: ~10%

Formulation Solutions

Chitosan Microspheres	27%
Chitosan Solution	55%
Starch Microspheres + Lysophosphatidylcholine	75%

(Illum et al., 2002).

FORMULATION ENHANCEMENT STRATEGIES

- PRODRUGS
- SOLUBILIZATION AGENTS
- ENZYME INHIBITORS
- ABSORPTION PROMOTERS
- BIOADHESIVES
- MICROSPHERES

KEY CONSIDERATION

Different excipients can lead to variations in **particle size**, which directly impacts absorption

Key Variables Influencing Bioavailability

Formulation Cont.

FDA Guidance: *"Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients"*

What are New Excipients?

Any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that:

a) Are not intended to exert therapeutic effects at the tended dosage (although they may improve product delivery)

b) Are not fully qualified by existing safety data with respect to:
   - Currently proposed level of exposure
   - Duration of exposure
   - Route of administration

REQUIRED NONCLINICAL STUDIES PACKAGE

Risk-Benefit Assessment *Establish permissible and safe limits*	**Genetic Toxicology** *Standard battery (ICH S2B)*
Pharmacological Activity *Standard Battery of tests (ICH S7A)*	**1-Mo. Repeat-Dose Toxicology** *Intranasal administration in rats & dogs*
Acute Toxicology Studies *Single-dose toxicity evaluation*	**Reproductive Toxicology** *ICH S5A and S5B guidelines*

KEY CONSIDERATION

When optimizing formulation to improve bioavailability, consider if additional **nonclinical data** will be needed to support a new excipient

Key Variables Influencing Bioavailability

Dose Volume and Frequency

Physical Limitations within the Nasal Cavity

LIQUID NASAL SPRAYS

Range: **20 µL to 200 µL**

Standard: **100 µL** most common

POWDER DELIVERY DEVICES

Typical Limit: **50 mg**

Studies Report: **10-25 mg** maximum acceptance

Danger of Large Volumes

DRUG RUNDOWN

Drug runs down the posterior pharynx

UNWANTED ABSORPTION

Systemic absorption through gastrointestinal tract

REDUCED EFFICCACY

Non-linear effects on bioavailability

Clinical Evidence

Newman et al. (1994)

- ✓ 80 µL in two nostrils
- ✓ Similar coverage area to 140 µL in single dose

Newman et al. 1994

Harris et al. (1988)

- ✓ 100 µL in one nostril
- ✓ Larger deposition area vs. 50 µL in two nostrils

Harris et al. (1988a)

KEY FINIDNG

Both studies demonstrated that **higher deposition area** did **NOT** result in **higher bioavailability/efficacy**

Key Variables Influencing Bioavailability

Location of Action

BA/BE assessments for **locally acting nasal products** are challenging compared to systemically absorbed products because **conventional PK bridging approach often does not apply;** the drug may not be measurable systemically, and even if it is, it does not adequately represent the activity at the site of action.

Mechanism of Action

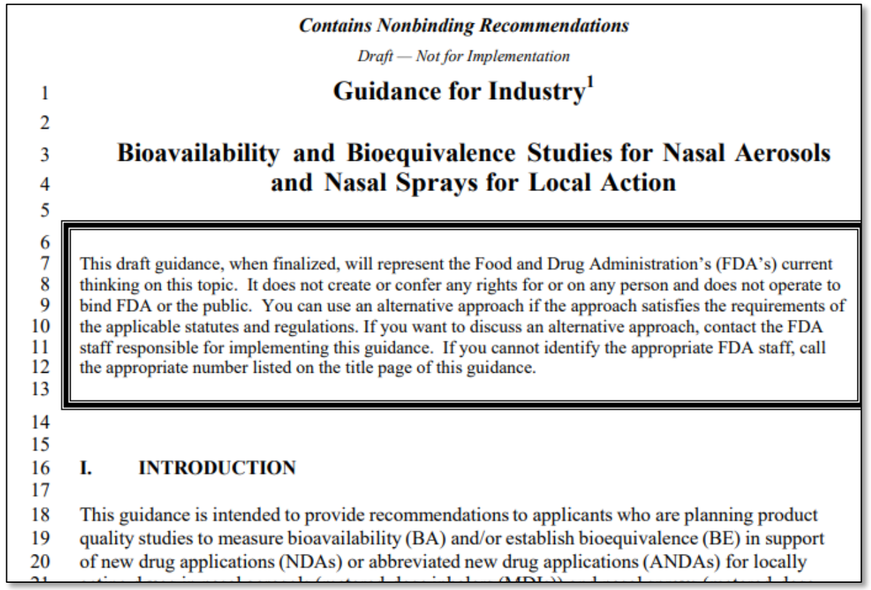
Locally acting drugs are **topically deposited** and directly available at **sites of action**

Systemic Absorption Routes

1) Drug absorbed via the **nasal mucosa**
2) Drug ingested and absorbed through the **gastrointestinal tract**

Formulation-Specific Data Requirements

Type of formulation influences required BE/BE data → Solution **vs** Suspension



Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]

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

BA/BE Study Considerations

Must evaluate both local delivery & systemic absorption

Local availability depends on:

- ✓ Particle size & distribution
- ✓ Drug dissolution
- ✓ Mucosal absorption
- ✓ Nasal clearance rate

Key Variables Influencing Bioavailability

Delivery Device

Impact on Absorption

Plume geometry significantly impacts **absorption** as it affects the spray's **reach and distribution**

Targeting Strategy Example

Narrow spray pattern for targeting the olfactory region to increase **nose-to-brain delivery**

Olfactory Region: Located at roof of nasal cavity; ~5-7% of epithelial surface area

Device Design Factors

Device design alone can impact plume geometry

Orifice Diameter **Orifice Diameter**

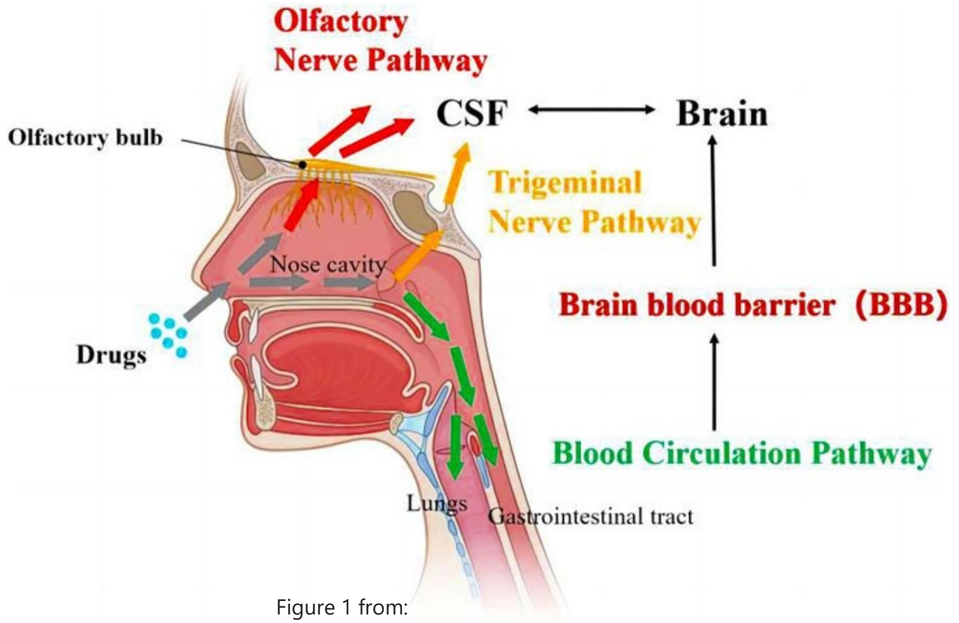


Figure 1 from:
Yang X, Tan J, Guan J. Lipid-based nanoparticles via nose-to-brain delivery: a mini review. *Frontiers in Cell and Developmental Biology*. 2023; 11

Bridging Study Considerations

Usability variations must be taken into account when considering bridging studies/products:

Actuation Force: Variations in force required for device activation

Administration Technique: Patient-to-patient variability in device use

Start at the End: Building the Strategy

LD Selection, TPP, & Annotated Labeling

SELECTION OF LD

Strategic principles for LD Selection:

- ✓ **Flexibility:** LD does not have to be another nasal product
- ✓ **Advantage:** Can help reduce the **variability** in the comparison of the LD

TARGET PRODUCT PROFILE

Outlines key **development and labeling details**

- ✓ **Pro Tip:** Options/ranges are still helpful!

ANNOTAED LABEL STRATEGY

List out what sections of the label are desired to be based on the LD labeling, and what claims are new

- ✓ **Leverage from LD:** Sections based on LD labeling
- ✓ **New Claims:** New substantiating data

In addition to Safety and Efficacy, don't forget:

- Drug Interactions
- Nonclinical
- Specific Populations
- Clinical Pharmacology

Success Story

Intranasal naloxone products were approved via the 505(b)(2) pathway using **injectable Narcan** as the LD.

Includes OTC nasal naloxone products

FDA Engagement in Bridging Strategy

Derisking Variability with Clear Guidance Upfront

Utilization of early FDA interactions is KEY when attempting to implement nasal bridging strategies

The CHALLENGE

Lack of clear guidance due to numerous factors that could impact bridging means development programs need to be **aligned with the Agency**

The OPPORTUNITY

Nonclinical programs can often by **streamlined**

- ✓ Reduced study requirements
- ✓ Faster development timelines
- ✓ Lower development costs

The SOLUTION

Early alignment with FDA through strategic interactions

Proactive engagement before committing to expensive studies

The VALUE

Early alignment can help streamline downstream **clinical development** by **de-risking variability**

Early FDA Meeting → **Clear Strategy** → **Reduced Risk**

