Guidance for Industry

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

DRAFT GUIDANCE

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

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

Biopharmaceutics
April 2003

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U.S. Department of Health and Human Services
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Note: The following stand alone documents will be provided when completed.

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

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

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

[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.

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

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

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Product quality studies provide information that pertains to the identity, strength, quality, purity, and potency of a drug product. These studies include information on chemistry, manufacturing, and controls (CMC), microbiology, BE and certain aspects of BA. A BE study is normally used to compare a test product (T) to a reference product (R) C the to-be-marketed product is compared to a pivotal clinical trial material, and a generic product is compared to a reference listed drug. A BE study thus provides information on product quality. BA studies for ensuring product quality relate to the release of the active ingredient or active moiety from the drug product (Williams et al., 2000). BA studies may also address biopharmaceutical and clinical pharmacology issues, such as absorption, distribution, and elimination of the active ingredient and its metabolites and dose proportionality. These latter BA/PK studies provide information beyond product quality BA characterization and would also be included in the Human Pharmacokinetics section (Item 6) of an NDA. These latter studies are not the subject of this guidance. Rather, this guidance discusses studies that focus on product performance (i.e., release of a drug substance from a drug product). Subsequent references to BA studies in this guidance *refer only to BA studies for ensuring product quality*.

This guidance should be used with other, more general CMC and BA and BE guidances available from CDER.[3] Product quality information is different from, yet complementary to, the clinical safety and efficacy information that supports approval of an NDA. For information on the type of safety and efficacy studies that may be requested 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, we recommend appropriate CDER review staff be consulted.

Note: Detailed CMC information relevant to nasal aerosols and nasals sprays is presented in the final guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* C

[3] Guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

Chemistry, Manufacturing, and Controls Documentation.[4] The document provides complementary information on the BA/BE testing methods recommended in this guidance.

A. BA and BE Data

Bioavailability is defined at 21 CFR 320.1 as Athe 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 Athe 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 used to measure BA in an NDA can 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) a criterion to allow the comparison, based on means and/or variances for BA measures, (2) a confidence interval for the criterion, and (3) a BE limit (goalpost) for the criterion.

BA and BE data must be provided in accordance with the regulations.[5] BA and BE can be established using in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in vitro studies, or, in certain cases, using in vitro studies alone.[6] 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. The drug is then absorbed and becomes available at local sites of action. A drug administered nasally and intended for local action has the potential to produce systemic activity, although plasma levels do not in general reflect the amount of drug reaching nasal 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 (Daley-Yates et al., 2001). For these reasons, BA and BE studies generally would consider both local delivery and systemic exposure or systemic absorption.

1. Local Delivery BA/BE Concepts

For local delivery, BA is a function of several factors, including release of the drug substance from the drug product and availability to local sites of action. Release of the drug from the drug product produces droplet or drug particle sizes and distribution

[4] A draft guidance, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products C Chemistry, Manufacturing, and Controls Documentation*, was issued in October 1998. Once finalized, it will represent the Agency's thinking on this topic.

[5] 21 CFR 320.21, Requirements for submission of in vivo bioavailability and bioequivalence data.

[6] 21 CFR 320.24, Types of evidence to establish bioavailability or bioequivalence.

patterns within the nose that are dependent upon the drug substance, formulation, and device characteristics. Availability to local sites of action is usually a function of droplet or drug particle sizes and distribution patterns, 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 (Newman et al., 1995; Borgstrom et al., 1996; Suman et al., 2002), 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, can not always be clearly established. Clinical endpoints may be highly variable (Welch et al., 1991; Meltzer et al., 1998) and relatively insensitive to dose differences over an eightfold or higher dose range (Advisory Committee for Pharmaceutical Science, 2001), thus insensitive in detecting potential differences between products. However, clinical studies can unequivocally establish effectiveness of the drug product.

In this guidance, the recommended approach for solution formulations of locally acting nasal drug products, both aerosols and sprays, is to rely on in vitro methods to assess BA. To establish BE, the recommended approach relies on (1) qualitative and quantitative sameness of formulation of test and reference products, (2) comparability in container and closure systems, and (3) in vitro methods that demonstrate equivalent performance. This approach is based on the premise that in vitro studies would be more sensitive indicators of drug delivery to nasal sites of action than would be clinical studies. For solution formulations, see Section IV.B.1.

The recommended approach for establishing BA and BE of suspension formulations of locally acting nasal drug products, both aerosols and sprays, is to conduct in vivo studies in addition to in vitro studies.[7] As with the solution formulation aerosols and sprays, to establish BE, the approach also relies on qualitative and quantitative sameness of formulation of test and reference products and comparability in container and closure systems. We recommend that in vitro studies be coupled with a clinical study for BA, or a BE study with a clinical endpoint (Section VI), to determine the delivery of drug substance to nasal sites of action. In vivo studies are recommended because of an inability at the present time to adequately characterize drug particle size distribution (PSD) in aerosols and sprays (Sections V.B.3, 4). Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation.

[7] Types of in vivo BE studies that may be submitted in support of an ANDA include, in addition to pharmacokinetic studies, tests in humans in which an acute pharmacological effect is measured as a function of time and appropriately designed comparative clinical trials for demonstration of BE (21 CFR 320.24).

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 on systemic absorption. Although systemic absorption may contribute to clinical efficacy for certain corticosteroids and antihistamines, the consequences of systemic absorption (e.g., hypothalamic-pituitary-adrenal (HPA) axis suppression by corticosteroids) are generally undesirable. In the absence of validated in vitro methodology for characterizing drug PSD for suspension products and when measurable plasma levels can be obtained, this guidance recommends PK studies to measure systemic exposure BA or to establish systemic exposure BE (see Section VII). For suspension products that do not produce sufficient plasma concentrations to allow assessment of systemic exposure, clinical studies or BE studies with a pharmacodynamic or clinical endpoint are recommended to measure systemic absorption BA and establish systemic absorption BE, respectively (Section VIII). For a schematic representation of recommended studies, see Appendix A: Decision Tree.

B. CMC 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 the release of the drug substance from the drug product. Some of the in vitro BA/BE tests described in this guidance may be the same as CMC tests for characterization and/or batch release. CMC and in vitro BA tests have acceptance criteria. In vitro BE tests have BE limits. A specification (test, method, acceptance criterion) for a CMC test for batch release or an in vitro BA test 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. In contrast, BE tests have limits that are not usually based on manufacturing experience, but are part of equivalence comparisons between test and reference products. BE limits may be based on a priori judgments and may be scaled to the variability of the reference product (see Appendices C, E). 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 an active ingredient have the potential to affect the BA of a drug product as a result of different solubilities and/or rates of dissolution. We recommend for an ANDA of a suspension formulation, data demonstrating comparable PSD and morphic form of the drug particles, size and number of drug aggregates in the dosage form, and hydrous or solvate form of the active drug in the dosage form to the reference listed drug, be

provided, where possible. Where impossible, the rationale for not providing this full set of comparative data is requested. For suspension formulations marketed in more than one strength, we recommend that the drug substance in each strength product be micronized under identical parameters, and the PSD of the resultant bulk drug used in each product strength be identical.

B. Container and Closure System

Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated accessories, and protective packaging, which together constitute the drug product. Similarly, nasal sprays usually 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, we recommend BE be documented on the basis of validated in vitro and vivo tests, or, in the case of solutions, 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 infeasible, we recommend that valve, pump, and actuator designs be as close as possible in all critical dimensions to those of the reference product. We recommend that metering chamber volumes and actuator orifice diameters be the same. For a nasal spray, spray characteristics can 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 the design of the swirl chamber. The external dimensions of the test actuator are expected to ensure comparable depth of nasal insertion to the reference actuator. A test product is expected to attain prime within the labeled number of actuations for the reference product. We recommend you consider the volume of components of the device that must be filled to deliver an actuation, 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 BA AND BE

A. NDAs

For product quality, we recommend that in vitro BA studies be provided in NDAs for solution and suspension products, and in vivo BA studies be provided for suspension products. These data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the in vivo performance of the product. 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 solution and suspension products) and in vivo tests (for suspension products) may be useful in certain circumstances 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). We recommend sponsors discuss the usefulness of these BE approaches with the appropriate CDER review staff.

B. ANDAs

For product equivalency, we recommend that the drug concentration in the test and reference product formulations not differ by more than "5 percent. In addition, we recommend that the inactive ingredients in the test product formulation be qualitatively (Q_1)[8] the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the formulation of the reference listed drug, and the container and closure recommendations of Section III be followed. 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 would not differ by more than "5 percent of the concentration or amount in the reference listed drug. We recommend a side-by-side Q_1 and Q_2 comparison of the compositions of the test and reference listed drug formulations be provided. Please also provide a side-by-side comparison of the components of the container and closure system, listing brand and model, dimensions of critical components (Section IIIB), and engineering drawings if possible.

1. Solution Formulations

We believe in vitro tests alone can be relied on to document BE for nasal solution formulation products intended for local action. This approach is based on an understanding that for solution products, equivalent in vitro performance and adherence to Q_1 and Q_2 recommendations and to container and closure recommendations will ensure comparable delivery to the nasal mucosa and to the respiratory and gastrointestinal tracts. Suggested methodology and validation approaches for the recommended tests are provided in Section V. Suggested statistical methods to allow comparisons will be discussed in the appendices to this document. 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 would not be sufficient in the face of failed in vitro studies.

2. Suspension Formulations with PK Systemic Exposure Data

To document BE for suspension formulation products intended for local action, we recommend both in vitro and in vivo data be used. In vivo studies would include both a BE study with a clinical endpoint (local delivery) and a pharmacokinetic study (systemic exposure). This approach is only applicable for those suspension formulation products that produce sufficiently high plasma concentrations of the moiety(ies) to be measured to allow reliable analytical measurement for an adequate length of time after nasal administration. Suggested methodology and validation approaches for the recommended tests are provided for in vitro studies in Section V, and for in vivo studies in Sections VI and VII. As with solutions, in vivo studies would not be sufficient in the face of failed in vitro studies (i.e., in vitro BE studies that fail to meet the statistical tests) even though the

[8] See 21 CFR 314.94(a)(9)(v).

BE study with a clinical endpoint or the PK study meets the statistical test. Conversely, ANDAs with acceptable in vitro data, but with in vivo data that fail to meet the statistical tests, would be insufficient to establish BE.

3. Suspension Formulations without PK Systemic Exposure Data

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 would not be sufficient in the face of in vitro studies that fail to document BE. As for suspensions with PK data, ANDAs with acceptable in vitro data, but with in vivo data that fail to meet the statistical tests, would be insufficient to establish BE.

C. Postapproval Change

This document does not cover postapproval changes. Sponsors planning such changes can consult the guidance for industry *Changes to an Approved NDA or ANDA* and contact the appropriate review division prior to instituting the change.

V. IN VITRO STUDIES

A. Batches and Drug Product Sample Collection

1. NDAs

We recommend in vitro BA studies for nasal aerosols and sprays be performed on samples from three or more batches: a pivotal clinical trial batch to provide linkage of in vitro performance to in vivo data; a primary stability batch; and if feasible, a production-scale batch. This selection of batches will ensure consistency of in vitro performance among the three types of batches. If a production-scale batch is unavailable, a second pivotal clinical trial batch or second primary stability batch can be substituted. When three batches are studied, we recommend the batches be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. We prefer that the three batches be studied at the same time, if possible, to remove interstudy variation from the estimation of between batch means and variances.

The BA batches to be studied would be equivalent to the to-be-marketed product and representative of production scale. The manufacturing process for these batches would 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,* Section II.B.3). Complete batch records, including batch numbers of device components used in the batches, would 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 can be noncomparative to other formulations or products. The in vitro tests and metrics are described in Section V.B of this guidance. 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 Appendix B.

2. ANDAs

In vitro BE studies for nasal aerosols and sprays would generally be performed on samples from each of three or more batches of the test product and three or more batches of the reference listed drug. Test product samples would be from the primary stability batches used to establish the expiration dating period. When three batches are studied, we recommend the test product be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. 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.[9]

The BE batches to be studied would be equivalent to the to-be-marketed product. The manufacturing process of these batches would simulate that of large-scale production batches for marketing. Complete batch records, including batch numbers of device components used in the batches or sublots (for solution nasal sprays) would accompany the BE submission.

Reference product samples would 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, are described in Appendices C, D and E.

B. Tests and Metrics

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

[9] 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 can be split-filled into three equal size sublots of product. The sublots would be prepared from three different batches of the same device (pump and actuator) components.

1. Single Actuation Content Through Container Life
2. Droplet Size Distribution by Laser Diffraction
3. Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor
4. Drug Particle Size Distribution by Microscopy
5. Spray Pattern
6. Plume Geometry
7. Priming and Repriming

These tests are relevant to all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, with the exception of drug particle size distribution by microscopy, which applies only to suspension products. The in vitro tests are summarized in Table 1.

We recommend you validate all in vitro tests for accuracy and precision prior to the study. For applicable studies, instrument settings established during prestudy validation would be used in the study. For comparative studies, use of the same settings will ensure that T and R are studied under the same instrumental conditions. The in vitro tests would be conducted on canisters or bottles selected in a random manner from the test batch, including units from the beginning, middle, and end of the production run. Actuation should be conducted in a manner that removes potential operator bias, either by employing automatic actuation, or by employing blinded procedures when manual actuation is used. However, we recommend automated actuation systems for all comparative in vitro BE tests. These systems are expected to decrease variability in drug delivery due to operator factors, thereby increasing the sensitivity for detecting potential differences between products in the above tests.[10] In addition, it is important that the analyst performing the postactuation evaluations of the collected data be blinded to the identity of the samples. We recommend analytical methods used for analysis of samples from the in vitro tests be validated.[11] Unexpected results and deviations from protocol or SOPs, with justification for deviations, would be reported. Examples include, but are not limited to, canisters or bottles replaced during in vitro analyses, failure to use the specific actuations required by the protocol, and experiments rejected due to assignable causes (e.g., instrument failure, sample collection, or processing errors). The original and reanalyzed data, with the reason for reanalysis, would be tabulated in the study report. The validation reports for the in vitro tests and analytical methods, the randomization procedure, and all test methods or SOPs for each test would accompany the data in the submission. When appropriate, we recommend the test method or SOP include a standardized shaking procedure prior to testing, following labeled instructions, if any.

[10] Automatic actuation systems can be stand-alone or accessories for spray characterization instruments. Systems can include settings for force, velocity, acceleration, length of stroke, and other relevant parameters. Selection of appropriate settings would be relevant to proper usage of the product by the trained patient, and for nasal sprays, may be available from pump suppliers for tests such as Droplet Size Distribution by Laser Diffraction and Spray Pattern. In the absence of recommendations from the pump supplier, we recommend that settings should be documented based on exploratory studies in which the relevant parameters are varied to simulate in vitro performance upon hand actuation. Selected settings used for the in vitro studies would be specified in the test method or SOP for each test for which the system is employed.

[11] A draft guidance for industry entitled *Analytical Procedures and Methods Validation* was issued in August 2000.

In addition to submission of all raw data, the agency would like to see supporting documentation for the following tests: Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry. Documentation includes instrument output reports and photographic or graphic material as applicable. We recommend that documents be clearly labeled to indicate the product (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as appropriate. For Droplet Size Distribution by Laser Diffraction, profiles of droplet size and obscuration or percent transmission over the complete life of the single sprays would be submitted. For Spray Pattern and Plume Geometry, we recommend each image display the relevant BA/BE measures described in this guidance. Supporting documentation for Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry would include representative copies, preferably electronic, of $20 percent of the total observations. For Spray Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic images rather than paper copies of $20 percent of the total observations would be submitted, as electronic files are definitive. For automated image analysis of Spray Pattern and Plume Geometry, in addition to the electronic images, we recommend paper copies of a few screen images be submitted as reference samples.

1. Single Actuation Content (SAC) Through Container Life

For noncomparative data, SAC through container life testing is used to characterize the delivery of drug discharged from the actuator of an aerosol or nasal spray relative to label claim through container life. For comparisons of T and R products, this test ensures that the T product delivers an equivalent amount of drug relative to the R product over the labeled number of actuations. The tests are distinct from and do not apply dose content uniformity (DCU) or spray content uniformity (SCU) acceptance criteria.

The dosage unit sampling apparatus for collection of an emitted dose from an aerosol is described in *U.S. Pharmacopeia* (USP) *25,* <601>. We recommend a suitable apparatus be used for collecting an emitted dose from a nasal spray. For both solution and suspension formulations of nasal aerosols and nasal sprays, the mass of drug per actuation would be based on a stability-indicating chemical assay unless use of a nonstability-indicating method is justified. Because the data at beginning (B) lifestage will also be used for confirmation of priming (Section V.B.7), SAC through container life would be based on ***single actuation data per determination***. For BA and BE submissions, the tests would determine delivered (emitted or ex-actuator) drug mass from primed units at the beginning of unit life, at the middle of unit life, and at the end of unit life[12] for nasal aerosols, and at beginning and end of unit life for nasal sprays. The delivered mass of drug substance would be expressed both as the actual amount and as a percentage of label claim. We recommend that mean and variability in SAC through

[12] Based on the labeled number of actuations, this guidance uses the terms *beginning lifestage (B), middle lifestage (M)*, and *end lifestage (E)* 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 actuations); and *end of unit life* (the actuation(s) corresponding to the label claim number of actuations).

container life be determined based on within and between unit (container) data and between batch (or sublot) data. For BE data, equivalence of T and R data would be based on the statistical methodology of Appendix C.

To use the SAC through container life data for priming studies, we recommend aerosols and sprays be unprimed prior to the conduct of the tests. Therefore, for aerosols, the test would be performed at such time that the product meets two conditions: (1) after the lagering period and (2) not less than one month after the last actuation conducted as part of batch release testing. During the time period between batch release and SAC through container life testing, the aerosol product would not be actuated. Also, during this one month period, both T and R aerosols would be stored in the valve upright position, unless labeling indicates that the product be stored in the valve down position, in which case the test would be conducted on products stored in the valve down position. For sprays, the SAC through container life test would be conducted not less than one month after completion of batch release testing. During the time period between batch release and SAC testing, the product would not be actuated.

2. Droplet Size Distribution by Laser Diffraction

Droplet size distribution is an important property influencing the nasal deposition of aerosols and sprays, and we recommend that it be thoroughly characterized.

a. Nasal sprays

We recommend that droplet size distribution be determined using laser diffraction or an appropriately validated alternate methodology.

Laser diffraction is a nonaerodynamic optical method of droplet sizing that measures the geometric size of droplets in flight. Modern laser diffraction instrumentation can provide plots of obscuration (optical concentration) or percent transmission (%T) and droplet size distribution (D_{10}, D_{50}, D_{90}) over the entire life of a single spray. Span ((D_{90} - D_{10})/D_{50}) can be computed from these data. These profile data indicate that each plume can be characterized by three phases: formation, fully developed, and dissipation. For nasal sprays, the general profile for obscuration or percent T versus time can be characterized by a rapid increase in obscuration, or decrease in percent T, early in the life of the spray (formation phase), followed by attainment of a plateau (fully developed phase), then a rapid decrease in obscuration, or increase in percent T, late in the life of the spray (dissipation phase). Changes in droplet size occur coincident with the changes in obscuration or percent T, with droplet sizes attaining plateau values within the same approximate time period as the plateau in obscuration or percent T. Profiles of the droplet size and obscuration or percent T over the complete life of the single sprays are recommended to be determined at each of two distances (see below) to establish the fully developed phase during which data would be collected. Droplet size distribution and span during the fully developed phase are

requested. The sponsor's protocol or SOP would state the criterion selecting the region of the plateau at which droplet size data will be determined (e.g., the average of all scans over the entire plateau, the data of a single scan (sweep) only at the maximum obscuration (or minimum percent T), or the average of a specified range of scans around this obscuration or percent T). This criterion would be established prior to the study for each of the two distances and implemented consistently during the study.

We would also like to see instrument setup and operation conditions. We recommend the instrument be operated within the manufacturer's recommended obscuration or percent T range, which would be stated in the submission, to avoid or minimize multiple scattering (due to high droplet concentration). Avoidance of multiple scattering is preferred to use of a correction algorithm that compensates for this effect.

Single spray droplet size distribution and span would be reported based on volume (mass) rather than count (number of droplets). We would like to request data be provided for nasal sprays at:

- Fully developed phase only
- B and E lifestages
- Two distances from the actuator orifice. For increased ability to detect potential differences between products, it is recommended that the studies be performed within a range of 2 to 7 cm from the orifice, with the two distances separated by 3 cm or more.

b. Nasal aerosols

Droplet size distribution can be determined using laser diffraction or appropriately validated alternate methodology.

We would like to see instrument setup and operation conditions. We recommend the instrument be operated within the manufacturer's recommended obscuration or percent T range, which would be stated in the submission, to avoid or minimize multiple scattering (due to high droplet concentration). Avoidance of multiple scattering is preferred to use of a correction algorithm that compensates for this effect.

Beam steering resulting from refractive index effects due to evaporation of propellant is an additional concern for nasal aerosols. Droplet size distribution would be characterized at distances from the actuator that eliminate or minimize beam steering, if possible. If a correction algorithm is used, we recommend an explanation of the corrections be provided.

We ask that single-spray droplet size distribution and span be reported based on volume (mass) rather than count (number of droplets). Data would be provided for nasal aerosols at:

- Fully developed phase only
- B and E lifestages
- Two distances from the actuator orifice

For both nasal sprays and nasal aerosols, mean D_{10}, D_{50}, D_{90} values for a given bottle or canister can be computed from the mean of up to three consecutive sprays from that unit at each lifestage. However, to assess precision, the data of each spray would also be reported.

3. Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor

Sizing of droplets or particles by multistage cascade impactor (CI) measures aerodynamic diameter based on inertial impaction, an important factor in the deposition of drug in the nasal passages. Analytical data should be based on a validated chemical assay.[11] We recommend that analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI. An analytical validation report would accompany the CI data report. The SOP or validation report would indicate the minimum quantifiable mass of drug deposited on each location reported.

a. Nasal sprays: Drug in Small Particles/Droplets

For nasal sprays, the majority of the emitted dose is deposited prior to or on the first stage of the CI test. Small droplets, for this test and dosage form defined as smaller in size than the nominal effective cutoff diameter (ECD) of the top stage of a suitable CI, may potentially be delivered to regions of the airways beyond the nose. This test is intended to determine the amount of drug in small particles/droplets. For example, for USP 25 Apparatus 1 (<601>), an eight stage CI operated with the standard 28.3 liter per minute configuration, small droplets are those under 9.0 microns. For BA, the CI test is intended to quantify the mass of drug in small droplets. For BE, the mass of drug in small droplets for the T product would be less than or equivalent to the corresponding mass of drug from the R product. The comparative test addresses a potential safety concern — an excess of small droplets due to T relative to R might deliver to regions beyond the nose excipients with possible adverse pulmonary effects. The CI test for nasal sprays is not intended to provide PSD of drug or aerosolized droplets.

Measurable levels of drug below the top stage of the CI would be a function of the specific drug product and the experimental setup and procedure, including the

number of actuations and assay sensitivity. Thus, we recommend a validated, highly sensitive assay be used. In Agency experience, a two-liter or larger induction port (expansion chamber) is preferred to a one-liter chamber. We prefer studies use the fewest number of actuations (generally not exceeding 10) justified by the sensitivity of the assay, to be more reflective of individual doses. Drug deposition would be reported in mass units. Mass balance accountability would be reported. Mass balance would be based on drug deposition on each of valvestem, actuator, adapters, induction port, any other accessories, the top stage, and all lower stages to the filter. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis. The total mass of drug below the top stage is of primary interest. Therefore the pooled mass of drug deposited on all lower stages and filter can be reported.

For BA and BE, CI test would be data requested only at the beginning lifestage. Statistical approaches will be provided in Appendices B and D, respectively.

b. Nasal aerosols: Particle/Droplet Size Distribution

CI studies for nasal aerosols would use an induction port (expansion chamber) that maximizes drug deposition below the top stage of the CI. For this reason, a one-liter induction port is preferred to the USP 25 (<601>) induction port, although other sizes may also be appropriate. Agency experience indicates that with a suitable induction port and CI, the amount of drug deposited below the top stage from nasal aerosols formulated with either chlorofluorocarbon or hydrofluoroalkane propellants is of the same order of magnitude as from orally inhaled aerosols. Therefore, unlike for nasal sprays in which the total mass of drug below the top stage is of interest, we recommend a particle/droplet size distribution be provided for this dosage form. Selection of the most suitable CI may be influenced by the effective cutoff diameters (ECDs) of stages of various brands of cascade impactors, the geometry of the induction port, and other factors. The number of actuations recommended for the CI study of aerosols is described in the draft guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products !Chemistry, Manufacturing, and Controls Documentation.* Drug deposition would be reported in mass units. Mass balance accountability would be reported.

For BA and BE, CI data would be requested only at the beginning lifestage. At this time, it is recommended that studies of nasal aerosols use USP 25 Apparatus 1 (<601>) operated at the standard 28.3 liter per minute configuration. We recommend determination of a profile based on drug deposition at 11 sites: (1) sum of valve stem plus actuator; (2) induction port; (3 - 10) eight individual stages; and (11) filter. Deposition in the valve stem plus actuator would be included to provide a profile of drug deposition ex-valve rather than ex-actuator. It should be noted that the in vitro BE limit for the profile comparison depends on

the number of stages and other accessory deposition sites. Statistical approaches for BA and BE will be provided in Appendices B and E, respectively.

4. Drug Particle Size Distribution by Microscopy

For suspension products, drug particle size may be important for rate of dissolution and availability to sites of action within the nose. Therefore, drug particle size distribution (PSD) and extent of agglomerates would be characterized in the spray or aerosol formulation prior to actuation, and in the spray following actuation. Determination of PSD and agglomerates in both the formulation and following actuation are intended to characterize the potential influence of the device on deagglomeration. Determination in the spray is only requested at the beginning lifestage. Nasal spray formulations frequently contain suspended drug substance in the presence of insoluble suspending agent, which complicates the particle size characterization. When examining formulations containing suspending agents, and currently available technology cannot be acceptably validated to determine drug particle size, a qualitative and semi-quantitative method for examination of drug and aggregated drug particle size distribution can be used. We recommend studies of nasal sprays include placebo product to provide an estimate of the occurrence of apparent drug particles (*false positives*) due to excipient. Evaluation may use light microscopy or other appropriate means.

For NDAs and ANDAs of both sprays and aerosols, we recommend drug PSD and agglomerates data be provided in the BA or BE submission, along with a description of the test method. Sponsors can submit representative photomicrographs, if desired. For BE, PSD by light microscopy, even if qualitative or semi-quantitative, can be useful to the applicant to estimate particle size relative to the precursor product prior to further product development and testing. These data are supportive, and formal statistical testing is not applicable.

5. Spray Pattern

Spray pattern studies characterize the spray either during the spray prior to impaction, or following impaction on an appropriate target such as a thin-layer chromatography (TLC) plate. Spray patterns for certain nasal spray products may be *spoked* or otherwise irregular in shape.

Spray patterns can be characterized and quantitated by either manual or automated image analysis, if validated. Both analyses will allow shape and size to be determined. Automated analysis systems may also allow determination of center of mass (COM; unweighted for image intensity) and/or center of gravity (COG; weighted for image intensity) within the pattern to be determined. COG is of greater interest and is preferred in the automated analyses of spray patterns. Automated image analysis is expected to increase objectivity in spray pattern measurement. The technology enables the perimeter of the true shape of the spray pattern to be determined, identifies COM and/or COG, and enables the area within the perimeter to be quantitated, thus its use is encouraged.

Equivalence of spray patterns between T and R products can be established based on a combination of qualitative and quantitative measures:

- Comparative visual inspection for shape. For the automated analyses, the true shapes identified by the software serve as the basis of comparison (qualitative). Establishment of qualitative sameness of T and R spray pattern shapes is a prerequisite to the quantitative analyses in the following two bullets.
- Equivalent area within the perimeter of the true shape for automated analysis, or equivalent D_{max} for manual analysis (quantitative)
- Equivalent ovality (ellipticity) ratio (quantitative)

a. For nonimpaction systems

Spray patterns can be visualized using a system based on a laser light sheet and high-speed digital camera that enables visualization of a pattern perpendicular to the axis of the nasal spray. The perimeter of the true shape, area within the perimeter (to include a high proportion, e.g., $ 95% of the total pattern), COG, and D_{max} (longest diameter) and D_{min} (shortest diameter) that pass through the COG and extend to the perimeter of the true shape, can be determined based on automated analysis using time-averaged images over the duration of a single spray. Software settings can be established during prestudy validation and the settings should be used consistently in the study. Statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio (D_{max} divided by D_{min}).

b. For impaction systems

The number of sprays per spray pattern would preferably be one. We recommend that the visualization technique be specific for the drug substance. If exploratory studies document that a drug-specific reagent cannot be found, a nonspecific visualization reagent can be used. We recommend that application of the reagent be controlled to maintain the details of the image intensity of the pattern.

<u>Manual analysis</u>

The approximate COM would be identified, and D_{max} and D_{min} drawn through this center. The two lines may not be orthogonal to each other. Representative plots can be submitted, and each figure can be marked with the COM, D_{max} and D_{min}, each based on visual analysis. The ovality ratio would be provided for each spray pattern. Statistical analysis at each distance would be based on equivalence of D_{max} and ovality ratio.

<u>Automated analysis</u>

The automated image analysis software can define the perimeter of the true shape of the spray pattern to include a high proportion (e.g, $ 95%) of the total pattern. T and R would both be sprayed on each TLC plate to ensure measurement of the spray pattern at the same intensity range for a given plate. D_{max} and D_{min} would pass through the COM or the COG, as appropriate, and extend to the perimeter of the true shape. Statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio.

c. For both nonimpaction and impaction systems

The information above would apply to spray patterns in which the COM or COG falls within the perimeter of the image of the actual spray pattern, and the D_{max} axis doesn't extend outside of the perimeter. Infrequently, the COM or COG may fall outside the perimeter of the spray pattern, and/or the D_{max} axis may cross the perimeter. Horseshoe-shaped and certain other patterns may cause such an effect. When this occurs, automated analysis using a system that has the capability of fitting the perimeter with an appropriate geometric shape is recommended. Statistical analysis at each distance would be based on equivalence of area within the perimeter of the ***true shape*** of the spray pattern (not within the fitted geometric shape), and ovality ratio, where D_{max} and D_{min} are computed from the ***fitted geometric shape*** (e.g., ellipse).

For all cases above, we recommend spray patterns be determined based on:

- Single actuations (nonimpaction systems), or preferably single actuations (impaction systems)
- Beginning lifestage only
- Two distances from the actuator orifice, which allow discriminatory capability between individual pump units and between T and R products. For nasal sprays, these distances are recommended to be at least 3 cm apart within the range of 3 to 7 cm.

For manual quantitation of spray patterns based on impaction studies such as TLC plate methodology, we recommend the submission include copies, preferably electronic, of images of representative spray patterns at two distances, and each figure would clearly indicate the estimated COM (manual analysis), D_{max} and D_{min}. When automated image analysis software is used for impaction studies, data would be presented in electronic files. For automated image analysis of either impaction or nonimpaction studies, electronic files would be definitive. Submission of electronic files is recommended to avoid printer-dependent variations in spatial calibration of images. These files would contain the images, showing the COG or COM and the perimeter of the true shape of the spray pattern, and the accompanying quantitation reports. Each image would also include a legible scale used for measurement.

Some automated image analysis software may not include automated quantitation of spray pattern images. For such cases, the analyst would determine and display the quantitative parameters on the electronic image. As mentioned above, quantitation of electronic images would be definitive.

6. Plume geometry

Plume geometry describes a side view of the aerosol cloud parallel to the axis of the plume, and we recommend it be based on high-speed photography, a laser light sheet and high speed digital camera, or other suitable methods. The image would be *snapshot*, not time-averaged. Quantitation can be by manual analysis or automated image analysis.

During the very early life of an aqueous nasal spray plume, formulation may exit the actuator orifice as a narrow stream that subsequently forms a relatively stable, fully developed, conical plume prior to separating from the orifice. We recommend plume angle, width, and height, all quantitated by the same analytical method, be reported at a single delay time while the fully developed phase of the plume is still in contact with the actuator tip. The applicant would provide documentation that the plume is fully developed at the selected delay time. The angle would be based on the conical region of the plume extending from a vertex that occurs at or near the actuator tip. Plume angle based on spray pattern dimensions and distance from actuator tip to an impaction surface is not appropriate. For this guidance, the recommended plume width would be the width at a distance equal to the greater of the two distances selected for characterization of the spray pattern. Plume width data would thus complementary to spray pattern data obtained at the same distance. Plume height would be the distance from the actuator orifice (sprays) or end of the inhaler tube (aerosols) to the leading edge of the plume. We request that the criteria for defining the plume angle, width, and height borders be provided.

Plume geometry would be performed at:

- Beginning lifestage only
- One side view only
- A single delay time

The submission would include photographs when quantitation is by manual analysis, or digital images when quantitation is by automated image analysis. Each image would also include a legible scale used for measurement, and the delay time would be clearly indicated. Images would clearly indicate the plume angle, width, and height. When automated image analysis is used, quantitation of electronic images would be definitive. Manual quantitation based on paper copies of electronic images would not be appropriate.

We recommend plume geometry measurements be summarized as mean, geometric mean, and %CV. Comparative data would be supportive, thus for BE studies, the ratio of

the geometric mean of the three batches of T to that of the three batches of R, based on log transformed data, would fall within 90 – 111% (point estimates) for plume angle and width. Due to subjectivity in the measurement of plume height, point estimates would not be applicable.

7. Priming and Repriming

Priming and repriming data will ensure delivery of the labeled dose of drug following labeled instructions for use. Priming would be established based on the same B lifestage data obtained for the single actuation content (SAC) through container life study (Section V.B.1). For products approved under an NDA, priming and repriming data based on single actuations would be provided in the CMC portion of the submission.

For products approved under an ANDA, the labeling would be the same as that for the R product, except for specific changes described in the regulations (21 CFR 314.94(a)(8)(iv)). For nasal sprays and some nasal aerosols, the R product labeling (package insert and/or patient package insert) describes the number of actuations 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). For these products, we request priming and repriming data for T and R products. Studies would follow the recommended time periods described in Section V.B.1 between lagering and/or batch release testing and conduct of the priming test. Priming and/or Repriming studies would not be requested when the R product lacks priming and/or repriming instructions, respectively.

We recommend that priming and repriming data for T in multiple orientations be provided in the CMC portion of the ANDA submission. Therefore, for the BE submission, studies can be based on products stored in the valve upright position, with the exception of nasal aerosols in which R labeling recommends storage in the valve down position. For the latter products, priming data, and repriming data when applicable, would be provided following storage in the valve down position. Priming studies would be based on the emitted dose of the single actuation at B lifestage immediately following the specified number of priming actuations in the R product labeling. For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95 – 105 percent of label claim. Repriming would be similarly established based on a single actuation following the specified number of repriming actuations in the R product labeling. Although noncomparative to R, the priming studies would be essential to the BE submission to document that each product delivers the labeled dose within the number of actuations stated in the R product labeling, thus ensuring that the SAC through container life studies are conducted on primed T and R products.

VI. CLINICAL STUDIES FOR LOCAL DELIVERY

A. General Information

1. NDAs

At the present time, of the classes of drugs covered in this guidance, only certain corticosteroids are formulated as suspension formulation nasal aerosols and nasal sprays and require in vivo studies as a component of the BE or BA submission (21 CFR 320.21). The same adequate and well-controlled clinical trials in humans conducted under an authorized IND, used to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR 320.24).

2. ANDAs

Clinical studies are at times incapable of showing a dose-response relationship and may not be consistently reproducible. However, a showing of dose-response is not necessary for BE studies with a clinical endpoint, as these studies are intended only to confirm the lack of important clinical differences between T and R suspension formulation nasal aerosol and nasal spray products (Advisory Committee for Pharmaceutical Science, 2001). For an ANDA, an authorized Bio-IND will be needed for the conduct of a BE study with a clinical endpoint.[13]

A determination of bioequivalence of a rhinitis BE study with a clinical endpoint for locally acting nasal suspension drug products would be based on the following premises for T relative to R products:

- Qualitative and quantitative sameness of formulation
- Comparability in container and closure systems
- Equivalence of in vitro tests
- Equivalence of systemic exposure or systemic absorption
- Equivalence of the local delivery study.

A number of FDA guidances provide information about the general conduct of clinical studies, including clinical studies to document BA and BE: *General Considerations for Clinical Trials* (International Conference on Harmonisation (ICH) E8); *Structure and Content of Clinical Study Reports* (ICH E3); *Good Clinical Practice: Consolidated Guidance* (ICH E6); *Statistical Principles for Clinical Trials* (ICH E9), and *Choice of Control Group and Related Issues in Clinical Trial*s (ICH E10).

B. Clinical Study Batches

[13] Office of Generic Drugs Policy and Procedure Guide # 36-92, *Submission of an "Investigational New Drug Application" to the Office of Generic Drugs (OGD),* October 13, 1992.

We recommend that the batch used for the BA study be the same pivotal clinical trial batch used in the in vitro BA studies (Section V.A). Where BE studies are conducted for an NDA, the batches of test and reference products would be the same batches employed in the in vitro testing. Each of the T and R batches used to establish local delivery BE for an ANDA would be one of the three batches used for the in vitro BE studies. We recommend that the inactive ingredients of the placebo (P) product meet Q_1 and Q_2 recommendations relative to the R product (Section IV.B); the P container and closure would meet the recommendations of Section III.B.

C. Clinical BE Study Design and Subject Inclusion Criteria

The study design would be the traditional treatment study in which T and R are assessed for a two-week duration. The two-week duration, in addition to allowing a comparison of equivalent efficacy, will also allow for an assessment of safety and tolerability over a reasonable period of use. We recommend the study be conducted at the lowest labeled adult recommended dose in an attempt to optimize study sensitivity. Primed products according to labeling instructions prior to dosing. Ensure that priming occurs out of range of the patients, to avoid inhalation of drug fired to waste. Documentation would rely on the inclusion of a test product placebo (P) dosed at the same frequency and number of actuations per nostril as T and R.

A study population consisting of seasonal allergic rhinitis (SAR) patients will allow documentation of BE, which may extend to all indications in product labeling for locally acting nasal corticosteroids. In addition to a history of SAR, we recommend patients have a positive test for relevant specific allergens (e.g., allergen skin test) and be experiencing a defined minimum level of symptom severity at the time of study enrollment. We discourage the inclusion of patients with other significant diseases including asthma, with the exception of mild intermittent asthma.

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study of 14 days duration, preceded by a 7-day placebo run-in period to establish a baseline and to identify placebo responders.[14] We recommend placebo responders be excluded from the study to increase the ability to show a significant difference between active and placebo treatments (efficacy analysis), and to increase sensitivity to detect potential differences between T and R products (equivalence analysis). The protocol would define *placebo responders* a priori. Whether the drug is labeled for once or twice daily dosing, clinical evaluations would be made twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo run-in period and the 14-day randomized treatment period. Scoring should be made immediately prior to each dose, to reflect the previous 12 hours (*reflective* scores) and how the patient is feeling at the time of evaluation (*instantaneous* or *snapshot* scores). Because the primary BE endpoint would be based on reflective symptom scores, placebo responders should be identified based on reflective scores, although BE endpoints would include both reflective and instantaneous scores.

[14] A draft guidance for industry entitled *Allergic Rhinitis: Clinical Development Programs for Drug Products* was issued in April 2000. This guidance discusses general protocol issues including blinding. Once finalized, it will represent the Agency's thinking on this topic.

We recommend baseline scoring preferably consist of reflective AM and PM scoring on Days 5, 6, and 7 of the placebo run-in period, and AM scoring (prior to drug dosing) on Day 1 of the 14 day randomized treatment period, resulting in 7 total AM and PM ratings. Placebo responders would be identified based on the mean total nasal symptom score (TNSS) over the 7 total AM and PM ratings. The study protocol would state the minimum qualifying reflective TNSS for enrollment at screening, and the same minimum qualifying TNSS would be met based on the mean of the 7 total AM and PM ratings prior to each patient's participation in the randomized portion of the study. We recommend randomization occur after evaluation of the 7 total AM and PM ratings, and the randomized portion of the study can start in the morning of Day 1 after the AM baseline scoring.

Symptom scores during the randomized treatment period would consist of the PM score on Day 1, and the 26 AM and PM ratings on Days 2 to 14, resulting in 27 total ratings. We recommend the study be multicenter to avoid potential investigator bias. A double dummy design is not recommended for study blinding of aqueous nasal sprays due to a concern that the doubled fluid volume may result in washing the drug from its nasal deposition sites, potentially resulting in an altered safety and efficacy profile. However, study blinding is a critical consideration, and we recommend a description of how the T, R and P products are to be masked be carefully described in the study protocol.

We recommend the ***equivalence analysis*** be conducted as an evaluable (per protocol) analysis rather than an intent-to-treat analysis. The evaluable population would consist of compliant patients who missed no more than a specified number of days of symptom scores, took no contraindicated concurrent medications, and had no protocol violations. The protocol would describe the specific criteria used to exclude randomized subjects, resulting in the reduced subset of subjects for analysis (*FDA Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*, Section III.B.9). In addition to the equivalence analysis, an ***efficacy analysis*** would be conducted to demonstrate study sensitivity to the T and R products. The efficacy analysis would be conducted as an intent-to-treat analysis, and the intent-to-treat population would be clearly defined. Because specific study recommendations are not provided in this guidance, we recommend a protocol for a BE study with a clinical endpoint for a specific suspension drug product be submitted prior to the conduct of the study to the appropriate review division at FDA.

D. Clinical BE Study Endpoints

The endpoints for the ***equivalence*** and ***efficacy analyses*** should be patient self-rated *TNSS*. These most often include a composite score of runny nose, sneezing, nasal itching, and congestion, although addition of non-nasal symptoms to the composite score maybe pertinent for certain drug products.[15] TNSS is a categorical variable, classified into a number of discrete categories, as opposed to a continuous variable. A common allergic rhinitis rating system uses a

[15] Draft guidance *Allergic Rhinitis: Clinical Development Programs for Drug Products*, was issued in April 2000, once finalized it will represent the Agency's thinking on this topic.

four-point scale with signs and symptoms ordered in severity from 0 (no symptoms) to 3 (severe symptoms), as follows[16]:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

We recommend the endpoints for the equivalence and efficacy analyses be expressed as mean change from baseline (pretreatment) of the TNSS, expressed in absolute units, rather than percent change from baseline. The study report would include the daily AM and PM 12-hour reflective symptom scores. In addition, the report would include the mean symptom score over the 7 total AM and PM ratings of the placebo run-in period and the mean symptom score over the 27 ratings of the randomized treatment period. For the equivalence and efficacy analyses, the ***primary*** endpoint would be reflective scores for the 12-hour pooled TNSS over the two-week randomized portion of the study. However, instantaneous scores would also be provided as a ***secondary*** endpoint. Statistical approaches for analysis of the rhinitis study data are provided in Appendix F.

Safety assessments would be made before (at screening or baseline) and at end-of-treatment. Adverse events would be reported daily.

VII. PK STUDIES FOR SYSTEMIC EXPOSURE

A. General Information

The Agency recommends that plasma concentration-time profiles from BA and BE studies be used to evaluate systemic exposure for suspension drug products that produce sufficiently high concentrations of the moiety(ies) to be measured to allow reliable analytical measurement for an adequate length of time after nasal administration. The recommended moiety(ies) to be measured in the BA and BE studies are described elsewhere.[17]

Systemic drug levels that occur with locally acting drug products are generally in the low ng/mL or low pg/mL range, depending on the drug and the drug product. Validated bioanalytical methodology may be available for many of the nasal corticosteroid drugs. For these drugs, pilot studies are not needed prior to conducting the full-scale PK study. If validated methodology is unavailable, a small-scale, single-dose pilot study, or when appropriate, a small-scale, multiple-

[16] Other scoring systems were proposed in the draft guidance *Allergic Rhinitis: Clinical Development Programs for Drug Products* April 2000. Once finalized, it will represent the Agency's thinking on this topic.

[17] *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations* (October 2000). Once finalized it will represent the Agency's thinking on this topic.

dose pilot study, may be helpful in assessing the proposed analytical methodology and determining whether sufficiently high drug concentrations are attained. A PK study for systemic exposure would be preferred to a PD or clinical study for systemic absorption (Section VIII). If a sponsor has convincing data based on unsuccessful attempts to conduct the PK study in order for a PD or clinical study for systemic absorption could be used. If systemic exposure were established based on a PK study, a PD or clinical study for systemic absorption (Section VIII) would not be requested.

B. Study Batches

The Agency recommends that the BA batch used for the PK systemic exposure study be a pivotal clinical trial batch. Alternatively, a PK batch similar to the batch used in a pivotal clinical trial can be used, in which case we recommend that any differences between the PK batch and the pivotal clinical trial batch be discussed with the appropriate CDER review division 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), make sure that in vitro BA data are provided for the PK batch using the same protocols as for the three batches.

For a BE study, the batches of T and R would be the same batches used for the clinical study for local delivery, and each of these batches would be one of the three batches used for the in vitro BE studies.

C. Study Design and Subject Inclusion Criteria

The BA study to characterize systemic exposure can be one of the same PK studies conducted to address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA study can be conducted in healthy subjects or allergic rhinitis (AR) patients. Where appropriate, the BA study would include a reference product that may be an oral or intravenous solution, oral suspension, or other nasal product. Consultation with the appropriate review division is recommended regarding whether a comparative or noncomparative BA study is appropriate.

For an NDA or an ANDA, the in vivo BE study would be conducted with a replicate or nonreplicate randomized crossover design. For aqueous nasal sprays, the study would be conducted at the maximum labeled adult dose to maximize plasma drug levels, while avoiding the possibility of alteration of the drug deposition pattern within the nose at higher volumes when dosed above label claim. The deposition pattern could be altered due to loss of drug from the nasal cavity at these higher volumes, due either to drainage into the nasopharynx or externally from the nasal cavity. Although alteration of the deposition pattern may be less likely for a nasal aerosol when dosed above the maximum labeled number of actuations, the same study design and dose as for aqueous nasal sprays would be followed. We recommend that subjects for the study be healthy, with exclusions primarily for reasons of safety. The study protocol would include information regarding time interval between doses to each nostril and subject head position during dosing.

This guidance recommends that the PK study generally be conducted as a single-dose study. Such studies are more sensitive than multiple dose studies in assessing rate of release of the drug substance from the drug product into the systemic circulation. In addition, the nasally dosed corticosteroids tend to have biologic half-lives ranging from less than one hour up to about eight hours. For these products, when dosed either once or twice daily, systemic accumulation is expected to be relatively low, thus a multiple dose study may not result in a more reliable analytical measurement. However, there may be drugs that, due to pharmacokinetic characteristics, yield higher concentrations in a multiple-dose study, enabling the drug moiety(ies) of interest to be measured more reliably than in a single-dose study. For these drugs, a multiple-dose PK study would be preferred to a single-dose study.

D. Study Measures

The following BA and BE measures are considered pivotal[17] in a single-dose study: $AUC_{0-tlast}$ (a measure of total exposure); AUC_{0-4} (a measure of total exposure); and C_{max} (peak exposure). If AUC_{0-4} cannot be determined reliably due to inability to estimate k_{el} accurately, total exposure would be based only on $AUC_{0-tlast}$. The following BA and BE measurements and plasma concentrations provide supportive PK characterization: plasma concentrations at each sampling time; T_{max}; and k_{el}. The following BA and BE measurements are considered-pivotal for a multiple-dose study: AUC_{0-J} (total exposure), where J is the dosing interval; and C_{max} (peak exposure). T_{max} data should also be provided as supportive characterization.

Statistical analysis information is provided in Appendix G.

VIII. PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION

A. General Information

As stated in Section VI.A, at present only certain corticosteroids are formulated as suspension products and require product quality in vivo studies. For those suspension drug products for which the moiety(ies) to be measured in the blood or plasma (Section VII) are too low to allow reliable analytical measurement for an adequate length of time, PD or clinical endpoint studies serve as measures of systemic absorption (Section II.A.2). However***, PK studies as measures of systemic exposure are preferred if at all possible***. As stated in Section VII, if a sponsor has convincing data based on unsuccessful attempts to conduct the PK study a PD or clinical study would be used in lieu of the PK study. The BA study to characterize systemic absorption may be one of the same clinical studies conducted to establish the safety of the drug product. The study would be conducted under an authorized IND in support of a forthcoming NDA (21 CFR 314.126).

If a PD or clinical study is to be conducted (see previous paragraph), the recommended systemic absorption BE study design for nasal corticosteroids would be assessment of the HPA axis. The study would be conducted at the maximum labeled adult dose of the nasal aerosol or nasal spray to maximize study sensitivity. However, the study design would be based on an understanding

that the maximum labeled dose over a 6-week period (Section VIII.C) may not result in detectable adrenal suppression by T and R because this dose may be at or near the bottom of the adrenal suppression dose-response curve. In addition to a test product placebo (P), we recommend an active control such as prednisone be included to ensure that the study is sufficiently sensitive to detect a drug effect (sensitivity analysis). Ensure that the active control dose is sufficiently large and the duration sufficiently long to produce a statistically significant response relative to placebo, with a duration sufficiently short to minimize undue exposure or risk to subjects. Determination of the optimum active control dose and dosing regimen may call for a pilot study by the sponsor. The pilot study may determine that an initial phase of the 6-week study period may use a matching active control placebo, with active control given over the remainder of the study period, in an effort to reduce patient exposure to the active control. The pilot study can also provide an estimate of the number of subjects to be included in the pivotal study to yield a statistically significant difference in the HPA axis endpoint between the active control and the test product placebo (i.e., the aerosol or spray placebo). It may also allow estimation of the number of subjects to be included to characterize any HPA axis effects or lack thereof and to allow conclusions about any relative effects of T versus P and R versus P ("relative assessment of the HPA axis"; Appendix G.B). Conduct of the study in allergic rhinitis (AR) patients will allow an efficacy assessment to evaluate compliance with the study protocol (efficacy analysis). Therefore, AR patients, rather than healthy, non-allergic patients are recommended as the study population. We also recommend that other measures of compliance be instituted, including before and after weighing of the aerosol or spray container and diary entry of drug use.

Because this section does not provide specific recommendations, we recommend sponsors submit prior to the conduct of the study a protocol for a BE study with a PD or clinical endpoint for a specific drug product to the appropriate review division at FDA. For an NDA, the same adequate and well-controlled clinical trials in humans conducted under an authorized IND, used to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR 320.24). For an ANDA, if the maximum single or total daily dose of the active control in the pilot or full-scale study exceeds that specified in the labeling of the selected active control drug product, an authorized Bio-IND will be needed.[13]

B. Clinical Study Batches

The Agency recommends the BA batch used for the study 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 would be batches used in in vitro testing. For an ANDA, the batches of T and R used for the systemic absorption study would be the same batches used for the clinical study for local delivery. Each of these batches would be one of the three batches used for the in vitro BE studies. Formulation and device recommendations for the P are described in Section VI.B. An active control such as prednisone is recommended. For blinding, matching active control placebo (identical in appearance to the active control) is also recommended.

C. Clinical BE Study Designs and Subject Inclusion Criteria

We recommend the study be conducted as a placebo and active-controlled, randomized, double-blind, parallel design comparing T and R for a 6-week duration. The study would not be conducted as a subset of the 2-week local delivery rhinitis study (Section VI). Subjects would be patients with a history of AR. The *relative assessment of HPA axis suppression* would be conducted as an evaluable (per protocol) analysis. The sensitivity analysis and efficacy analysis would be conducted as intent-to-treat analyses. The protocol would specify whether placebo responders will or will not be excluded from the analysis. We recommend that subjects be domiciled within the clinical study center during the days of HPA axis assessment. Domiciling the subjects during the 24-hour urine or plasma collection periods can help to conduct the study-related procedures reliably and completely. T and R would be dosed at the maximum labeled adult dose. P would be dosed at the same frequency and number of actuations per nostril as T and R. As stated above, the study would include an active control such as prednisone. Four study arms would be included: T, R, P, and the active control. The randomized portion of the study would be conducted according to a double-blinding design (i.e., all subjects would receive both the active control (either the active control itself or a matching placebo of the active control) and a spray or aerosol (either active or placebo)). The four treatment groups would be T plus matching active control placebo, R plus matching active control placebo, P plus matching active control placebo, and P plus active control. The matching active control placebo would be dosed on days when the active control is not taken, including the placebo run-in period. We recommend the number of centers conducting the HPA assessment be kept to a minimum to avoid center-to-center variability. A double-dummy design is not recommended for aqueous nasal sprays, as explained in Section VI.C. However, study blinding is a critical consideration, and we recommend a description of how the T, R and P products are to be masked be carefully described in the study protocol.[18]

The expected effect for the active control would be far larger than that for the T and R products. The sample size of the active control arm group may therefore be smaller in size than for the other study arms. We recommend the sample size for the T and R study arms be sufficient to characterize any HPA axis effects or lack thereof to allow conclusions about any relative effects of T versus P and R versus P, as stated in Section VIII.A.

We recommend timed urine or plasma samples for determination of 24-hour urinary free cortisol (UFC) or 24-hour plasma cortisol levels, respectively, be collected. Collections would be made prior to dosing (baseline) and during the last 24 hours of the 42 days of dosing (i.e., over the day 41 – 42 period) while the drug is being actively dosed.

D. Clinical BE Study Endpoints for Corticosteroids

Whether the drug is labeled for once or twice daily dosing, the endpoint can be either 24-hour urinary free cortisol (UFC), based on a full 24-hour urine collection, or plasma cortisol levels

[18] A draft guidance entitled *Allergic Rhinitis: Clinical Development Programs for Drug Products* was issued in April 2000. Once finalized, this guidance will represent the agency's thinking on this topic.

collected every 4 hours over a 24-hour period, with exclusion of the middle of the night sample. For the UFC endpoint, urinary creatinine would also be measured to confirm completeness of the 24-hour collection. The UFC value would not be corrected for creatinine. We recommend for the plasma cortisol endpoint, both AUC(0-24) and the trough (maximum effect) concentration during the dosing interval should be determined. The sensitivity analysis endpoint would be baseline-adjusted prior to analysis. Raw data would be provided for the relative assessment of HPA axis suppression. Efficacy analysis TNSS data would be expressed as change from baseline.

Statistical approaches for each of the analyses are provided in Appendix G.B.

IX. NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING

Reserve samples must be retained for BA and BE studies (21 CFR 320.38 and 320.63) conducted in vivo or in vitro. The regulations state that each reserve sample must consist of a sufficient quantity of samples to permit FDA to perform five times all of the release tests required in the application or supplemental application. Dose content uniformity or spray content uniformity release tests alone usually require 30 units (canisters or bottles) per batch. Performance of other release tests requires additional units. The number of reserve sample units required for three batches of T and R could exceed 1000 units (up to 250 units for each batch of T and R) based on the *five-times-quantity* requirement.

The Agency has determined that in lieu of the *five-times-quantity* requirement, the quantity of inhalant (nasal aerosol or nasal spray) test article (T) and reference standard (R) retained for testing and analyses be at least 50 units for each batch.[19] For NDAs, three batches are needed for BA studies. Thus, we recommend at least 50 units from each of the three batches of nasal spray or nasal aerosol be retained. However, where the reference product is another nasal aerosol or nasal spray, at least 50 units of that batch would also be retained. For ANDAs, at least 50 units of each of three batches would be retained for each of T and R used in in vivo or in vitro BE studies. For NDAs and ANDAs, if the in vivo or in vitro studies include placebo aerosols or sprays, at least 50 units of each placebo batch would also be retained. These recommendations apply only to nasal aerosols and nasal sprays for local action covered in this guidance and which are marketed as multiple dose products, typically labeled to deliver 30 or more actuations per canister or bottle. The number of reserves for nasal aerosols and nasal sprays delivering less than 30 actuations per canister or bottle is not addressed in this guidance. Additional information regarding retention of BA and BE testing samples is pending.[20]

[19] Quantity of Reserve Samples, Preamble to final rule, Retention of Bioavailability and Bioequivalence Testing Samples, 58 FR 25918-26, 1993, IIC21.

[20] A draft guidance for industry entitled *Handling and Retention of BA and BE Testing Samples* was issued in August 2002. Once finalized, it will represent the Agency's thinking on this topic.

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 due to different volumes of product or other factors) 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

We recommend the BA of lower or higher strength solution formulation nasal sprays 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 would follow the recommendations described in Section III regarding formulation and container and closure system. Abbreviated in vitro testing, as follows, 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
Single Actuation Content Through Container Life	B, E[a]	B, E
Priming and Repriming	Yes	Yes
Droplet Size Distribution by Laser Diffraction	B, E	B
Drug in Small Particles/Droplets by Cascade Impactor	B	No
Spray Pattern	B	B
Plume Geometry	B	No

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

With the exception of the reduced testing, the Agency recommends the same protocols and acceptance criteria used to establish BE of the high-strength products be used for the low strength products. In vivo studies are not needed for documentation of BA or BE of solution formulation nasal sprays. Initial documentation of BE of the low-strength product would be based on all applicable in vitro tests described in Section V. For subsequent documentation of BE for the high-strength product, all applicable in vitro tests described above for the high-strength product would be conducted.

B. Suspension Formulation Nasal Sprays

We recommend BA of lower strength suspension formulation nasal sprays 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, we suggest BA for systemic absorption be documented through pharmacodynamic or clinical studies.

BE conditions for the lower strength product would include:

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

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

4. Proportionally similar Single Actuation Content Through Container Life between high- and low-dose test product and high- and low-dose reference product

In vivo studies would not be needed for documentation of BE of the lower strength products.

For cases in which an ANDA applicant initially documents BE on the low-strength suspension formulation product, and subsequently submits an ANDA for the high-strength product, full in vitro and in vivo documentation of BE would be provided for the high-strength product.

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 would 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 would 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, re-establishing proper priming, given a change in the volume of components of the device that will be filled to deliver an actuation, may in some cases be appropriate (Section V.B.7).

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TABLE 1
RECOMMENDED IN VITRO STUDIES FOR BA AND BE OF NASAL AEROSOLS AND NASAL SPRAYS

TEST[1]	BA AND BE STUDY MEASURE(S)	BE MEASURE(S) FOR STATISTICAL EVALUATION	LIFESTAGE(S) B (beginning), M (middle), E (end)	STATISTICAL EVALUATION FOR BE PBE (population bioequivalence)	GUIDANCE SECTIONS
Single Actuation Content Through Container Life	Drug mass per single actuation	Same as previous column	B, M, E (aerosols) B, E (sprays)	PBE	V.B.1, App. B, C
Droplet Size Distribution by Laser Diffraction	D_{10}, D_{50}, D_{90}, span at 2 distances	D_{50}, span	B, E	PBE	V.B.2, App. B, C
Drug in Small Particles/Droplets by Cascade Impactor	Drug mass below upper stage	Same as previous column	B (sprays)	PBE modified to be one-sided with respect to the mean comparison	V.B.3, App. B, D
Particle/Droplet Size Distribution by Cascade Impactor	Drug mass on individual accessories, stages, etc – profile analysis	Deposition profile	B (aerosols)	Profile analysis	V.B.3, App. B, E
Drug Particle Size Distribution by Microscopy for suspensions	Drug CMD; extent of agglomerates	Same as previous column	B	Not applicable	V.B.4
Spray Pattern	Automated analysis: area, ovality ratio at 2 distances or Manual analysis: D_{max}, ovality ratio at 2 distances	Qualitative – shape comparison Quantitative - Same as previous column	B	PBE for area and ovality ratio (automated analysis) or D_{max} and ovality ratio manual analysis	V.B.5, App. C
Plume Geometry	Height, width, and cone angle of one side view at one delay time	Width and cone angle of one side view at one delay time	B	Point estimates	V.B.6
Priming and Repriming	Drug mass per single actuation at first primed or reprimed actuation	Same as previous column for Priming, and Repriming if in precursor product (R) labeling	B (Priming) Lifestage not specified (Repriming)	Point estimate relative to label claim if in precursor product (R) labeling	V.B.7

[1] Although alternate test methods may be appropriate for certain tests, if validated, we recommend sponsors planning to use such methods contact the appropriate reviewing division prior to use.