Guidance for Industry

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

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

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.

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[1] 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.

This guidance covers BA and BE studies of prescription corticosteroids, antihistamines, anticholinergic drug products, and the over-the-counter (OTC) mast-cell stabilizer cromolyn sodium. The guidance does not cover studies of nasal sprays included in an applicable OTC monograph or studies of (1) metered-dose products intended to deliver drug systemically via the nasal route[2] or (2) drugs in nasal nonmetered dose atomizer (squeeze) bottles that require premarket approval.

Note: Detailed chemistry, manufacturing, and controls information relevant to nasal aerosols and nasals sprays are presented in two draft guidances, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler(DPI) Drug Products — Chemistry, Manufacturing, and Controls Documentation* (October 1998) and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Product* (available June 1999). These draft guidances, when finalized, will provide complementary information on the BA/BE testing methods recommended in this guidance.

II. BACKGROUND

A. BIOAVAILABILITY AND BIOEQUIVALENCE DATA

Bioavailability is defined at 21 CFR 320.1 as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." *Bioequivalence* is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." BA and BE are closely related, and the same approach to measure BA in an NDA should generally be followed in establishing BE for an NDA or ANDA. Although BA may be comparative, establishing BE specifically involves a comparison of the BA of one product with the BA of another product. BE is usually established using (1) criteria based on means and/or variances for BA measures, (2) BE intervals (goalposts), which are standards to allow a determination of equivalence when confidence intervals are computed using the specified criteria, and (3) confidence intervals for the criteria.

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[2] 21 CFR 341. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use.

BA and BE data should be provided in accordance with the regulations.[3] BA and BE may be established by in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in vitro studies, or, with suitable justification, by in vitro studies alone.[4] BA and BE assessments for locally acting nasal aerosols and sprays are complicated because delivery to the sites of action does not occur primarily after systemic absorption. Droplets and/or drug particles are deposited topically, then absorbed and becomes available at local sites of action. Systemic exposure following nasal administration can occur either from drug absorbed into the systemic circulation from the nasal mucosa, or after ingestion and absorption from the gastrointestinal tract. A drug administered nasally and intended for local action is therefore likely to produce systemic activity, although plasma levels of the drug do not reflect the amount of the drug reaching nasal sites of action. For these reasons, BA and BE studies should consider both local delivery and systemic exposure or systemic absorption.

1. Local Delivery BA/BE Concepts

For local delivery, BA is determined by several factors, including release of drug substance from the drug product and availability to local sites of action. Release of drug from the drug product is characterized by distribution patterns and droplet or drug particle size within the nose that are dependent upon drug substance, formulation, and device characteristics. Availability to local sites of action is a function of the above release factors, as well as drug dissolution in the case of suspension products, absorption across mucosal barriers to nasal receptors, and rate of removal from the nose. From a product quality perspective, the critical issues are release of drug substance from drug product and delivery to the mucosa. Other factors are of lesser importance. A critical question in assessing product quality BA and BE is the extent to which one can rely on in vitro methods alone, or upon in vitro methods plus clinical endpoints, to measure (benchmark) BA and/or establish BE. In vitro methods are less variable, easier to control, and more likely to detect differences between products if they exist, but the clinical relevance of these tests, or the magnitude of the differences in the tests, is not always clearly established. Clinical endpoints may be highly variable and relatively insensitive in detecting differences between products, but can unequivocally establish effectiveness.

In this guidance, the recommended approach for solution formulations of locally acting nasal drug products is to rely on in vitro methods to assess BA and BE. This approach is based on the assumption that in vitro studies would be more sensitive indicators of drug delivery to nasal sites of action than would be clinical studies. Drug particle size

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[3] 21 CFR 320.21, Requirements for submission of in vivo bioavailability and bioequivalence data.

[4] 21 CFR 320.24, Types of evidence to establish bioavailability or bioequivalence.

distribution (PSD) in suspension formulations has the potential to influence the rate and extent of availability to nasal sites of action and to the systemic circulation. For suspension formulation products, however, due to the inability to adequately characterize drug PSD (see section V.B.2), in vivo studies should be conducted as part of the studies establishing product quality BA and BE. In vitro studies should be coupled with a clinical study for BA, or a BE study with a clinical endpoint for BE, to determine the delivery of drug substance to local nasal sites of action. An in vivo systemic exposure or systemic absorption study should also be conducted for suspensions (see section II.A.2). For solution formulations, see section IV.B.1.

2. Systemic Exposure and Systemic Absorption BA/BE Concepts

Locally acting drugs are intended to produce their effects upon delivery to nasal sites of action without relying upon systemic absorption. Although systemic absorption may contribute to clinical efficacy for certain corticosteroids and antihistamines, the consequences of systemic absorption (e.g., HPA suppression by corticosteroids) are generally undesirable. In the absence of validated in vitro methodology for characterization of drug PSD for suspension products, and when measurable plasma levels can be obtained, this guidance recommends PK studies to measure systemic exposure BA or establish systemic exposure BE (section VII). For suspension products that do not produce sufficient concentrations to assess systemic exposure, clinical studies or BE studies with a clinical endpoint should be used to measure systemic absorption BA and establish systemic absorption BE, respectively (section VIII). For a schematic representation of recommended studies, see the Decision Tree for In Vivo Product Quality BA and BE Studies for Nasal Aerosols and Nasal Sprays (p. 35).

BA recommendations in this guidance are limited to *product quality* BA. For investigational new drugs (INDs) and NDAs, not only should product quality BA be provided, but BA/PK studies should also be included in the Human Pharmacokinetics section (Item 6) of the NDA for nasal aerosols and nasal sprays for local action, whether formulated as solutions or suspensions, and whether or not validated methods of determining drug PSD are available. These PK data provide biopharmaceutic and clinical pharmacology information beyond product quality BA characterization.

B. CMC TESTS AND IN VITRO BA TESTS (NONCOMPARATIVE) VERSUS BE TESTS (COMPARATIVE)

Generally CMC tests help characterize the identity, strength, quality, purity, and potency of the drug product and assist in setting specifications (tests, methods, acceptance criteria) to allow batch release. These tests have a different purpose than do BA/BE tests, which focus on release

of drug substance from drug product. Some of the in vitro BA/BE tests described in this guidance for nasal aerosols and sprays may be the same as CMC tests for characterization and/or batch release. A specification (test, method, acceptance criterion) for a CMC test for batch release is usually based on general or specific manufacturing experience. For example, a CMC test such as dose content uniformity has acceptance criteria based on repeated manufacturing of batches. Bioequivalence limits for BE studies are not usually based on manufacturing experience, but are part of equivalence comparisons between test and reference products. Equivalence comparisons normally include (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit for the criterion. BE limits may be based on a priori judgments and may be scaled to variability of the reference product (see Section IX). When conducted premarket for an NDA, some of the in vitro BA tests described in this guidance can be noncomparative and serve primarily to document (benchmark) the product quality BA of a pioneer product.

III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM

A. FORMULATION

Particle size, morphic form, and state of solvation of the active ingredient have the potential to affect the BA of the drug product as a result of different solubilities and/or rates of dissolution. For an ANDA of a suspension formulation, the PSD of the active drug in the dosage form should be the same as that of the reference listed drug, as discussed in Section V.B. Comparative information on the morphic form of the drug particles, and size and number of drug aggregates in the dosage form, should be provided. In addition, documentation of the same anhydrous or solvate form should be provided. For suspension formulations marketed in more than one strength, the drug substance in each strength product should be micronized under identical parameters, and the PSD of the resultant bulk drug should be identical in each strength product.

B. CONTAINER AND CLOSURE SYSTEM

Nasal aerosols consist of the formulation, container, valve, actuator, dust cap, associated accessories (e.g., spacers), and protective packaging, which together constitute the drug product. Similarly, nasal sprays consist of the formulation, container, pump, actuator, protection cap, and protective packaging, which together constitute the drug product.

For nasal aerosols and nasal sprays approved under an ANDA, BE should be documented on the basis of validated in vivo and vitro tests, or, in some cases, validated in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is greatest when the test product uses the same brand and model of devices (particularly the metering valve or pump and the actuator) as used in the reference product. If this is not feasible, valve, pump, and actuator

designs should be as close as possible in all critical dimensions to those of the reference product. Metering chamber volumes should be the same. For nasal aerosols, overall actuator design (Byron 1990), including actuator orifice diameter, should be the same. For a nasal spray, spray characteristics may be affected by features of the pump design, including the precompression mechanism, actuator design, including specific geometry of the orifice (Kublic and Vidgren 1998), and design of the swirl chamber. The external dimensions of the test actuator should ensure comparable depth of nasal insertion to the reference actuator. A test product should attain prime within the labeled number of actuations for the reference product. Consideration should be given to the *dead volume* of the device, including the internal diameter and length of the diptube, because this volume can influence the number of actuations required to prime a spray pump.

IV. DOCUMENTATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

A. INDs/NDAs

For INDs/NDAs, in vitro BA studies for solutions and suspensions, and in vivo studies for suspensions, should be provided. These data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the in vivo performance of the product based on the clinical efficacy and either systemic exposure for a PK study, or systemic absorption for a clinical safety study. Where the formulation and/or method of manufacture of the pivotal clinical trial product changes in terms of physicochemical characteristics of the drug substance, the excipients, or the device characteristics, BE data using in vitro tests (for solutions and suspensions) and in vivo tests (for suspensions) may be useful in certain circumstances during the preapproval period to ensure that the to-be-marketed product (T) is comparable to very similar clinical trial batches and/or to batches used for stability testing (R) (section V.A.1). Sponsors should discuss the usefulness of these BE approaches with appropriate CDER review staff.

B. ANDAs

1. Solution Formulations

In vivo studies, such as seasonal allergic rhinitis (SAR) studies to establish equivalent delivery to nasal sites, or HPA suppression studies for corticosteroids to establish equivalent systemic absorption, are not considered necessary for nasally administered solution drug products intended for local action. Thus, reliance on in vitro tests alone to document BE is suitable for nasal solution formulation products intended for local action. This approach is based on an understanding that for solution products, equivalent in vitro performance, inactive ingredients that are qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and adherence to container and closure recommendations of section III will ensure comparable

delivery to the nasal mucosa and to the gastrointestinal tract. Quantitatively *essentially the same* has been determined by CDER to mean that the concentration or amount of the inactive ingredient(s) in the test product should not differ by more than ±5 percent of the concentration or amount in the reference listed drug. Suggested methodology and validation approaches for the recommended tests are provided in section V. Suggested methods to allow comparisons using a criterion, BE limits, and a confidence interval approach are discussed in section IX. When in vitro data fail to meet acceptance criteria, the applicant is encouraged to modify the test product to attain equivalent in vitro performance. Because of insensitivity to potential differences between T and R, in vivo studies will not be sufficient in the face of in vitro studies that fail to document BE.

2. Suspension Formulations with PK Systemic Exposure Data

To document BE for suspension nasal formulation products intended for local action, both in vitro and in vivo data should be used. Inactive ingredients also should be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and the container and closure recommendations of section III should be followed. In vivo studies should include both a pharmacokinetic study (systemic exposure) and a BE study with a clinical endpoint (local delivery). This approach is only applicable for those suspension formulation products that produce sufficiently high drug concentrations in blood or plasma after nasal administration to obtain meaningful AUC and C_{max} data. Methodology and validation approaches for the recommended tests are provided for the in vitro studies in section V, and for the in vivo studies in sections VI and VII. As with solutions, in vivo studies will not be sufficient in the face of in vitro studies that fail to establish BE (i.e., in vitro BE studies that fail to meet the statistical test discussed in section IX result in a failed BE study) even though the BE study with a clinical endpoint or the PK study meets the statistical test.

3. Suspension Formulations without PK Systemic Exposure Data

For suspension nasal formulation products, inactive ingredients should be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and the container and closure recommendations of section III should be followed. In addition, for those products intended for local action that produce blood or plasma levels that are too low for adequate measurement, given current assay constraints, a BE study with a clinical endpoint to establish equivalent local delivery to nasal sites (section VI) and a study with a pharmacodynamic or clinical endpoint to establish equivalent systemic absorption (section VIII) are recommended. In vivo studies that meet the statistical test will not be sufficient in the face of in vitro studies that fail to document BE.

C. POSTAPPROVAL CHANGE

For an NDA submitted under 505(b)(1) of the Food, Drug, and Cosmetic Act, the primary need for BE documentation would be between the reference product before and the reference product after very limited changes. For an ANDA and for an NDA submitted in accordance with section 505(b)(2) of the Food, Drug, and Cosmetic Act, the primary documentation of BE for the changed product is the reference or pioneer product. At this time, no guidance is available as to when BE should be redocumented in the presence of any postapproval changes, either for an NDA or ANDA. Sponsors planning such changes should contact the appropriate review division prior to instituting the change.

V. BIOAVAILABILITY AND BIOEQUIVALENCE: IN VITRO STUDIES

A. BATCHES AND DRUG PRODUCT SAMPLE COLLECTION

1. INDs/NDAs

In vitro product quality BA studies for nasal aerosols and sprays should generally be performed on samples from three batches. The batches should include a pivotal clinical trial batch, a primary stability batch, and if feasible, a production scale batch, to provide linkage of in vitro performance to in vivo data. If a production scale batch is not available, a second pivotal clinical trial batch can be substituted.

The above BA batches should be equivalent to the to-be-marketed product. The manufacturing process of these batches should simulate that of large-scale production batches for marketing (additional information on large-scale batches is provided in the International Conference on Harmonisation (ICH) guidance for industry Q1A *Stability Testing of New Drug Substances and Products* (September 1994), section V.B). Complete batch records, including batch numbers of device components used in the batches, should accompany the BA submission.

In vitro BA studies are intended to characterize the means and variances of measures of interest for canisters (nasal aerosols) or bottles (nasal sprays) within a batch and between batches, where applicable. However, under 21 CFR 320.1 and 320.21, the studies may be noncomparative to other formulations or products. The in vitro tests and metrics are described in section V.B. The test method or standard operating procedure (SOP) for each test should accompany the data in the submission. The recommended number of canisters or bottles of each batch to be used in the above studies, and recommendations for statistical analyses, are described in section IX.

2. ANDAs

In vitro BE studies for nasal aerosols and sprays should generally be performed on samples from each of three batches of the test product and three batches of the reference listed drug. Test product samples should be from the primary stability batches used to establish the expiration dating period. Test product should preferably be manufactured from three different batches of the drug substance, different batches of critical excipients, and container and closure components. For nasal sprays formulated as solutions, in vitro BE tests can alternatively be performed on three sublots of product prepared from one batch of the solution.[5]

The above BE batches should be equivalent to the to-be-marketed product. The manufacturing process of these batches should simulate that of large-scale production batches for marketing (ICH Q1A *Stability Testing of New Drug Substances and Products* (September 1994), section V.B). Complete batch records, including batch numbers of device components used in the batches or sublots (for solution nasal sprays) should accompany the BE submission.

Reference product samples should be from three different batches available in the marketplace. The recommended in vitro tests and metrics are described in section V.B. The recommended number of canisters or bottles of each product and batch to be used in the above studies, and recommended statistical approaches, including suggested boundaries for each of the studies, are described in section IX.

B. TESTS AND METRICS

In vitro BA and BE for locally acting drugs delivered by nasal aerosol or nasal spray are characterized by six tests:

1. Dose or Spray Content Uniformity Through Container Life
2. Droplet and Drug Particle Size Distribution
3. Spray Pattern
4. Plume Geometry
5. Priming and Repriming
6. Tail Off Profile

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[5] For solution formulation nasal sprays, variability in in vitro BE study data between batches is expected to be due primarily to variability in the device components of the product rather than in the solution. Therefore, a single batch of solution may be split-filled into three equal size sublots of product. The sublots should be prepared from three different batches of the same device (pump and actuator) components.

The in vitro test information described below is summarized in Table 1 (p. 35).

All in vitro tests should be conducted on test canisters or bottles selected in a randomized manner from the test batch, including units from the beginning, middle and end of the production run. BE tests should be conducted in a blinded manner, or should use another approach that removes potential analyst bias, without interfering with product performance. Automated actuation stations are recommended for all comparative in vitro BE tests to decrease variability in drug delivery due to operator factors (including removal of potential analyst bias in actuation) and increase the sensitivity for detecting potential differences between products in any of the above tests.[6] The blinding procedure should also be extended to postactuation evaluations. The randomization procedure and the test method or SOP for each test should accompany the data in the submission.

1. Dose or Spray Content Uniformity Through Container Life

Sampling apparatus for collection of dosage units from aerosols is described in *U.S. Pharmacopeia 23/National Formulary 18* (Tenth Suppl, 15 May 1998). A suitable apparatus should be used for collection of dosage units from nasal sprays. For both solution and suspension formulations of nasal aerosols and nasal sprays, the mass of drug delivered per single (unit) dose should be determined based on a stability-indicating chemical assay. A single dose represents the minimum number of sprays per nostril specified in the product labeling. For a nasal product for which the minimum single usual dose is one actuation in each nostril, the single dose should be based on one actuation. For a nasal product for which the minimum usual dose is two actuations in each nostril, the single dose should not exceed two actuations. For BA and BE studies, dose or spray content uniformity data should be determined on primed units at the beginning of unit life, at the middle of unit life, and at the end of unit life[7] for nasal aerosols, and at beginning and end of unit life for nasal sprays. Mean dose or spray content uniformity and variability

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[6] Automated actuation stations may be stand-alone systems or accessories for laser diffraction instruments. Stations may include settings for actuation force, actuation velocity, hold time, return time, delay time between actuations, length of stroke, and number of actuations. Selection of appropriate settings should be relevant to proper usage of the nasal aerosol or nasal spray by the trained patient, and should be documented based on exploratory studies in which actuation force, actuation time, and other relevant parameters are varied These studies should accompany the validation data. Selected settings used for the comparative in vitro study should be specified in the SOP for each test for which the automatic device is employed.

[7] Based on the labeled number of full medication doses, this guidance uses the terms *beginning life stage, middle life stage*, and *end life stage* interchangeably with the terms *beginning of unit life* (the first actuation(s) following the labeled number of priming actuations); *middle of unit life* (the actuation(s) corresponding to 50 percent of the labeled number of full medication doses); and *end of unit life* (the actuation(s) corresponding to the label claim number of full medication doses)

in content uniformity is to be determined based on within and between canister or bottle data, and, for nasal aerosols and suspension formulation nasal sprays, between batch data. Analytical data should be validated,[8] and the analytical validation report should accompany the content uniformity report. For BE data, equivalence of T and R data should be based on the methodology of section IX.A.1.

2. Droplet and Drug Particle Size Distribution (PSD)

To increase nasal deposition and minimize deposition in the lungs and GI tract, aerosol droplets should generally have a mass median aerodynamic diameter (MMAD) greater than 10 to 20 microns (Task Group on Lung Dynamics, 1966). As MMAD decreases over the 5-20 micron range, the Task Group report indicates that reduced nasopharyngeal deposition and increased pulmonary deposition occur. Droplet size distribution measurements are thus critical to delivery of drug to the nose. For BA and BE, studies of droplet size distribution and PSD by validated methods should be performed. For suspension products, drug particle size may be important to rate of dissolution and availability to sites of action within the nose. Therefore, drug or drug and aggregate PSD should be characterized in the formulation both within the can or bottle and within the aerosolized droplets. Present agency experience suggests that drug and drug aggregate PSD characterization cannot be acceptably validated for nasal aerosols and nasal sprays. In this circumstance, drug and drug aggregate PSD studies should be performed, and these supportive characterization data, along with available validation information, should be submitted.

a. Particle size distributions

Droplet Size Distribution

For all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, droplet size distribution should be determined utilizing a method suitable for fully characterizing the droplet size. Laser diffraction methodology, or appropriately validated alternate methodology, is recommended.

Particle Size Distribution

For all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, PSD should be determined using a suitable aerodynamic

[8] A draft guidance for industry is under development on analytical procedures, validation data, and samples for drug substances and drug products.

method (e.g., multistage cascade impactor (CI), multistage liquid impinger (MSLI)).

Drug and Aggregate PSDs

Nasal spray suspension formulations typically contain micronized drug within an aqueous vehicle with partially undissolved suspending agents and other ingredients. Nasal aerosol suspension formulations contain micronized drug suspended within propellants, and may contain a surfactant and/or cosolvent. Light microscopy may be considered for estimating drug and drug aggregate PSD of these products.

b. Instrumental methods

Laser Diffraction

Laser diffraction is a nonaerodynamic optical method of droplet or particle sizing which measures the geometric size of droplets or particles in flight. To characterize the beginning, middle, and end of the plume, measurements should be made at three distances from the delivery orifice. Multiple actuations may be performed at each lifestage to assess precision. The droplet size distributions due to each actuation, and the means, standard deviations (SDs), and percent coefficients variation (CVs) should be reported. At each distance, measurements should be made at different delay times in order to characterize the size distribution of droplets or particles within the plume upon formation, as the plume has started to dissipate, and at some intermediate time (Sciarra and Cutie, 1989). Selected delay times may be based on obscuration levels or other suitable means.[9]

Droplet size distribution data (D_{10}, D_{50}, D_{90}), and span ((D_{90} - D_{10})/D_{50}) should be reported based on volume (mass). Droplet size distribution data by count (number of droplets) are not requested. All instrument/computer printouts should be submitted, including cumulative percent undersize tables, histograms of PSD, obscuration values, and other details and statistics. The manufacturer's recommended obscuration ranges for the laser diffraction instrument should be submitted.

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[9] *Obscuration* refers to the percentage of laser light obscured or scattered out of the beam by the sample, and is influenced by sample concentration and width of the plume. Following actuation, obscuration levels are initially low, increase as the plume develops, then decrease as the plume dissipates.

Comparative laser diffraction data are requested at beginning, middle, and end of unit life. For BE, statistical comparisons should be based on D_{50} and span.

Multistage Cascade Impaction (CI) or Multistage Liquid Impinger (MSLI)

Sizing of droplets or particles by CI or MSLI measures aerodynamic diameter based on inertial impaction, an important factor in the deposition of drug in the nasal passages. CI or MSLI data should be provided for all nasal sprays and nasal aerosols to characterize the size distribution of drug based on aerodynamic mass diameters. The greatest percentage of the emitted dose is deposited prior to or on the first stage of the CI for both nasal aerosols and nasal sprays. Thus, equivalence of aerodynamic drug particle size distribution of test and reference products, although conducted by validated procedures, does not ensure equivalent PSD of drug within the aerosolized droplets. Characterization of drug PSD by CI or MSLI, along with the other recommended in vitro tests, does not allow waiver of in vivo BE studies for suspension formulation products (see section II.A).

For BA and BE, CI or MSLI drug deposition profile data should be based on three size range groups. Group 1 includes summation of drug deposition in or on the valve stem, actuator, inlet port, and upper stage, which should have a nominal effective cutoff diameter (ECD) (e.g., greater than or equal to 9.0, 10.0, 13.0, or 16.0 microns). Group 2 includes drug deposition on the stage immediately below the upper stage (e.g., greater than or equal to 5.0 microns). Group 3 includes summation of drug deposition below the Group 2 stage, including the filter. For Group 1 only, deposition should also be reported for each of the individual accessories and the upper stage. Deposition should be reported in mass units. Mass balance accountability (sum of all drug deposited from the valvestem to the filter) should be documented.

Selection of the most suitable cascade impactor may be influenced by the ECDs of stages of various brands of cascade impactors, the geometry of the induction port, and other factors. Studies should use the fewest number of actuations justified by the sensitivity of the analytical method (generally not exceeding 10), in order to be more reflective of the PSD of individual doses. Analytical data should be based on a validated chemical assay. The analytical validation report should accompany the CI data report. The SOP or validation report should indicate the minimum quantifiable amount of drug deposited on each of the three groups of deposition sites and on each accessory or stage of the Group 1 data.

For BA and BE, cascade impactor data are requested at the beginning and end of unit life. Middle of unit life data are not requested. For BE, statistical

comparisons of drug deposition on the three groups should be based on profile analysis (section IX.D).

Light Microscopy

Light microscopy may provide drug and aggregate PSD data. However, the method is limited in its ability to fully characterize PSD by the resolution limit of light microscopy (about 0.5 micron or higher) which may not be adequate for sizing micronized drug. A second limitation is potential difficulty in distinguishing drug from undissolved excipient in suspension formulation nasal sprays. Due to these limitations, acceptable validation of the microscopic data may not be possible. In the presence of these limitations, this guidance recommends that comparative drug and aggregate PSD data should be submitted as supportive BA and BE characterization data for suspension formulation nasal aerosols and sprays. The occurrence of drug particles and aggregates within appropriate size ranges should be tabulated for each analysis, and histograms of the drug and aggregate PSD should be provided. Count median diameter (CMD) and geometric standard deviation (GSD) based on single particle data (aggregates excluded) should be provided. Studies of nasal sprays should include test product placebo to provide an estimate of the occurrence of apparent drug particles (*false positives*) due to undissolved excipient. PSD by light microscopy provides supportive BE information.

3. Spray Pattern

Spray pattern characterizes the spray following impaction on an appropriate target (e.g., a thin-layer chromatography (TLC) plate). It provides information about the shape and density of the plume following actuation. Spray patterns should be determined on single actuations at three appropriate distances from the actuator to the target at the beginning and end of unit life. The visualization technique should preferably be specific for the drug substance. End of unit life testing is requested to ensure comparability to performance at beginning of unit life. Clear, legible photographs or photocopies of the spray patterns, not hand-drawn representations obtained by tracing the pattern, should be provided. The widest (D_{max}) and shortest (D_{min}) diameters, and the ovality ratio (D_{max}/D_{min}) should be provided for each spray pattern. The SOP should include a figure describing the procedure for measurement of D_{max} and D_{min}. For BE, statistical comparisons should be based on ovality ratio and either D_{max} or D_{min} data (section IX.B).

Spray pattern and plume geometry (below) are recommended to assist in establishing functional equivalence of products as a result of differences in the device components of T and R products. Comparable spray pattern and plume geometry data for T and R,

combined with other in vitro tests (and in vivo studies for suspensions), ensure equivalent drug deposition patterns, resulting in equivalent delivery of drug to nasal sites of action and equivalent systemic exposure or absorption.

4. Plume Geometry

Plume geometry describes two side views, at 90 degrees to each other (two perpendicular planes) and relative to the axis of the plume, of the aerosol cloud when actuated into space. Plume geometry should be based on high-speed photography or other suitable methods. Photographs should be of high quality and should clearly show the dense cloud and individual large droplets or agglomerates of droplets in the vicinity of the cloud. Plume geometry may be performed only at the beginning of unit life. Plumes should be characterized at three or more times after a single actuation, chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of plumes should be used to measure plume length, plume width, and plume (spray cone) angle. All photographs and data characterizing the plume dimensions in two planes should be submitted, including the scale used to indicate actual size. Comparative BE data are supportive (section IX.C).

5. Priming and Repriming

Priming and repriming data provide information to ensure delivery of the labeled dose of drug, and thus are part of the in vitro BA and BE assessment. Similar studies should be conducted on nasal sprays. For products approved under an NDA, priming and repriming data based on single actuations should be provided for multiple orientations.

For products approved under an ANDA, the labeling is the same as that for the reference listed drug, except for specific changes described in the regulations (21 CFR 314.94(a)(8)(iv). For nasal sprays and some nasal aerosols, the reference product labeling (package insert and/or patient package insert) describes the number of actuations necessary to prime the product on initial use and on repriming following one or more periods of nonuse (e.g., 24 hours and 7 days following last dose). Comparative priming and repriming data are requested to document that priming of the test product is attained within the number of priming actuations stated in the reference product labeling. For reference product nasal aerosols lacking priming recommendations, priming studies are recommended to characterize the test product relative to the reference product. In the absence of reference product priming recommendations, an adequate number of single actuations should be studied to ensure that test and reference products have each attained an emitted dose equal to the labeling claim. Repriming studies of test products are requested only when the reference product labeling includes repriming instructions.

Priming and repriming data for the test product in multiple orientations should be provided in the CMC portion of the ANDA submission. Therefore, comparative BE studies may be based on products stored in the valve upright position. For any nasal aerosol product in which the reference product labeling recommends storage in the valve down position, additional comparative priming and repriming data should be provided for this orientation. For suspension products, the unprimed canister or bottle should be shaken for a standardized time (e.g., 5 seconds) and a dose should then be immediately collected. For nasal aerosols, a standardized period (e.g., 30-60 seconds) should be allowed between successive actuations. Doses may be collected in the same apparatus used for the dose or spray content uniformity through container life test. When priming and/or repriming information is included in the labeling, comparison of equivalence should be based on the emitted dose of the single actuation immediately following the specified number of priming or repriming actuations (section IX.B). The emitted dose of each earlier actuation should also be provided. When priming information is not specified, the emitted dose of each successive actuation up to and including attainment of label claim should be provided. Comparative BE data in the absence of priming are supportive (section IX.C).

6. Tail Off Profile

Whereas dose or spray content uniformity conducted at the end of the labeled number of actuations ensures that the product delivers the labeled dose through the number of actuations stated in product labeling, the tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations (i.e., from end of unit life to product exhaustion). Tail off profile characteristics may vary as a function of valve or pump design, bottle geometry, and other factors, and may be characterized in terms of uniformity of decline, rate of decline, and intercanister or interbottle variability in unit dose (Schultz, 1995). For BA assessment, tail off data are noncomparative. For BE assessment, comparative tail off profiles are requested to ensure similarity in drug delivery as the product nears exhaustion. Data should be based on the emitted dose of individual actuations. Comparative BE data are supportive; however, the test product should be no more erratic in dose delivery than the reference product, and the rate of decline in delivery should be generally similar between products.

VI. BIOAVAILABILITY AND BIOEQUIVALENCE: CLINICAL STUDIES FOR LOCAL DELIVERY

A. GENERAL INFORMATION

The same adequate and well-controlled clinical trials in humans used to establish the safety and effectiveness of the drug product (21 CFR 314.126) may be used, in some cases, to establish BA

or, when comparative, BE (21 CFR 320.24). Although BA and BE studies with a clinical endpoint are sometimes incapable of showing a dose-response relationship and may not be consistently reproducible (21 CFR 320.24(b)(4)), they are sometimes the only means available to document BA and BE in drug products intended for local delivery and action. A number of FDA guidances provide information about the general conduct of clinical studies, including clinical studies to document BA and BE. These include: *General Considerations for Clinical Trials* (International Conference on Harmonisation (ICH) E8, December 1997); *Structure and Content of Clinical Study Reports* (ICH E3, July 1996); *Good Clinical Practice: Consolidated Guideline* (ICH E6, May 1997); and *Statistical Principles for Clinical Trials* (ICH E9, May 1997).

B. BE CLINICAL STUDY ENDPOINTS

Clinical evaluations should be made at baseline and during treatment. The efficacy endpoint should be patient self-rated total nasal symptom scores (TNSS). These most often include a composite score of runny nose, sneezing, nasal itching, and for drugs other than antihistamines, congestion. The efficacy endpoint should be expressed as change from baseline (pretreatment) of the TNSS, expressed in absolute units and percent change. In addition to the efficacy measures, all three study designs should incorporate safety assessments.

C. CLINICAL STUDY BATCHES

The product quality BA batch used for the study should be the same pivotal clinical trial batch used in the in vitro BA studies (section V.A). Where BE studies are needed for an NDA, the batches of test and reference products should be the same batches employed in the in vitro testing. The product quality batches used to establish the local delivery BE for an ANDA should be the test and reference batches employed in the in vitro BE testing.

D. CLINICAL BE STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA

A BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should document sensitivity of the study to discriminate between differing doses (i.e., show a dose-response relationship). This documentation typically relies on the inclusion of a second dose of the reference product, and preferably of the test product, that may be higher or lower, to demonstrate that the efficacy response is different between the two doses. Doses may differ by two or fourfold, and to increase study sensitivity, the lower dose examined may be below the minimum labeled dose (e.g., one-half or one-quarter of the recommended dose, depending on the limitations of the formulation).

Although many clinical study design options may be considered to establish BE, outlined below are three suggested study designs for evaluating clinical responses for nasally administered drugs for seasonal allergic rhinitis (SAR): (1) traditional treatment, (2) day(s) in the park, and (3)

environmental exposure unit (EEU). The three study designs use SAR patients as the study population to document BE for all indications in product labeling for nasally administered drug products covered in this guidance. Recommended studies are designed as treatment studies rather than prophylaxis studies. Depending on the time to onset of therapeutic effect of the drug being tested, the medication effect can be evaluated after a single dose (e.g., antihistamines) or after short-term treatment (e.g., corticosteroids). In all three study designs, an assessment of onset of action and efficacy at the end of the dosing interval is recommended, because both measures are important clinically and may offer better dose discrimination.

Because specific study recommendations are not provided in this guidance, a protocol for a BE study with a clinical endpoint for a specific suspension drug product should be submitted to the appropriate review division at FDA.[10] For the three study designs, a pilot study may be useful to determine the optimal dosing duration and doses to be used in the BE study.

1. Traditional Treatment Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study with a single-blind placebo lead-in period (generally 1 to 14 days) in which efficacy and safety of the test product are assessed for a 2-week duration. Symptom assessment should be made at least twice daily (i.e., *reflective* scores) and also at the end-of-dosing interval (i.e., *instantaneous* scores). Evaluation of both reflective and instantaneous assessments of the total nasal symptom score are critical in establishing BE with a clinical endpoint. Safety measures should include physical examination, laboratory monitoring (chemistry, liver function tests, hematology, urinalysis, serum pregnancy testing in females), monitoring of vital signs, adverse event reporting, and performance of 12 lead ECGs before and after treatment with study drug.

2. Day(s) in the Park Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study in a park setting in which subjects are exposed to relevant outdoor allergens. On the study day, patients should undergo a baseline period of evaluation in the park setting to establish a minimum level of allergic rhinitis symptoms prior to randomization to study drug treatment. Patients should remain outdoors in the park for a prespecified length of time over one to two consecutive days. Nasal symptoms should be evaluated on a periodic basis throughout the full dosing interval to characterize onset of action and end-of-dosing interval efficacy. Safety assessment generally involves adverse event reporting.

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[10] A draft guidance on clinical development programs for allergic rhinitis drug therapy is under development.

3. Environmental Exposure Unit (EEU) Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study in a controlled indoor environment termed an *EEU chamber*. Repeated pretreatment exposure to the relevant allergen allows screening for symptomatic responders for enrollment in the treatment phase. On the study day, patients should be exposed to the allergen in the EEU and monitored for a baseline period to ensure a minimum level of allergic rhinitis symptoms prior to randomization to study drug treatment. Patients should remain in the EEU for a prespecified length of time over one or two days. Nasal symptoms should be evaluated on a periodic basis throughout the full dosing interval to characterize onset of action and end-of-dosing interval efficacy. Safety assessment generally involves adverse event reporting.

Subjects employed in each of the three study designs should be patients with a history of SAR, and a positive allergy test for specific allergens (e.g., allergen skin test). Patients with other significant diseases should be excluded from the study. Patients should be experiencing a defined minimum level of symptom severity at the time of study enrollment.

VII. BIOAVAILABILITY AND BIOEQUIVALENCE: PK SYSTEMIC EXPOSURE STUDIES

Plasma concentration-time profiles from BA and BE studies should be used to evaluate systemic exposure for suspension drug products that produce sufficiently high drug concentrations of the active ingredient and/or active moiety after nasal administration to obtain meaningful AUC and C_{max} data. The product quality BA study to characterize systemic exposure may be one of the same PK studies conducted to address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA study may be conducted in healthy subjects or SAR patients. The BA batch used for the PK systemic exposure study preferably should be a pivotal clinical trial batch. Alternatively, a PK batch similar to a batch used in a pivotal clinical trial may be used, in which case, any differences between the PK batch and the pivotal clinical trial batch should be discussed with appropriate CDER review staff prior to the study. If the PK batch is not one of the three batches used for the in vitro BA studies (section V.A.1), in vitro BA data should be provided for the PK batch using the same protocols as for the three batches.

For an NDA or an ANDA, the in vivo BE study should be conducted with a replicate crossover or nonreplicate crossover design. The study may be single or multiple dose. The batches of test and reference product should be batches employed in the in vitro testing. For an ANDA, the batches of test and reference used for the systemic exposure study should be the same batches used for the clinical study for local delivery, and each of these batches should be one of the three batches used for the in vitro BE studies. Subjects for the study should be healthy (non-SAR

patients), with exclusions primarily for reasons of safety. Several actuations from the drug product in each nostril may be needed to achieve measurable concentrations of the active ingredient and/or active moiety in an accessible biological fluid such as blood or plasma. For an ANDA, an IND in accordance with 21 CFR 320.31 will be needed when the number of doses in a single-dose or multiple-dose study exceed the single or total daily dose specified in the labeling of the approved NDA.

Attempts should be made in the conduct of a PK systemic exposure study to minimize loss of drug due to excess fluid drainage into the nasopharynx or externally from the nasal cavity. The bioanalytical method should be validated for accuracy, precision, specificity and sensitivity. Statistical analysis should be conducted on the log-transformed data. Average BE may be used for studies with replicate crossover or nonreplicate crossover designs. Individual BE with scaling may be used for studies with replicate crossover designs. A pilot study is recommended to assess the analytical methodology and to estimate the numbers of actuations and subjects to be used in the full-scale study.

VIII. BIOAVAILABILITY AND BIOEQUIVALENCE: PHARMACODYNAMIC OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION

A. GENERAL INFORMATION

Clinical studies for BA, or BE studies with a pharmacodynamic or clinical endpoint, are needed to assess the systemic absorption of those suspension drug products for which PK systemic exposure studies (Section VII) are not feasible. Published data suggest that systemic BE of suspension formulation antihistamine nasal products may be established based on PK data (Heykants et al., 1995). At the present time, approved nasal mast-cell stabilizer nasal spray and anticholinergic nasal spray products are solutions for which BE may be established based upon in vitro studies only. These types of studies will thus generally be needed only for corticosteroid nasal aerosols and nasal sprays. The product quality BA study to characterize systemic absorption may be one of the same clinical studies conducted to establish the safety of the active ingredient and/or active moiety in the drug product. Because this section does not provide specific recommendations for clinical studies for systemic absorption, sponsors should submit a protocol for a BE study with a pharmacodynamic or clinical endpoint for a specific drug product to the appropriate review division at FDA.

B. BE STUDY ENDPOINTS FOR CORTICOSTEROIDS

The recommended systemic absorption BE study design for nasal corticosteroids is suppression of the HPA axis. The endpoint may be either 24-hour urinary free cortisol adjusted for urinary creatinine, based on a full 24-hour urine collection, or serum cortisol levels collected every 4

hours over a 24-hour period, with exclusion of the middle of the night sample. Endpoints for placebo and test and reference treatments should be baseline-adjusted prior to statistical analyses.

C. CLINICAL STUDY BATCHES

The product quality BA batch used for the study should be a pivotal clinical trial batch used in the in vitro BA studies (section V.A). For BE studies for an NDA, the batches of T and R should be batches used in in vitro testing. For an ANDA, the batches of test and reference product used for the systemic absorption study should be the same batches used for the clinical study for local delivery. Each of these batches should be one of the three batches used for the in vitro BE studies.

D. CLINICAL STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA

The study can be conducted as a placebo-controlled, randomized, multiple-dose parallel design comparing test and reference products. The study should be conducted in healthy, nonallergic volunteers not previously exposed to corticosteroids, and subjects should be domiciled within the clinical study center during the dosing days. Three treatments, test and reference products at the labeled dose (maximum labeled dose when labeling includes more than one dose) and a placebo of the test product, should be used. Each treatment period should consist of 14 days of dosing. Timed urine or serum samples for determination of 24-hour urinary free cortisol or 24-hour serum cortisol levels should be collected prior to dosing (baseline) and during the last 24-hours of the 14 days of dosing. In addition, we recommend determining two to three interval 24-hour urinary free cortisol or 24-hour serum cortisol levels (e.g., performing additional assessments on days 4, 7, and/or 10) to better profile the onset of the effect of test and reference products, should detectable adrenal suppression occur.

Alternatively, the study could be conducted as a placebo-controlled, randomized, multiple-dose crossover design comparing test and reference (Wilson et al., 1998). As in the parallel design study, the study should be conducted in healthy, non-allergic volunteers not previously exposed to cortocosteroids. During the dosing days, subjects should be domiciled within the clinical study center to ensure compliance with the study protocol. Three treatments, test and reference at the labeled dose (maximum labeled dose when labeling includes more than one dose), and a placebo of the test product should be used. Each treatment period should consist of 14 days of dosing. A shorter dosing duration would be considered with adequate scientific justification. Washout periods between treatments should be adequate to eliminate the possibility of a carryover effect. Urine or serum samples for determination of 24-hour urinary free cortisol or 24-hour serum cortisol levels should be collected prior to each dosing period (baseline data) and during the last 24-hours of each dosing period. In addition, we recommend determining two to three interval 24-hour urinary free cortisol or 24-hour serum cortisol levels (e.g., performing additional assessments on days 4, 7, and/or 10) to better profile the onset of the effect of test and reference products,

should detectable adrenal suppression occur.

IX. STATISTICAL ANALYSES

In vitro studies yield both profile and nonprofile data, which require different statistical analyses. Noncomparative BA in vitro data analyses for both profile and nonprofile data are discussed in section IX.A. For BE studies, methods of comparison for nonprofile analyses are discussed in section IX.B, for supportive nonprofile and profile analyses in section IX.C, and for profile analyses in section IX.D. Methods for comparison of categorical endpoints from the SAR studies are discussed in section IX.E.

A. IN VITRO BA DATA

Means, SDs, and percent CVs should be reported for the measures recommended in this guidance to document BA.

μ_T	=	T means (log scale)
σ_{BT}	=	T between batch standard deviations (log scale)
σ_{CT}	=	T between canister standard deviations (log scale)
σ_{LT}	=	T within canister between life stage standard deviation

The overall means for the formulation should be averaged over all bottles or canisters, life stages (except for priming and repriming evaluations), and batches. In addition to overall means, means at each lifestage for each batch averaged over all bottles or canisters, and for each lifestage averaged over all batches, are requested. For profile data, means, SDs, and percent CVs should be reported for deposition in each of Groups 1, 2 and 3 of the CI or MSLI data, as well as on the individual accessories and stage within Group 1.

B. IN VITRO BE DATA: NONPROFILE ANALYSES USING A CONFIDENCE INTERVAL APPROACH

Nonprofile analyses should be applied to the following tests: (1) dose or spray content uniformity through container life; (2) droplet size distribution; (3) spray pattern; and (4) priming and/or repriming, when this information is specified in the labeling.

1. Study Protocol

Data for the BE criterion should be based on testing a suitable number of bottles or canisters from each of three batches of the T and R drug products. Each bottle or canister should be tested for the measure (parameter) of interest at beginning and end, or

beginning, middle, and end of unit life, as indicated in section V and Table 1. Rather than evaluate performance at each life stage separately, a criterion is recommended that combines the multiple life stages. In doing so, the multiple life stages are considered as providing measures of the same underlying quantity. The recommended criterion considers deviations from uniformity across bottle or canister life stages; results are ideally uniform. Lack of uniformity between life stages should be treated as another variance component in the criterion.

For suspension formulation nasal sprays and solution formulation and suspension formulation nasal aerosols, the number of canisters or bottles (units) of product to be studied should not be fewer than 30 for each of the test and reference products (i.e., no fewer than 10 from each of three batches). For solution formulation nasal sprays, no fewer than 10 units from each of the three batches or three sublots should be studied. The number of units is a function of T to R product means and variances. Estimates of these mean differences and variances will necessitate pilot studies.

2. Criterion for Comparisons, Confidence Interval, and Bioequivalence Limit

The equivalence approach for nonprofile tests relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit for the criterion.

a. Criterion for comparison

The in vitro population BE criterion and BE limit are:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_R^2} \leq \theta$$

where:

μ_T, μ_R	=	T and R means (log scale)
σ_{BT}, σ_{BR}	=	between batch T and R standard deviations (log scale)
σ_{CT}, σ_{CR}	=	between canister T and R standard deviations (log scale)
σ^2_R	=	$\sigma^2_{BR} + \sigma^2_{CR} + \sigma^2_{LR}$
σ^2_T	=	$\sigma^2_{BT} + \sigma^2_{CT} + \sigma^2_{LT}$
σ_{LT}, σ_{LR}	=	within T and R canister between life stage standard deviation
θ	=	in vitro BE (upper) limit

The overall means for the two formulations should be averaged over all bottles or canisters, life stages (except for priming and repriming evaluations), and batches.

The general approach should be to calculate a 95 percent upper bound for the criterion. If this upper bound is less than or equal to the upper limit, θ, the test product may be judged to be bioequivalent to the reference product at the 5 percent level. The criterion will be further discussed in the guidance for industry on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (draft December 1997), when finalized. A population, rather than average, bioequivalence criterion is recommended in order to estimate whether the test product may be more variable than the reference product. The test product should be as or more consistent in the delivery of drug than is the reference product. An individual BE approach is not appropriate for in vitro data because there are no subjects, thus no subject-by-formulation interaction.

b. Determining a 95 percent upper bound

CDER recommends that a method of moments approach be used for estimating the means and variances needed to determine the population bioequivalence criterion. Approaches based on restricted maximum likelihood (REML) may be used in special cases. For determining the 95 percent upper bound, CDER recommends using a method analogous to one proposed for individual bioequivalence (Hyslop, Hsuan and Holder 1998).

c. Specification of the population BE upper limit

The general form of the upper limit, θ, is analogous to the form of the population BE criterion, which is

$$\frac{(\text{mean difference in natural log scale})^2 + \text{variance terms}}{\text{comparison variance}}$$

The corresponding form for the upper limit is then

$$\frac{(\text{average BE limit in natural log scale})^2 + \text{variance terms offset}}{\text{scaling variance}}$$

This formula contains three values to be specified: (1) average BE limit, (2) variance terms offset, (3) and scaling variance. These values will be specified when this guidance is finalized based on simulation work now in progress.

Average BE Limit

Due to the low variability of in vitro measurements, at the present time CDER recommends that the limit not be be larger than 90/111 (i.e., the ratio of geometric means would fall within 0.90 and 1.11). A value of 0.90 is tentatively recommended as the average BE limit. This value should be used in calculating the population BE limit (refer to θ in the equation in section IX.B.2.a, above).

Variance Terms Offset

This value arises to allow some difference among the total variances that may be inconsequential. In this regard, the variance terms offset is analogous to the average BE limit. The variance terms offset also helps correct for the effect on power and sample size for the need to estimate the variances. Because of the low variability of in vitro measurements, the variance terms offset, denoted ϵ_P in the draft guidance on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (December 1997), when finalized, should be taken as 0.0. CDER is also considering ϵ_P equal to 0.01.

Scaling Variance

This value adjusts the BE criterion depending on the reference product variance. When this variance is greater than the scaling variance, σ_{T0}^2, the limit is widened. When this variance is less than the scaling variance, the limit is narrowed.

Mixed scaling should be employed for in vitro studies, as described in the draft guidance on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (December 1997), when finalized. With mixed scaling, when the reference variance ***in the study*** is less than the scaling variance, the population BE criterion should be modified to its *constant-scaled* form:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_{T0}^2}$$

Mixed scaling is used to avoid penalizing test products for cases with very low reference variance. It is CDER's current intent to select σ_{T0} for in vitro studies so that most studies will use constant scaling and thus, that σ_{T0} will be at least 0.10.

The upper limit may be interpreted by reference to a population distance ratio (PDR). The PDR is the ratio of the test-reference distance (in the log scale) to the reference-reference distance. In contrast to individual BE, the distances for population BE are based on administration to separate individuals (further details will be provided in the guidance for industry on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (draft December 1997), when finalized. The population BE criterion, denoted by PBC, is related to the PDR by

$$PDR = (1 + \frac{PBC}{2})^{\frac{1}{2}}$$

Substituting the BE limit θ for PBC expresses the upper limit in the PDR scale. The specification of 0.90 for the average limit, 0.0 for the variance offset, and 0.10 for the scaling standard deviation corresponds to an upper limit for PDR of 1.25.

C. IN VITRO BE DATA: SUPPORTIVE NONPROFILE AND PROFILE ANALYSES

The following tests provide supportive characterization data: (1) plume geometry; (2) tail off profile; (3) priming data, when reference product labeling does not specify priming information; and (4) drug CMD and drug and aggregate PSD data from microscopic analyses. The comparative data requested in section V should be provided, based upon the same number of bottles or canisters recommended in the protocol of section IX.A.1. Statistical criteria need not be applied.

D. IN VITRO BE DATA: PROFILE ANALYSES USING A CONFIDENCE INTERVAL APPROACH

Profile analyses apply to cascade impactor (CI) or multistage liquid impinger (MSLI) data for nasal aerosols and nasal sprays. Analyses may rely on a criterion for comparisons of means and variances relative to a BE limit, with calculation of a 90 percent confidence interval. The general approach is adaptable to cascade impactors of varying numbers of stages and accessories, or groups of stages and accessories. As discussed in section V.B.2, profile comparisons may be based on drug deposition within three groups.

1. Study Protocol

Data for the BE criterion should be based on testing a suitable number of bottles or

canisters from each of three batches of the T and R drug products (or three sublots for solution formulation nasal sprays). Each canister should be tested for deposition at the beginning and end life stages, as indicated in section V.B.2. The number of canisters to be studied from each batch, which should not be less than 10, is a function of test to reference product means and variances. Estimates of these mean differences and variances will require pilot studies.

2. Criterion for Comparison

The criterion considered appropriate for the profile comparison is:

$Rd \leq \theta$

where:

Rd	=	in vitro BE criterion
θ	=	in vitro BE limit

Rd is derived with the following notation:

Let:

P_R, P_T	=	population mean profile across the batches of the reference product and test product
F_{BR}, F_{BT}	=	distribution of deviation of batch mean from population mean profile of the reference product and test product
F_{CR}, F_{CT}	=	distribution of deviation of canister mean from batch mean profile of reference product and test product
p_R, p_T	=	observed profile of a given puff of reference product and test product (i.e., p_R has a compound distribution of MN(100, P_R), F_{BR} and F_{CR}, and p_T has a compound distribution of MN(100, P_T), F_{BT} , and F_{CT}, where MN(100, P) is a multinomial distribution with n=100 and P=(p_1, p_2, …, p_S) for an impactor of S stages)

and:

d_{TR}	=	observed distance between p_R and p_T, the test-reference distance
$d_{RR'}$	=	observed distance between p_R and $p_{R'}$, the reference-

		reference distance (i.e., reference-reference deviation)
rd	=	$d_{TR}/d_{RR'}$, observed ratio of test-reference distance to reference-reference deviation

The in vitro BE measure is defined by

Rd = E(rd)

where:

E(rd)	=	expected value of rd

Further information on d_{TR}, $d_{RR'}$, rd, and the in vitro profile comparison procedure is provided in Appendix A.

3. Determining a 95 Percent Upper Bound

Since there is no exact or asymptotic distribution of the average rd, the 95% upper bound should be determined by the 95th percentile of the empirical sampling distribution generated by a random sample of the matched triplet (test, reference 1, reference 2) of canisters. A description of the procedure is provided in Appendix B.

4. Specification of the Upper Limit

Reserved (simulation studies to develop specifications for the upper limit are ongoing).

E. IN VIVO BE DATA: CATEGORICAL ENDPOINTS

Reserved (statistical analyses are under development).

X. MULTIPLE STRENGTHS

A small number of nasal sprays for local action are available in two strengths. Current examples are: (1) ipratropium bromide nasal spray, a solution formulation; and (2) beclomethasone dipropionate nasal spray, a suspension formulation. Lower strengths of a product ordinarily would achieve the lower dose per actuation using a lower concentration formulation, without changing the actuator and metering valve or pump (other than diptube) used in the higher strength product The following sections describe recommended BA and BE studies for low strengths of nasal sprays for which BA or BE for the higher strengths has previously been established.

Recommendations are also provided for cases in which BA or BE is initially established on the low-strength product. No approved nasal aerosols are available in multiple strengths, thus BA and BE recommendations are not considered for these products.

A. SOLUTION FORMULATION NASAL SPRAYS

BA of lower or higher strength solution formulation nasal sprays should be based on conduct of all applicable in vitro tests described in section V. These studies are generally noncomparative in character. Documentation of BE between T and R products should follow the recommendations described in section III regarding formulation and container and closure system. Abbreviated in vitro testing (section V) is recommended to document BE of the low-strength T product to the low-strength R product, provided BE of the high-strength product has been documented.

In vitro test	High Strength	Low Strength
Dose content uniformity	BE[1]	BE
Priming and repriming	Yes	Yes
Tail off	Yes	Yes
Droplet size distribution		
By laser diffraction	BME	B
By cascade impactor	BE	No
Spray pattern	BE	B
Plume geometry	B	No

[1] Beginning (B), Middle (M), End (E)

With the exception of the reduced testing, the same protocols and acceptance criteria used to establish BE of the high strength products should be used for the low strength products. In vivo studies are not needed for documentation of BA or BE of solution formulation nasal sprays. For cases in which BE is documented for the low-strength product, to subsequently document BE for the high-strength product, all applicable in vitro tests described in section V should be conducted.

B. SUSPENSION FORMULATION NASAL SPRAYS

BA of lower strength suspension formulation nasal sprays should be based on conduct of all applicable in vitro tests described in section V and systemic exposure studies, assuming availability of bioanalytical methodology to allow measurement of systemic concentrations. In the absence of this methodology, BA for systemic absorption should be documented through clinical studies. BE conditions for the lower strength product should be the following:

1. Documentation of BE for the high-strength test products and high-strength reference

products, based on acceptable comparative formulations and container and closure systems, comparative in vitro data, and comparative in vivo data

2. Acceptable comparative formulations and container and closure systems for the low-strength test products and low-strength reference products

3. Acceptable comparative studies for low-strength test products and low-strength reference products for all applicable in vitro tests in section V

4. Proportionally similar unit dose between high- and low-dose test product and high- and low-dose reference product

5. Equivalent droplet and drug PSD between high- and low-dose test product and high- and low-dose reference product

Provided the above conditions are met, in vivo studies are not needed for documentation of BE of the lower strength products.

For cases in which an ANDA applicant initially documents BE on the low-strength product, and subsequently submits an ANDA for the high-strength product, full in vitro and in vivo documentation of BE should be provided for the high-strength product. For cases in which an ANDA applicant has documented BE for its high-strength product and wishes to conduct applicable in vitro tests and in vivo study on the low-strength product, BE criteria need not include in vitro comparisons between high- and low-strength products.

XI. SMALLER CONTAINER SIZES

Nasal aerosols and nasal sprays may be available in two container sizes. Current examples are: (1) beclomethasone dipropionate nasal aerosol, a suspension formulation; (2) fluticasone propionate nasal spray, a suspension formulation; and (3) cromolyn sodium nasal spray, a solution formulation. Smaller container sizes of nasal aerosols should be formulated with the same components and composition, metering valve, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Smaller container sizes of nasal sprays should be formulated with the same components and composition, pump, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Where this is the case, no further documentation of either BA or BE is necessary. However, reestablishing proper priming, given a change in the dead volume of the pump and actuator, may in some cases be appropriate (see section V.B.5).

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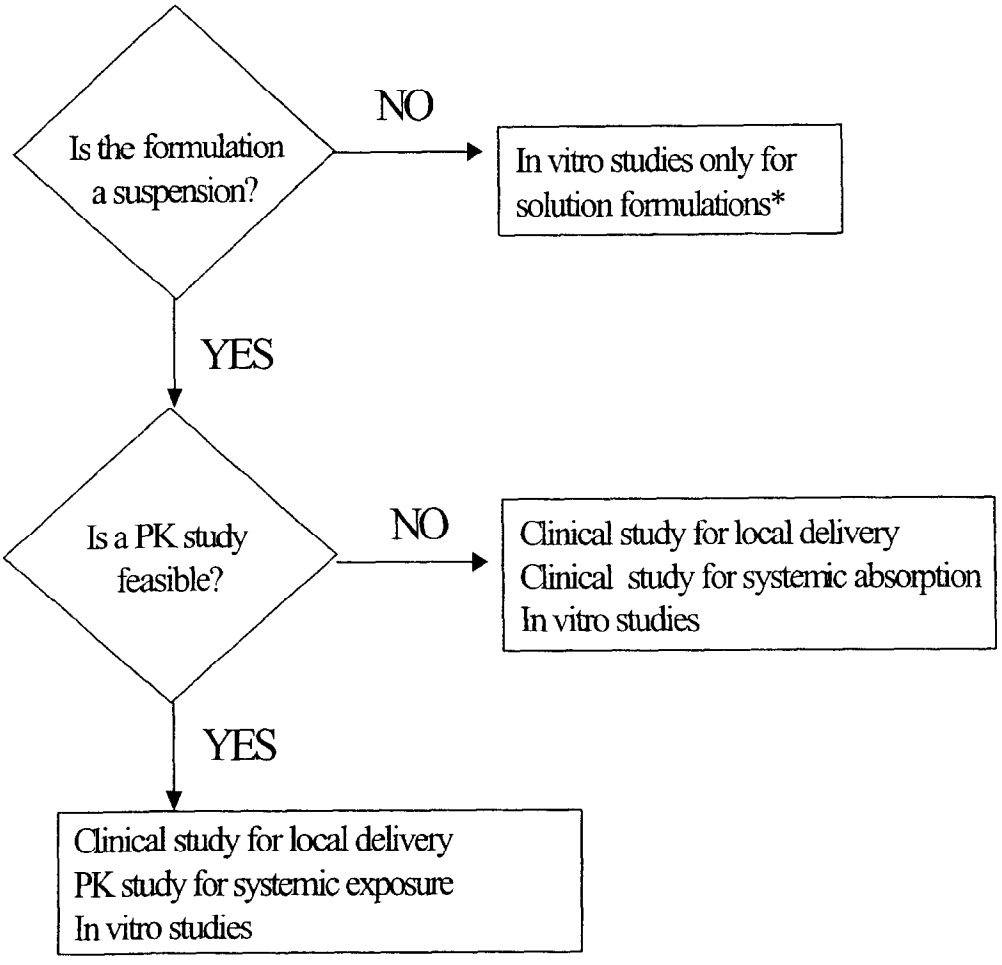
Decision Tree For Product Quality
BA and BE Studies For Nasal Aerosols and Nasal Sprays



*See Section II (A) regarding additional in vivo BA studies needed for solution and suspension formulations.

Table 1
In Vitro BA and BE Studies for Nasal Aerosols and Nasal Sprays

TEST	BA AND BE STUDY MEASURE(S)[1]	BE MEASURES[2]	LIFESTAGE(S) B (beginning) M (middle) E (end)	CONFIDENCE INTERVAL OR SUPPORTIVE CHARACTERIZATION FOR BE	GUIDANCE SECTIONS
Dose or spray content uniformity through container life	Drug mass per single dose	Same as previous column	B, M, E (aerosols) B, E (sprays)	Confidence interval	V.B.1, IX.B
Droplet size distribution	D_{10}, D_{50}, D_{90}, span	D_{50}, span	B, M, E	Confidence intervals	V.B 2, IX B
Particle size distribution (CI or MSLI)	Deposition profile over 3 groups	Same as previous column	B, E	Confidence interval	V.B 2, IX.D
Drug and aggregate PSD of suspensions (light microscopy)	Drug CMD and GSD, aggregate PSD	Drug CMD	B	Supportive characterization	V.B 2, IX.C
Spray pattern	D_{max}, D_{min}, ovality ratio	D_{max} or D_{min}, ovality ratio	B, E	Confidence intervals	V.B 3, IX.B
Plume geometry	Length, width, spray cone angle (if feasible)	Same as previous column	B	Supportive characterization	VB.4, IX C
Priming and repriming	Drug mass per single actuation	Same as previous column for: • priming, and • repriming if in precursor product (R) labeling	From first actuation (priming), from first actuation after specified period of nonuse (repriming)	Confidence interval for priming and repriming if in precursor product (R) labeling; supportive characterization of priming when not in labeling	V.B.5, IX.B, IX.C
Tail off	Drug mass per single actuation	Same as previous column	From end of labeled number of actuations to exhaustion	Supportive characterization	V.B.6, IX.C

[1] Data requested as part of the BA or BE submission.
[2] Measures requested for comparative in vitro BE documentation.

APPENDIX A
IN VITRO PROFILE COMPARISON PROCEDURE BASED ON CHI-SQUARE DIFFERENCES

This appendix describes a method of comparing cascade impactor (CI) or multistage liquid impinger (MSLI) deposition profiles on "S" stages or accessories, or groups of stages and accessories, from droplet and/or particle sizing studies. Equivalence may be assessed by comparing the profile difference between test product and reference product canisters (nasal aerosols) or bottles (nasal sprays) to the profile variation between reference product canisters or bottles. The profile comparison is based on chi-square differences.

The following table represents the population mean profiles P_T and P_R of one test canister and one reference canister, respectively.

Product	Stage										
	1	2	3	4	.	.	s	.	.	S	Total
Test	P_{T1}	P_{T2}	P_{T3}	P_{T4}	.	.	P_{Ts}	.	.	P_{TS}	100
Reference	P_{R1}	P_{R2}	P_{R3}	P_{R4}	.	.	P_{Rs}	.	.	P_{RS}	100

The profile difference between test and reference product canisters is assessed by the chi-square measure as follows:

$$D_{TR} = (P_{T1} - P_{R1})^2/((P_{T1} + P_{R1})/2) + (P_{T2} - P_{R2})^2/((P_{T2} + P_{R2})/2) + \ \ldots \ +$$

$$(P_{TS} - P_{RS})^2/((P_{TS} + P_{RS})/2)$$

Similarly, the profile variation (i.e., difference) between any two canisters of the reference product is:

$$D_{RR'} = (P_{R1} - P_{R'1})^2/((P_{R1} + P_{R'1})/2) + (P_{R2} - P_{R'2})^2/((P_{R2} + P_{R'2})/2) + \ \ldots \ +$$

$$(P_{RS} - P_{R'S})^2/((P_{RS} + P_{R'S})/2)$$

The approach involves a comparison of D_{TR}, the profile difference between one test canister and one reference canister, to $D_{RR'}$, the profile variation between two canisters of the reference product, where the latter is based on two randomly selected reference canisters. The comparison of profile differences is given by the ratio of D_{TR} to $D_{RR'}$. A large D_{TR} is one that is large relative to the variation that would be expected between two canisters of the reference product.

In order to estimate D_{TR} and $D_{RR'}$, the observed data of one canister of test product and two different canisters of reference product need to be matched as a triplet. The observed profiles of the three canisters of a given triplet may be represented in the following table.

Product	Stage										
	1	2	3	4	.	.	s	.	.	S	Total
Test	p_{T1}	p_{T2}	p_{T3}	p_{T4}	.	.	p_{Ts}	.	.	p_{TS}	100
Reference 1	p_{R1}	p_{R2}	p_{R3}	p_{R4}	.	.	p_{Rs}	.	.	p_{RS}	100
Reference 2	$p_{R'1}$	$p_{R'2}$	$p_{R'3}$	$p_{R'4}$	.	.	$p_{R's}$	.	.	$p_{R'S}$	100

The observed profile difference d_{TR} between test and reference products is:

$$d_{TR} = (p_{T1} - (p_{R1} + p_{R'1})/2)^2/((p_{T1} + (p_{R1} + p_{R'1})/2)/2) + (p_{T2} - (p_{R2} + p_{R'2})/2)^2/((p_{T2} + (p_{R2} + p_{R'2})/2)/2)$$

$$+ \ \ldots \ + (p_{TS} - (p_{RS} + p_{R'S})/2)^2/((p_{TS} + (p_{RS} + p_{R'S})/2)/2).$$

The reference product canister-to-canister variation within the triplet is estimated by the profile difference between the two paired reference canisters, R and R':

$$d_{RR'} = (p_{R1} - p_{R'1})^2/((p_{R1} + p_{R'1})/2) + (p_{R2} - p_{R'2})^2/((p_{R2} + p_{R'2})/2) + \ \ldots \ + (p_{RS} - p_{R'S})^2/((p_{RS} + p_{R'S})/2).$$

For a given triplet of canisters (Test, Reference 1, Reference 2), the ratio of d_{TR} to $d_{RR'}$ may be obtained as follows:

$$rd = d_{TR}/d_{RR'}.$$

Assuming that there are N(T, R, R') triplets in the sample, the unbiased estimate of Rd [=E(rd)] is the sample mean of the N observed $d_{TR}/d_{RR'}$ values.

For an experiment consisting of three lots each of test and reference products, and with 10 canisters per lot, the lots can be matched into six different combinations of triplets with two different reference lots in each triplet. The 10 canisters of a test lot can be paired with the 10 canisters of each of the two reference lots in $(10 \text{ factorial})^2 = (3{,}628{,}800)^2$ combinations in each of the lot-triplets. Hence a random sample of the N canister-pairing of the six Test-Reference 1-Reference 2 lot-triplets is needed. Rd is estimated by the sample mean of the rd's calculated for the triplets in the selected sample of N:

$\hat{}Rd$ = sample mean of $(d_{TR}/d_{RR'})$.

APPENDIX B

DETERMINATION OF THE 95% UPPER BOUND FOR IN VITRO PROFILE COMPARISONS

Assume the profile comparison is to be carried out with a random sample with no replacement of N = 500 matches (from the population of 6 x (10 factorial)^2 matches). The average of the 500 sample rd's (= d_{TR} /$d_{RR'}$) gives ^Rd. The 95% upper bound of Rd is the 95th percentile of the 500 calculated rd's (i.e., the 25th largest rd among the 500 calculated rd's).