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# 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### *DRAFT GUIDANCE*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**

# **Guidance for Industry**

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

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Biopharmaceutics  
April 2003**

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

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

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

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

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

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

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

# Guidance For Industry<sup>1</sup>

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. 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<sup>2</sup> or studies of (1) metered-dose products intended to deliver drug systemically via the nasal route or (2) drugs in nasal nonmetered dose atomizer (squeeze) bottles that require premarket approval.

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

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

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

41  
42 FDA's guidance documents, including this guidance, do not establish legally enforceable  
43 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
44 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
45 cited. The use of the word *should* in Agency guidances means that something is suggested or  
46 recommended, but not required.

47  
48

### **II. BACKGROUND**

49  
50  
51 Product quality studies provide information that pertains to the identity, strength, quality, purity,  
52 and potency of a drug product. These studies include information on chemistry, manufacturing,  
53 and controls (CMC), microbiology, BE and certain aspects of BA. A BE study is normally used  
54 to compare a test product (T) to a reference product (R) C the to-be-marketed product is  
55 compared to a pivotal clinical trial material, and a generic product is compared to a reference  
56 listed drug. A BE study thus provides information on product quality. BA studies for ensuring  
57 product quality relate to the release of the active ingredient or active moiety from the drug  
58 product (Williams et al., 2000). BA studies may also address biopharmaceutical and clinical  
59 pharmacology issues, such as absorption, distribution, and elimination of the active ingredient  
60 and its metabolites and dose proportionality. These latter BA/PK studies provide information  
61 beyond product quality BA characterization and would also be included in the Human  
62 Pharmacokinetics section (Item 6) of an NDA. These latter studies are not the subject of this  
63 guidance. Rather, this guidance discusses studies that focus on product performance (i.e., release  
64 of a drug substance from a drug product). Subsequent references to BA studies in this guidance  
65 *refer only to BA studies for ensuring product quality.*

66  
67 This guidance should be used with other, more general CMC and BA and BE guidances  
68 available from CDER.<sup>3</sup> Product quality information is different from, yet complementary to, the  
69 clinical safety and efficacy information that supports approval of an NDA. For information on  
70 the type of safety and efficacy studies that may be requested for a new active ingredient/active  
71 moiety intended for local action in the nose, or for a new product such as a nasal aerosol that  
72 may include an active ingredient/active moiety previously approved in a nasal spray, we  
73 recommend appropriate CDER review staff be consulted.

74  
75 Note: Detailed CMC information relevant to nasal aerosols and nasals sprays is presented in the  
76 final guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products C*

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<sup>3</sup> Guidances are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

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77 *Chemistry, Manufacturing, and Controls Documentation.*<sup>4</sup> The document provides  
78 complementary information on the BA/BE testing methods recommended in this guidance.  
79

### 80 A. BA and BE Data

81  
82 *Bioavailability* is defined at 21 CFR 320.1 as the rate and extent to which the active ingredient  
83 or active moiety is absorbed from a drug product and becomes available at the site of action. For  
84 drug products that are not intended to be absorbed into the bloodstream, bioavailability may be  
85 assessed by measurements intended to reflect the rate and extent to which the active ingredient  
86 or active moiety becomes available at the site of action. *Bioequivalence* is defined as the  
87 absence of a significant difference in the rate and extent to which the active ingredient or active  
88 moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the  
89 site of drug action when administered at the same molar dose under similar conditions in an  
90 appropriately designed study. BA and BE are closely related, and the same approach used to  
91 measure BA in an NDA can generally be followed in establishing BE for an NDA or ANDA.  
92 Although BA may be comparative, establishing BE specifically involves a comparison of the BA  
93 of one product with the BA of another product. BE is usually established using (1) a criterion to  
94 allow the comparison, based on means and/or variances for BA measures, (2) a confidence  
95 interval for the criterion, and (3) a BE limit (goalpost) for the criterion.  
96

97 BA and BE data must be provided in accordance with the regulations.<sup>5</sup> BA and BE can be  
98 established using in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in  
99 vitro studies, or, in certain cases, using in vitro studies alone.<sup>6</sup> BA and BE assessments for  
100 locally acting nasal aerosols and sprays are complicated because delivery to the sites of action  
101 does not occur primarily after systemic absorption. Droplets and/or drug particles are deposited  
102 topically. The drug is then absorbed and becomes available at local sites of action. A drug  
103 administered nasally and intended for local action has the potential to produce systemic activity,  
104 although plasma levels do not in general reflect the amount of drug reaching nasal sites of action.  
105 Systemic exposure following nasal administration can occur either from drug absorbed into the  
106 systemic circulation from the nasal mucosa, or after ingestion and absorption from the  
107 gastrointestinal tract (Daley-Yates et al., 2001). For these reasons, BA and BE studies generally  
108 would consider both local delivery and systemic exposure or systemic absorption.  
109

#### 110 1. Local Delivery BA/BE Concepts

111  
112 For local delivery, BA is a function of several factors, including release of the drug  
113 substance from the drug product and availability to local sites of action. Release of the  
114 drug from the drug product produces droplet or drug particle sizes and distribution

---

<sup>4</sup> 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.

<sup>5</sup> 21 CFR 320.21, Requirements for submission of in vivo bioavailability and bioequivalence data.

<sup>6</sup> 21 CFR 320.24, Types of evidence to establish bioavailability or bioequivalence.

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115 patterns within the nose that are dependent upon the drug substance, formulation, and  
116 device characteristics. Availability to local sites of action is usually a function of droplet  
117 or drug particle sizes and distribution patterns, as well as drug dissolution in the case of  
118 suspension products, absorption across mucosal barriers to nasal receptors, and rate of  
119 removal from the nose. From a product quality perspective, the critical issues are release  
120 of drug substance from drug product and delivery to the mucosa. Other factors are of  
121 lesser importance.

122  
123 A critical question in assessing product quality BA and BE is the extent to which one can  
124 rely on in vitro methods alone, or upon in vitro methods plus clinical endpoints, to  
125 measure (benchmark) BA and/or establish BE. In vitro methods are less variable  
126 (Newman et al., 1995; Borgstrom et al., 1996; Suman et al., 2002), easier to control, and  
127 more likely to detect differences between products if they exist, but the clinical relevance  
128 of these tests, or the magnitude of the differences in the tests, can not always be clearly  
129 established. Clinical endpoints may be highly variable (Welch et al., 1991; Meltzer et al.,  
130 1998) and relatively insensitive to dose differences over an eightfold or higher dose range  
131 (Advisory Committee for Pharmaceutical Science, 2001), thus insensitive in detecting  
132 potential differences between products. However, clinical studies can unequivocally  
133 establish effectiveness of the drug product.

134  
135 In this guidance, the recommended approach for solution formulations of locally acting  
136 nasal drug products, both aerosols and sprays, is to rely on in vitro methods to assess BA.  
137 To establish BE, the recommended approach relies on (1) qualitative and quantitative  
138 sameness of formulation of test and reference products, (2) comparability in container  
139 and closure systems, and (3) in vitro methods that demonstrate equivalent performance.  
140 This approach is based on the premise that in vitro studies would be more sensitive  
141 indicators of drug delivery to nasal sites of action than would be clinical studies. For  
142 solution formulations, see Section IV.B.1.

143  
144 The recommended approach for establishing BA and BE of suspension formulations of  
145 locally acting nasal drug products, both aerosols and sprays, is to conduct in vivo studies  
146 in addition to in vitro studies.<sup>7</sup> As with the solution formulation aerosols and sprays, to  
147 establish BE, the approach also relies on qualitative and quantitative sameness of  
148 formulation of test and reference products and comparability in container and closure  
149 systems. We recommend that in vitro studies be coupled with a clinical study for BA, or  
150 a BE study with a clinical endpoint (Section VI), to determine the delivery of drug  
151 substance to nasal sites of action. In vivo studies are recommended because of an  
152 inability at the present time to adequately characterize drug particle size distribution  
153 (PSD) in aerosols and sprays (Sections V.B.3, 4). Drug PSD in suspension formulations  
154 has the potential to influence the rate and extent of drug availability to nasal sites of  
155 action and to the systemic circulation.

---

<sup>7</sup> 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).



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### **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

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202 provided, where possible. Where impossible, the rationale for not providing this full set of  
203 comparative data is requested. For suspension formulations marketed in more than one strength,  
204 we recommend that the drug substance in each strength product be micronized under identical  
205 parameters, and the PSD of the resultant bulk drug used in each product strength be identical.  
206

### **B. Container and Closure System**

207  
208  
209 Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated  
210 accessories, and protective packaging, which together constitute the drug product. Similarly,  
211 nasal sprays usually consist of the formulation, container, pump, actuator, protection cap, and  
212 protective packaging, which together constitute the drug product.  
213

214 For nasal aerosols and nasal sprays approved under an ANDA, we recommend BE be  
215 documented on the basis of validated in vitro and vivo tests, or, in the case of solutions, validated  
216 in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is  
217 greatest when the test product uses the same brand and model of devices (particularly the  
218 metering valve or pump and the actuator) as used in the reference product. If this is infeasible,  
219 we recommend that valve, pump, and actuator designs be as close as possible in all critical  
220 dimensions to those of the reference product. We recommend that metering chamber volumes  
221 and actuator orifice diameters be the same. For a nasal spray, spray characteristics can be  
222 affected by features of the pump design, including the precompression mechanism, actuator  
223 design, including specific geometry of the orifice (Kubic and Vidgren 1998), and the design of  
224 the swirl chamber. The external dimensions of the test actuator are expected to ensure  
225 comparable depth of nasal insertion to the reference actuator. A test product is expected to attain  
226 prime within the labeled number of actuations for the reference product. We recommend you  
227 consider the volume of components of the device that must be filled to deliver an actuation,  
228 including the internal diameter and length of the diptube because this volume can influence the  
229 number of actuations required to prime a spray pump.  
230

## **IV. DOCUMENTATION OF BA AND BE**

### **A. NDAs**

231  
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233  
234  
235  
236 For product quality, we recommend that in vitro BA studies be provided in NDAs for solution  
237 and suspension products, and in vivo BA studies be provided for suspension products. These  
238 data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the  
239 in vivo performance of the product. Where the formulation and/or method of manufacture of the  
240 pivotal clinical trial product changes in terms of physicochemical characteristics of the drug  
241 substance, the excipients, or the device characteristics, BE data using in vitro tests (for solution  
242 and suspension products) and in vivo tests (for suspension products) may be useful in certain  
243 circumstances to ensure that the to-be-marketed product (T) is comparable to very similar  
244 clinical trial batches and/or to batches used for stability testing (R) (Section V.A.1). We  
245 recommend sponsors discuss the usefulness of these BE approaches with the appropriate CDER  
246 review staff.

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### 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<sub>1</sub>)<sup>8</sup> the same and quantitatively (Q<sub>2</sub>) 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<sub>1</sub> and Q<sub>2</sub> 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<sub>1</sub> and Q<sub>2</sub> 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

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<sup>8</sup> See 21 CFR 314.94(a)(9)(v).

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

293

### 294 3. *Suspension Formulations without PK Systemic Exposure Data*

295

296 For those products intended for local action that produce blood or plasma levels that are  
297 too low for adequate measurement, given current assay constraints, a BE study with a  
298 clinical endpoint to establish equivalent local delivery to nasal sites (Section VI) and a  
299 study with a pharmacodynamic or clinical endpoint to establish equivalent systemic  
300 absorption (Section VIII) are recommended. In vivo studies that meet the statistical test  
301 would not be sufficient in the face of in vitro studies that fail to document BE. As for  
302 suspensions with PK data, ANDAs with acceptable in vitro data, but with in vivo data  
303 that fail to meet the statistical tests, would be insufficient to establish BE.

304

### 305 C. **Postapproval Change**

306

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

310

311

## 312 V. **IN VITRO STUDIES**

313

### 314 A. **Batches and Drug Product Sample Collection**

315

#### 316 1. *NDAs*

317

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

330

331 The BA batches to be studied would be equivalent to the to-be-marketed product and  
332 representative of production scale. The manufacturing process for these batches would  
333 simulate that of large-scale production batches for marketing (additional information on  
334 large-scale batches is provided in the International Conference on Harmonisation (ICH)

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335 guidance for industry Q1A *Stability Testing of New Drug Substances and Products*,  
336 Section II.B.3). Complete batch records, including batch numbers of device components  
337 used in the batches, would accompany the BA submission.  
338

339 In vitro BA studies are intended to characterize the means and variances of measures of  
340 interest for canisters (nasal aerosols) or bottles (nasal sprays) within a batch and between  
341 batches, where applicable. However, under 21 CFR 320.1 and 320.21, the studies can be  
342 noncomparative to other formulations or products. The in vitro tests and metrics are  
343 described in Section V.B of this guidance. The recommended number of canisters or  
344 bottles of each batch to be used in the above studies, and recommendations for statistical  
345 analyses, are described in Appendix B.  
346

### 347 2. *ANDAs*

348

349 In vitro BE studies for nasal aerosols and sprays would generally be performed on  
350 samples from each of three or more batches of the test product and three or more batches  
351 of the reference listed drug. Test product samples would be from the primary stability  
352 batches used to establish the expiration dating period. When three batches are studied,  
353 we recommend the test product be manufactured, preferably from three different batches  
354 of the drug substance, different batches of critical excipients, and different batches of  
355 container and closure components. However, the container (canister or bottle) can be  
356 from the same batch. For nasal sprays formulated as solutions, in vitro BE tests can  
357 alternatively be performed on three sublots of product prepared from one batch of the  
358 solution.<sup>9</sup>  
359

360 The BE batches to be studied would be equivalent to the to-be-marketed product. The  
361 manufacturing process of these batches would simulate that of large-scale production  
362 batches for marketing. Complete batch records, including batch numbers of device  
363 components used in the batches or sublots (for solution nasal sprays) would accompany  
364 the BE submission.  
365

366 Reference product samples would be from three different batches available in the  
367 marketplace. The recommended in vitro tests and metrics are described in Section V.B.  
368 The recommended number of canisters or bottles of each product and batch to be used in  
369 the above studies, and recommended statistical approaches, are described in Appendices  
370 C, D and E.  
371

### 372 **B. Tests and Metrics**

373

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

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<sup>9</sup> 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.

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385
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

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

389  
390 We recommend you validate all in vitro tests for accuracy and precision prior to the study. For  
391 applicable studies, instrument settings established during prestudy validation would be used in  
392 the study. For comparative studies, use of the same settings will ensure that T and R are studied  
393 under the same instrumental conditions. The in vitro tests would be conducted on canisters or  
394 bottles selected in a random manner from the test batch, including units from the beginning,  
395 middle, and end of the production run. Actuation should be conducted in a manner that removes  
396 potential operator bias, either by employing automatic actuation, or by employing blinded  
397 procedures when manual actuation is used. However, we recommend automated actuation  
398 systems for all comparative in vitro BE tests. These systems are expected to decrease variability  
399 in drug delivery due to operator factors, thereby increasing the sensitivity for detecting potential  
400 differences between products in the above tests.<sup>10</sup> In addition, it is important that the analyst  
401 performing the postactuation evaluations of the collected data be blinded to the identity of the  
402 samples. We recommend analytical methods used for analysis of samples from the in vitro tests  
403 be validated.<sup>11</sup> Unexpected results and deviations from protocol or SOPs, with justification for  
404 deviations, would be reported. Examples include, but are not limited to, canisters or bottles  
405 replaced during in vitro analyses, failure to use the specific actuations required by the protocol,  
406 and experiments rejected due to assignable causes (e.g., instrument failure, sample collection, or  
407 processing errors). The original and reanalyzed data, with the reason for reanalysis, would be  
408 tabulated in the study report. The validation reports for the in vitro tests and analytical methods,  
409 the randomization procedure, and all test methods or SOPs for each test would accompany the  
410 data in the submission. When appropriate, we recommend the test method or SOP include a  
411 standardized shaking procedure prior to testing, following labeled instructions, if any.

---

<sup>10</sup> 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.

<sup>11</sup> A draft guidance for industry entitled *Analytical Procedures and Methods Validation* was issued in August 2000.

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412  
413 In addition to submission of all raw data, the agency would like to see supporting documentation  
414 for the following tests: Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume  
415 Geometry. Documentation includes instrument output reports and photographic or graphic  
416 material as applicable. We recommend that documents be clearly labeled to indicate the product  
417 (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as  
418 appropriate. For Droplet Size Distribution by Laser Diffraction, profiles of droplet size and  
419 obscuration or percent transmission over the complete life of the single sprays would be  
420 submitted. For Spray Pattern and Plume Geometry, we recommend each image display the  
421 relevant BA/BE measures described in this guidance. Supporting documentation for Droplet  
422 Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry would include  
423 representative copies, preferably electronic, of \$20 percent of the total observations. For Spray  
424 Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic  
425 images rather than paper copies of \$20 percent of the total observations would be submitted, as  
426 electronic files are definitive. For automated image analysis of Spray Pattern and Plume  
427 Geometry, in addition to the electronic images, we recommend paper copies of a few screen  
428 images be submitted as reference samples.

### *1. Single Actuation Content (SAC) Through Container Life*

431  
432 For noncomparative data, SAC through container life testing is used to characterize the  
433 delivery of drug discharged from the actuator of an aerosol or nasal spray relative to label  
434 claim through container life. For comparisons of T and R products, this test ensures that  
435 the T product delivers an equivalent amount of drug relative to the R product over the  
436 labeled number of actuations. The tests are distinct from and do not apply dose content  
437 uniformity (DCU) or spray content uniformity (SCU) acceptance criteria.

438  
439 The dosage unit sampling apparatus for collection of an emitted dose from an aerosol is  
440 described in *U.S. Pharmacopeia* (USP) 25, <601>. We recommend a suitable apparatus  
441 be used for collecting an emitted dose from a nasal spray. For both solution and  
442 suspension formulations of nasal aerosols and nasal sprays, the mass of drug per  
443 actuation would be based on a stability-indicating chemical assay unless use of a  
444 nonstability-indicating method is justified. Because the data at beginning (B) lifestage  
445 will also be used for confirmation of priming (Section V.B.7), SAC through container life  
446 would be based on ***single actuation data per determination***. For BA and BE  
447 submissions, the tests would determine delivered (emitted or ex-actuator) drug mass from  
448 primed units at the beginning of unit life, at the middle of unit life, and at the end of unit  
449 life<sup>12</sup> for nasal aerosols, and at beginning and end of unit life for nasal sprays. The  
450 delivered mass of drug substance would be expressed both as the actual amount and as a  
451 percentage of label claim. We recommend that mean and variability in SAC through

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<sup>12</sup> 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).

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

455  
456 To use the SAC through container life data for priming studies, we recommend aerosols  
457 and sprays be unprimed prior to the conduct of the tests. Therefore, for aerosols, the test  
458 would be performed at such time that the product meets two conditions: (1) after the  
459 laging period and (2) not less than one month after the last actuation conducted as part  
460 of batch release testing. During the time period between batch release and SAC through  
461 container life testing, the aerosol product would not be actuated. Also, during this one  
462 month period, both T and R aerosols would be stored in the valve upright position, unless  
463 labeling indicates that the product be stored in the valve down position, in which case the  
464 test would be conducted on products stored in the valve down position. For sprays, the  
465 SAC through container life test would be conducted not less than one month after  
466 completion of batch release testing. During the time period between batch release and  
467 SAC testing, the product would not be actuated.

468

### 469 2. *Droplet Size Distribution by Laser Diffraction*

470

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

473

#### 474 a. Nasal sprays

475

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

478

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



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497 requested. The sponsor's protocol or SOP would state the criterion selecting the  
498 region of the plateau at which droplet size data will be determined (e.g., the  
499 average of all scans over the entire plateau, the data of a single scan (sweep) only  
500 at the maximum obscuration (or minimum percent T), or the average of a  
501 specified range of scans around this obscuration or percent T). This criterion  
502 would be established prior to the study for each of the two distances and  
503 implemented consistently during the study.  
504

505 We would also like to see instrument setup and operation conditions. We  
506 recommend the instrument be operated within the manufacturer's recommended  
507 obscuration or percent T range, which would be stated in the submission, to  
508 avoid or minimize multiple scattering (due to high droplet concentration).  
509 Avoidance of multiple scattering is preferred to use of a correction algorithm that  
510 compensates for this effect.  
511

512 Single spray droplet size distribution and span would be reported based on  
513 volume (mass) rather than count (number of droplets). We would like to request  
514 data be provided for nasal sprays at:  
515

- 516 • Fully developed phase only
- 517 • B and E lifestages
- 518 • Two distances from the actuator orifice. For increased ability to detect  
519 potential differences between products, it is recommended that the studies be  
520 performed within a range of 2 to 7 cm from the orifice, with the two distances  
521 separated by 3 cm or more.  
522

523 b. Nasal aerosols  
524

525 Droplet size distribution can be determined using laser diffraction or  
526 appropriately validated alternate methodology.  
527

528 We would like to see instrument setup and operation conditions. We recommend  
529 the instrument be operated within the manufacturer's recommended obscuration  
530 or percent T range, which would be stated in the submission, to avoid or  
531 minimize multiple scattering (due to high droplet concentration). Avoidance of  
532 multiple scattering is preferred to use of a correction algorithm that compensates  
533 for this effect.  
534

535 Beam steering resulting from refractive index effects due to evaporation of  
536 propellant is an additional concern for nasal aerosols. Droplet size distribution  
537 would be characterized at distances from the actuator that eliminate or minimize  
538 beam steering, if possible. If a correction algorithm is used, we recommend an  
539 explanation of the corrections be provided.  
540

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

- 544
- 545 • Fully developed phase only
  - 546 • B and E lifestages
  - 547 • Two distances from the actuator orifice
- 548

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

553

### 554 3. *Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by* 555 *Cascade Impactor*

556

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

566

#### 567 a. Nasal sprays: Drug in Small Particles/Droplets

568

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

583

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

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

599  
600 For BA and BE, CI test would be data requested only at the beginning lifestage.  
601 Statistical approaches will be provided in Appendices B and D, respectively.  
602

### b. Nasal aerosols: Particle/Droplet Size Distribution

603  
604  
605 CI studies for nasal aerosols would use an induction port (expansion chamber)  
606 that maximizes drug deposition below the top stage of the CI. For this reason, a  
607 one-liter induction port is preferred to the USP 25 (<601>) induction port,  
608 although other sizes may also be appropriate. Agency experience indicates that  
609 with a suitable induction port and CI, the amount of drug deposited below the top  
610 stage from nasal aerosols formulated with either chlorofluorocarbon or  
611 hydrofluoroalkane propellants is of the same order of magnitude as from orally  
612 inhaled aerosols. Therefore, unlike for nasal sprays in which the total mass of  
613 drug below the top stage is of interest, we recommend a particle/droplet size  
614 distribution be provided for this dosage form. Selection of the most suitable CI  
615 may be influenced by the effective cutoff diameters (ECDs) of stages of various  
616 brands of cascade impactors, the geometry of the induction port, and other factors.  
617 The number of actuations recommended for the CI study of aerosols is described  
618 in the draft guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI)*  
619 *Drug Products ! Chemistry, Manufacturing, and Controls Documentation*. Drug  
620 deposition would be reported in mass units. Mass balance accountability would  
621 be reported.  
622

623 For BA and BE, CI data would be requested only at the beginning lifestage. At  
624 this time, it is recommended that studies of nasal aerosols use USP 25 Apparatus  
625 1 (<601>) operated at the standard 28.3 liter per minute configuration. We  
626 recommend determination of a profile based on drug deposition at 11 sites: (1)  
627 sum of valve stem plus actuator; (2) induction port; (3 - 10) eight individual  
628 stages; and (11) filter. Deposition in the valve stem plus actuator would be  
629 included to provide a profile of drug deposition ex-valve rather than ex-actuator.  
630 It should be noted that the in vitro BE limit for the profile comparison depends on

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

633

### 634 4. *Drug Particle Size Distribution by Microscopy*

635

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

651

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

659

### 660 5. *Spray Pattern*

661

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

666

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

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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.

### Manual analysis

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.

### Automated analysis

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

728  
729 c. For both nonimpaction and impaction systems

730  
731 The information above would apply to spray patterns in which the COM or COG  
732 falls within the perimeter of the image of the actual spray pattern, and the  $D_{\max}$   
733 axis doesn't extend outside of the perimeter. Infrequently, the COM or COG may  
734 fall outside the perimeter of the spray pattern, and/or the  $D_{\max}$  axis may cross the  
735 perimeter. Horseshoe-shaped and certain other patterns may cause such an effect.  
736 When this occurs, automated analysis using a system that has the capability of  
737 fitting the perimeter with an appropriate geometric shape is recommended.  
738 Statistical analysis at each distance would be based on equivalence of area within  
739 the perimeter of the *true shape* of the spray pattern (not within the fitted  
740 geometric shape), and ovality ratio, where  $D_{\max}$  and  $D_{\min}$  are computed from the  
741 *fitted geometric shape* (e.g., ellipse).

742  
743 For all cases above, we recommend spray patterns be determined based on:

- 744
- 745 • Single actuations (nonimpaction systems), or preferably single actuations
  - 746 (impaction systems)
  - 747 • Beginning lifestage only
  - 748 • Two distances from the actuator orifice, which allow discriminatory capability
  - 749 between individual pump units and between T and R products. For nasal
  - 750 sprays, these distances are recommended to be at least 3 cm apart within the
  - 751 range of 3 to 7 cm.
- 752

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

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

770

### 771 6. *Plume geometry*

772

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

777

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

794

795 Plume geometry would be performed at:

796

- 797 • Beginning lifestage only
- 798 • One side view only
- 799 • A single delay time

800

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

808

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

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

815

### 816 7. *Priming and Repriming*

817

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

823

824 For products approved under an ANDA, the labeling would be the same as that for the R  
825 product, except for specific changes described in the regulations (21 CFR  
826 314.94(a)(8)(iv)). For nasal sprays and some nasal aerosols, the R product labeling  
827 (package insert and/or patient package insert) describes the number of actuations to prime  
828 the product on initial use and on repriming following one or more periods of nonuse (e.g.,  
829 24 hours and 7 days following last dose). For these products, we request priming and  
830 repriming data for T and R products. Studies would follow the recommended time  
831 periods described in Section V.B.1 between lagging and/or batch release testing and  
832 conduct of the priming test. Priming and/or Repriming studies would not be requested  
833 when the R product lacks priming and/or repriming instructions, respectively.

834

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

851

852

## 853 **VI. CLINICAL STUDIES FOR LOCAL DELIVERY**

854



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### 855 A. General Information

856

#### 857 1. NDAs

858

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

866

#### 867 2. ANDAs

868

869 Clinical studies are at times incapable of showing a dose-response relationship and may  
870 not be consistently reproducible. However, a showing of dose-response is not necessary  
871 for BE studies with a clinical endpoint, as these studies are intended only to confirm the  
872 lack of important clinical differences between T and R suspension formulation nasal  
873 aerosol and nasal spray products (Advisory Committee for Pharmaceutical Science,  
874 2001). For an ANDA, an authorized Bio-IND will be needed for the conduct of a BE  
875 study with a clinical endpoint.<sup>13</sup>

876

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

880

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

886

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

893

### 894 B. Clinical Study Batches

895

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<sup>13</sup> 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.

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896 We recommend that the batch used for the BA study be the same pivotal clinical trial batch used  
897 in the in vitro BA studies (Section V.A). Where BE studies are conducted for an NDA, the  
898 batches of test and reference products would be the same batches employed in the in vitro  
899 testing. Each of the T and R batches used to establish local delivery BE for an ANDA would be  
900 one of the three batches used for the in vitro BE studies. We recommend that the inactive  
901 ingredients of the placebo (P) product meet Q<sub>1</sub> and Q<sub>2</sub> recommendations relative to the R product  
902 (Section IV.B); the P container and closure would meet the recommendations of Section III.B.  
903

### **C. Clinical BE Study Design and Subject Inclusion Criteria**

904  
905  
906 The study design would be the traditional treatment study in which T and R are assessed for a  
907 two-week duration. The two-week duration, in addition to allowing a comparison of equivalent  
908 efficacy, will also allow for an assessment of safety and tolerability over a reasonable period of  
909 use. We recommend the study be conducted at the lowest labeled adult recommended dose in an  
910 attempt to optimize study sensitivity. Primed products according to labeling instructions prior to  
911 dosing. Ensure that priming occurs out of range of the patients, to avoid inhalation of drug fired  
912 to waste. Documentation would rely on the inclusion of a test product placebo (P) dosed at the  
913 same frequency and number of actuations per nostril as T and R.  
914

915 A study population consisting of seasonal allergic rhinitis (SAR) patients will allow  
916 documentation of BE, which may extend to all indications in product labeling for locally acting  
917 nasal corticosteroids. In addition to a history of SAR, we recommend patients have a positive  
918 test for relevant specific allergens (e.g., allergen skin test) and be experiencing a defined  
919 minimum level of symptom severity at the time of study enrollment. We discourage the  
920 inclusion of patients with other significant diseases including asthma, with the exception of mild  
921 intermittent asthma.  
922

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

---

<sup>14</sup> 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.

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937  
938 We recommend baseline scoring preferably consist of reflective AM and PM scoring on Days 5,  
939 6, and 7 of the placebo run-in period, and AM scoring (prior to drug dosing) on Day 1 of the 14  
940 day randomized treatment period, resulting in 7 total AM and PM ratings. Placebo responders  
941 would be identified based on the mean total nasal symptom score (TNSS) over the 7 total AM  
942 and PM ratings. The study protocol would state the minimum qualifying reflective TNSS for  
943 enrollment at screening, and the same minimum qualifying TNSS would be met based on the  
944 mean of the 7 total AM and PM ratings prior to each patient's participation in the randomized  
945 portion of the study. We recommend randomization occur after evaluation of the 7 total AM and  
946 PM ratings, and the randomized portion of the study can start in the morning of Day 1 after the  
947 AM baseline scoring.

948  
949 Symptom scores during the randomized treatment period would consist of the PM score on Day  
950 1, and the 26 AM and PM ratings on Days 2 to 14, resulting in 27 total ratings. We recommend  
951 the study be multicenter to avoid potential investigator bias. A double dummy design is not  
952 recommended for study blinding of aqueous nasal sprays due to a concern that the doubled fluid  
953 volume may result in washing the drug from its nasal deposition sites, potentially resulting in an  
954 altered safety and efficacy profile. However, study blinding is a critical consideration, and we  
955 recommend a description of how the T, R and P products are to be masked be carefully described  
956 in the study protocol.

957  
958 We recommend the *equivalence analysis* be conducted as an evaluable (per protocol) analysis  
959 rather than an intent-to-treat analysis. The evaluable population would consist of compliant  
960 patients who missed no more than a specified number of days of symptom scores, took no  
961 contraindicated concurrent medications, and had no protocol violations. The protocol would  
962 describe the specific criteria used to exclude randomized subjects, resulting in the reduced subset  
963 of subjects for analysis (*FDA Guideline for the Format and Content of the Clinical and*  
964 *Statistical Sections of an Application*, Section III.B.9). In addition to the equivalence analysis,  
965 an *efficacy analysis* would be conducted to demonstrate study sensitivity to the T and R  
966 products. The efficacy analysis would be conducted as an intent-to-treat analysis, and the intent-  
967 to-treat population would be clearly defined. Because specific study recommendations are not  
968 provided in this guidance, we recommend a protocol for a BE study with a clinical endpoint for a  
969 specific suspension drug product be submitted prior to the conduct of the study to the appropriate  
970 review division at FDA.

### 971 D. Clinical BE Study Endpoints

972  
973  
974 The endpoints for the *equivalence* and *efficacy analyses* should be patient self-rated *TNSS*.  
975 These most often include a composite score of runny nose, sneezing, nasal itching, and  
976 congestion, although addition of non-nasal symptoms to the composite score maybe pertinent for  
977 certain drug products.<sup>15</sup> *TNSS* is a categorical variable, classified into a number of discrete  
978 categories, as opposed to a continuous variable. A common allergic rhinitis rating system uses a

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<sup>15</sup> 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.

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979 four-point scale with signs and symptoms ordered in severity from 0 (no symptoms) to 3 (severe  
980 symptoms), as follows<sup>16</sup>:

- 981
- 982 • 0 = absent symptoms (no sign/symptom evident)
  - 983 • 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily  
984 tolerated)
  - 985 • 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but  
986 tolerable)
  - 987 • 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with  
988 activities of daily living and/or sleeping)
- 989

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

1000

1001 Safety assessments would be made before (at screening or baseline) and at end-of-treatment.  
1002 Adverse events would be reported daily.

1003

1004

## 1005 VII. PK STUDIES FOR SYSTEMIC EXPOSURE

### 1006 A. General Information

1007

1008

1009 The Agency recommends that plasma concentration-time profiles from BA and BE studies be  
1010 used to evaluate systemic exposure for suspension drug products that produce sufficiently high  
1011 concentrations of the moiety(ies) to be measured to allow reliable analytical measurement for an  
1012 adequate length of time after nasal administration. The recommended moiety(ies) to be  
1013 measured in the BA and BE studies are described elsewhere.<sup>17</sup>

1014

1015 Systemic drug levels that occur with locally acting drug products are generally in the low ng/mL  
1016 or low pg/mL range, depending on the drug and the drug product. Validated bioanalytical  
1017 methodology may be available for many of the nasal corticosteroid drugs. For these drugs, pilot  
1018 studies are not needed prior to conducting the full-scale PK study. If validated methodology is  
1019 unavailable, a small-scale, single-dose pilot study, or when appropriate, a small-scale, multiple-

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<sup>16</sup> 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.

<sup>17</sup> *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.

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1020 dose pilot study, may be helpful in assessing the proposed analytical methodology and  
1021 determining whether sufficiently high drug concentrations are attained. A PK study for systemic  
1022 exposure would be preferred to a PD or clinical study for systemic absorption (Section VIII). If a  
1023 sponsor has convincing data based on unsuccessful attempts to conduct the PK study in order for  
1024 a PD or clinical study for systemic absorption could be used. If systemic exposure were  
1025 established based on a PK study, a PD or clinical study for systemic absorption (Section VIII)  
1026 would not be requested.

1027

### **B. Study Batches**

1029

1030 The Agency recommends that the BA batch used for the PK systemic exposure study be a  
1031 pivotal clinical trial batch. Alternatively, a PK batch similar to the batch used in a pivotal  
1032 clinical trial can be used, in which case we recommend that any differences between the PK  
1033 batch and the pivotal clinical trial batch be discussed with the appropriate CDER review division  
1034 prior to the study. If the PK batch is not one of the three batches used for the in vitro BA studies  
1035 (Section V.A.1), make sure that in vitro BA data are provided for the PK batch using the same  
1036 protocols as for the three batches.

1037

1038 For a BE study, the batches of T and R would be the same batches used for the clinical study for  
1039 local delivery, and each of these batches would be one of the three batches used for the in vitro  
1040 BE studies.

1041

### **C. Study Design and Subject Inclusion Criteria**

1043

1044 The BA study to characterize systemic exposure can be one of the same PK studies conducted to  
1045 address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA  
1046 study can be conducted in healthy subjects or allergic rhinitis (AR) patients. Where appropriate,  
1047 the BA study would include a reference product that may be an oral or intravenous solution, oral  
1048 suspension, or other nasal product. Consultation with the appropriate review division is  
1049 recommended regarding whether a comparative or noncomparative BA study is appropriate.

1050

1051 For an NDA or an ANDA, the in vivo BE study would be conducted with a replicate or  
1052 nonreplicate randomized crossover design. For aqueous nasal sprays, the study would be  
1053 conducted at the maximum labeled adult dose to maximize plasma drug levels, while avoiding  
1054 the possibility of alteration of the drug deposition pattern within the nose at higher volumes  
1055 when dosed above label claim. The deposition pattern could be altered due to loss of drug from  
1056 the nasal cavity at these higher volumes, due either to drainage into the nasopharynx or  
1057 externally from the nasal cavity. Although alteration of the deposition pattern may be less likely  
1058 for a nasal aerosol when dosed above the maximum labeled number of actuations, the same study  
1059 design and dose as for aqueous nasal sprays would be followed. We recommend that subjects  
1060 for the study be healthy, with exclusions primarily for reasons of safety. The study protocol  
1061 would include information regarding time interval between doses to each nostril and subject  
1062 head position during dosing.

1063

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1064 This guidance recommends that the PK study generally be conducted as a single-dose study.  
1065 Such studies are more sensitive than multiple dose studies in assessing rate of release of the drug  
1066 substance from the drug product into the systemic circulation. In addition, the nasally dosed  
1067 corticosteroids tend to have biologic half-lives ranging from less than one hour up to about eight  
1068 hours. For these products, when dosed either once or twice daily, systemic accumulation is  
1069 expected to be relatively low, thus a multiple dose study may not result in a more reliable  
1070 analytical measurement. However, there may be drugs that, due to pharmacokinetic  
1071 characteristics, yield higher concentrations in a multiple-dose study, enabling the drug  
1072 moiety(ies) of interest to be measured more reliably than in a single-dose study. For these drugs,  
1073 a multiple-dose PK study would be preferred to a single-dose study.

### D. Study Measures

1074  
1075  
1076 The following BA and BE measures are considered pivotal<sup>17</sup> in a single-dose study:  $AUC_{0-t_{last}}$  (a  
1077 measure of total exposure);  $AUC_{0-4}$  (a measure of total exposure); and  $C_{max}$  (peak exposure). If  
1078  $AUC_{0-4}$  cannot be determined reliably due to inability to estimate  $k_{el}$  accurately, total exposure  
1079 would be based only on  $AUC_{0-t_{last}}$ . The following BA and BE measurements and plasma  
1080 concentrations provide supportive PK characterization: plasma concentrations at each sampling  
1081 time;  $T_{max}$ ; and  $k_{el}$ . The following BA and BE measurements are considered-pivotal for a  
1082 multiple-dose study:  $AUC_{0-J}$  (total exposure), where J is the dosing interval; and  $C_{max}$  (peak  
1083 exposure).  $T_{max}$  data should also be provided as supportive characterization.

1084  
1085  
1086 Statistical analysis information is provided in Appendix G.

## VIII. PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION

### A. General Information

1087  
1088  
1089  
1090  
1091  
1092 As stated in Section VI.A, at present only certain corticosteroids are formulated as suspension  
1093 products and require product quality in vivo studies. For those suspension drug products for  
1094 which the moiety(ies) to be measured in the blood or plasma (Section VII) are too low to allow  
1095 reliable analytical measurement for an adequate length of time, PD or clinical endpoint studies  
1096 serve as measures of systemic absorption (Section II.A.2). However, ***PK studies as measures of***  
1097 ***systemic exposure are preferred if at all possible***. As stated in Section VII, if a sponsor has  
1098 convincing data based on unsuccessful attempts to conduct the PK study a PD or clinical study  
1099 would be used in lieu of the PK study. The BA study to characterize systemic absorption may be  
1100 one of the same clinical studies conducted to establish the safety of the drug product. The study  
1101 would be conducted under an authorized IND in support of a forthcoming NDA (21 CFR  
1102 314.126).

1103  
1104  
1105 If a PD or clinical study is to be conducted (see previous paragraph), the recommended systemic  
1106 absorption BE study design for nasal corticosteroids would be assessment of the HPA axis. The  
1107 study would be conducted at the maximum labeled adult dose of the nasal aerosol or nasal spray  
1108 to maximize study sensitivity. However, the study design would be based on an understanding

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1109 that the maximum labeled dose over a 6-week period (Section VIII.C) may not result in  
1110 detectable adrenal suppression by T and R because this dose may be at or near the bottom of the  
1111 adrenal suppression dose-response curve. In addition to a test product placebo (P), we  
1112 recommend an active control such as prednisone be included to ensure that the study is  
1113 sufficiently sensitive to detect a drug effect (sensitivity analysis). Ensure that the active control  
1114 dose is sufficiently large and the duration sufficiently long to produce a statistically significant  
1115 response relative to placebo, with a duration sufficiently short to minimize undue exposure or  
1116 risk to subjects. Determination of the optimum active control dose and dosing regimen may call  
1117 for a pilot study by the sponsor. The pilot study may determine that an initial phase of the  
1118 6-week study period may use a matching active control placebo, with active control given over  
1119 the remainder of the study period, in an effort to reduce patient exposure to the active control.  
1120 The pilot study can also provide an estimate of the number of subjects to be included in the  
1121 pivotal study to yield a statistically significant difference in the HPA axis endpoint between the  
1122 active control and the test product placebo (i.e., the aerosol or spray placebo). It may also allow  
1123 estimation of the number of subjects to be included to characterize any HPA axis effects or lack  
1124 thereof and to allow conclusions about any relative effects of T versus P and R versus P  
1125 (“relative assessment of the HPA axis”; Appendix G.B). Conduct of the study in allergic rhinitis  
1126 (AR) patients will allow an efficacy assessment to evaluate compliance with the study protocol  
1127 (efficacy analysis). Therefore, AR patients, rather than healthy, non-allergic patients are  
1128 recommended as the study population. We also recommend that other measures of compliance  
1129 be instituted, including before and after weighing of the aerosol or spray container and diary  
1130 entry of drug use.

1131  
1132 Because this section does not provide specific recommendations, we recommend sponsors  
1133 submit prior to the conduct of the study a protocol for a BE study with a PD or clinical endpoint  
1134 for a specific drug product to the appropriate review division at FDA. For an NDA, the same  
1135 adequate and well-controlled clinical trials in humans conducted under an authorized IND, used  
1136 to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21  
1137 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR  
1138 320.24). For an ANDA, if the maximum single or total daily dose of the active control in the  
1139 pilot or full-scale study exceeds that specified in the labeling of the selected active control drug  
1140 product, an authorized Bio-IND will be needed.<sup>13</sup>

### **B. Clinical Study Batches**

1141  
1142  
1143  
1144 The Agency recommends the BA batch used for the study be a pivotal clinical trial batch used in  
1145 the in vitro BA studies (Section V.A). For BE studies for an NDA, the batches of T and R would  
1146 be batches used in in vitro testing. For an ANDA, the batches of T and R used for the systemic  
1147 absorption study would be the same batches used for the clinical study for local delivery. Each  
1148 of these batches would be one of the three batches used for the in vitro BE studies. Formulation  
1149 and device recommendations for the P are described in Section VI.B. An active control such as  
1150 prednisone is recommended. For blinding, matching active control placebo (identical in  
1151 appearance to the active control) is also recommended.

1152

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### 1153 **C. Clinical BE Study Designs and Subject Inclusion Criteria**

1154  
1155 We recommend the study be conducted as a placebo and active-controlled, randomized, double-  
1156 blind, parallel design comparing T and R for a 6-week duration. The study would not be  
1157 conducted as a subset of the 2-week local delivery rhinitis study (Section VI). Subjects would be  
1158 patients with a history of AR. The *relative assessment of HPA axis suppression* would be  
1159 conducted as an evaluable (per protocol) analysis. The sensitivity analysis and efficacy analysis  
1160 would be conducted as intent-to-treat analyses. The protocol would specify whether placebo  
1161 responders will or will not be excluded from the analysis. We recommend that subjects be  
1162 domiciled within the clinical study center during the days of HPA axis assessment. Domiciling  
1163 the subjects during the 24-hour urine or plasma collection periods can help to conduct the study-  
1164 related procedures reliably and completely. T and R would be dosed at the maximum labeled  
1165 adult dose. P would be dosed at the same frequency and number of actuations per nostril as T  
1166 and R. As stated above, the study would include an active control such as prednisone. Four  
1167 study arms would be included: T, R, P, and the active control. The randomized portion of the  
1168 study would be conducted according to a double-blinding design (i.e., all subjects would receive  
1169 both the active control (either the active control itself or a matching placebo of the active  
1170 control) and a spray or aerosol (either active or placebo)). The four treatment groups would be T  
1171 plus matching active control placebo, R plus matching active control placebo, P plus matching  
1172 active control placebo, and P plus active control. The matching active control placebo would be  
1173 dosed on days when the active control is not taken, including the placebo run-in period. We  
1174 recommend the number of centers conducting the HPA assessment be kept to a minimum to  
1175 avoid center-to-center variability. A double-dummy design is not recommended for aqueous  
1176 nasal sprays, as explained in Section VI.C. However, study blinding is a critical consideration,  
1177 and we recommend a description of how the T, R and P products are to be masked be carefully  
1178 described in the study protocol.<sup>18</sup>

1179  
1180 The expected effect for the active control would be far larger than that for the T and R products.  
1181 The sample size of the active control arm group may therefore be smaller in size than for the  
1182 other study arms. We recommend the sample size for the T and R study arms be sufficient to  
1183 characterize any HPA axis effects or lack thereof to allow conclusions about any relative effects  
1184 of T versus P and R versus P, as stated in Section VIII.A.

1185  
1186 We recommend timed urine or plasma samples for determination of 24-hour urinary free cortisol  
1187 (UFC) or 24-hour plasma cortisol levels, respectively, be collected. Collections would be made  
1188 prior to dosing (baseline) and during the last 24 hours of the 42 days of dosing (i.e., over the day  
1189 41 – 42 period) while the drug is being actively dosed.

### 1190 **D. Clinical BE Study Endpoints for Corticosteroids**

1191  
1192  
1193 Whether the drug is labeled for once or twice daily dosing, the endpoint can be either 24-hour  
1194 urinary free cortisol (UFC), based on a full 24-hour urine collection, or plasma cortisol levels

---

<sup>18</sup> 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.



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1195 collected every 4 hours over a 24-hour period, with exclusion of the middle of the night sample.  
1196 For the UFC endpoint, urinary creatinine would also be measured to confirm completeness of the  
1197 24-hour collection. The UFC value would not be corrected for creatinine. We recommend for  
1198 the plasma cortisol endpoint, both AUC(0-24) and the trough (maximum effect) concentration  
1199 during the dosing interval should be determined. The sensitivity analysis endpoint would be  
1200 baseline-adjusted prior to analysis. Raw data would be provided for the relative assessment of  
1201 HPA axis suppression. Efficacy analysis TNSS data would be expressed as change from  
1202 baseline.

1203

1204 Statistical approaches for each of the analyses are provided in Appendix G.B.

1205

1206

### **IX. NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING**

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1208  
1209 Reserve samples must be retained for BA and BE studies (21 CFR 320.38 and 320.63) conducted  
1210 in vivo or in vitro. The regulations state that each reserve sample must consist of a sufficient  
1211 quantity of samples to permit FDA to perform five times all of the release tests required in the  
1212 application or supplemental application. Dose content uniformity or spray content uniformity  
1213 release tests alone usually require 30 units (canisters or bottles) per batch. Performance of other  
1214 release tests requires additional units. The number of reserve sample units required for three  
1215 batches of T and R could exceed 1000 units (up to 250 units for each batch of T and R) based on  
1216 the *five-times-quantity* requirement.

1217

1218 The Agency has determined that in lieu of the *five-times-quantity* requirement, the quantity of  
1219 inhalant (nasal aerosol or nasal spray) test article (T) and reference standard (R) retained for  
1220 testing and analyses be at least 50 units for each batch.<sup>19</sup> For NDAs, three batches are needed for  
1221 BA studies. Thus, we recommend at least 50 units from each of the three batches of nasal spray  
1222 or nasal aerosol be retained. However, where the reference product is another nasal aerosol or  
1223 nasal spray, at least 50 units of that batch would also be retained. For ANDAs, at least 50 units  
1224 of each of three batches would be retained for each of T and R used in in vivo or in vitro BE  
1225 studies. For NDAs and ANDAs, if the in vivo or in vitro studies include placebo aerosols or  
1226 sprays, at least 50 units of each placebo batch would also be retained. These recommendations  
1227 apply only to nasal aerosols and nasal sprays for local action covered in this guidance and which  
1228 are marketed as multiple dose products, typically labeled to deliver 30 or more actuations per  
1229 canister or bottle. The number of reserves for nasal aerosols and nasal sprays delivering less  
1230 than 30 actuations per canister or bottle is not addressed in this guidance. Additional  
1231 information regarding retention of BA and BE testing samples is pending.<sup>20</sup>

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<sup>19</sup> Quantity of Reserve Samples, Preamble to final rule, Retention of Bioavailability and Bioequivalence Testing Samples, 58 FR 25918-26, 1993, IIC21.

<sup>20</sup> 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.

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### 1234 X. MULTIPLE STRENGTHS

1235  
1236 A small number of nasal sprays for local action are available in two strengths. Current examples  
1237 are (1) ipratropium bromide nasal spray, a solution formulation, and (2) beclomethasone  
1238 dipropionate nasal spray, a suspension formulation. Lower strengths of a product ordinarily  
1239 would achieve the lower dose per actuation using a lower concentration formulation, without  
1240 changing the actuator and metering valve or pump (other than diptube due to different volumes  
1241 of product or other factors) used in the higher strength product. The following sections describe  
1242 recommended BA and BE studies for low strengths of nasal sprays for which BA or BE for the  
1243 higher strengths has previously been established. Recommendations are also provided for cases  
1244 in which BA or BE is initially established on the low-strength product. No approved nasal  
1245 aerosols are available in multiple strengths, thus BA and BE recommendations are not  
1246 considered for these products.

#### 1247 1248 A. Solution Formulation Nasal Sprays

1249  
1250 We recommend the BA of lower or higher strength solution formulation nasal sprays be based on  
1251 conduct of all applicable in vitro tests described in Section V. These studies are generally  
1252 noncomparative in character. Documentation of BE between T and R products would follow the  
1253 recommendations described in Section III regarding formulation and container and closure  
1254 system. Abbreviated in vitro testing, as follows, is recommended to document BE of the low-  
1255 strength T product to the low-strength R product, provided BE of the high-strength product has  
1256 been documented.

1257

1258 In vitro test	High Strength	Low Strength
1260 Single Actuation Content		
1261 Through Container Life	B, E <sup>a</sup>	B, E
1262 Priming and Repriming	Yes	Yes
1263 Droplet Size Distribution		
1264 by Laser Diffraction	B, E	B
1265 Drug in Small Particles/Droplets		
1266 by Cascade Impactor	B	No
1267 Spray Pattern	B	B
1268 Plume Geometry	B	No

1269

1270 <sup>a</sup> Beginning (B), Middle (M), End (E)

1271  
1272 With the exception of the reduced testing, the Agency recommends the same protocols and  
1273 acceptance criteria used to establish BE of the high-strength products be used for the low  
1274 strength products. In vivo studies are not needed for documentation of BA or BE of solution  
1275 formulation nasal sprays. Initial documentation of BE of the low-strength product would be  
1276 based on all applicable in vitro tests described in Section V. For subsequent documentation of  
1277 BE for the high-strength product, all applicable in vitro tests described above for the high-  
1278 strength product would be conducted.

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### **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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### REFERENCES

- 1324  
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1328 Advisory Committee for Pharmaceutical Science Meeting, “Report from the Orally Inhaled and  
1329 Nasal Drug Products Subcommittee,” Rockville, MD, Transcript, July 19, 2001, pp. 24-  
1330 91.
- 1331 Borgstrom L, Asking L, Beckman O, Bondesson E, K@lJn A, Olsson B. Dose Variation , within  
1332 and between individuals, with different inhalation systems. *Respiratory Drug Delivery V*,  
1333 Interpharm Press, Buffalo Grove, IL, 1996, pp. 19-24.
- 1334 Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate:  
1335 absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral,  
1336 intranasal and inhaled administration in man. *Br J Clin Pharmacol* 2001;51:400-9.
- 1337 Kublic H., Vidgren MT. Nasal Delivery Systems and Their Effect on Deposition and Absorption.  
1338 *Advanced Drug Delivery Reviews* 1998;29:157-77.
- 1339 Meltzer EO, Jalowayski AA, Orgel HA, Harris AG. Subjective and objective assessments in  
1340 patients with seasonal allergic rhinitis: Effects of therapy with mometasone furoate nasal  
1341 spray. *J Allergy Clin Immunol* 1998;102:39-49.
- 1342 Newman S, Steed K, Hooper G, K@lJn A, Borgstrom L. Comparison of gamma scintigraphy and  
1343 a pharmacokinetic technique for assessing pulmonary deposition of terbutaline sulphate  
1344 delivered by pressurized metered dose inhaler. *Pharm Res* 1995;12:231-6.
- 1345 Suman JD, Laube BL, Lin T, Brouet G, Dalby R. Validity of in vitro tests on aqueous spray  
1346 pumps as surrogates for nasal deposition. *Pharm Res* 2002;19:1-6.
- 1347 Task Group on Lung Dynamics: Deposition and Retention Models for Internal Dosimetry of the  
1348 Human Respiratory Tract. *Health Phys*, 1966;12:173-207.
- 1349 Welch MJ, Bronsky EA, Grossman J, Shapiro GG, Tinkelman DG, Garcia JD, Gillen MS.  
1350 Clinical evaluation of triamcinolone acetonide nasal aerosol in children with perennial  
1351 allergic rhinitis. *Annals Allergy* 1991;67:493-8.
- 1352 Williams RL, Adams W, Chen M-L, Hare D, Hussain A, Lesko L, Patnaik R, Shah V, FDA  
1353 Biopharmaceutics Coordinating Committee. Where are we now and where do we go next  
1354 in terms of the scientific basis for regulation on bioavailability and bioequivalence?  
1355 *Europ J Drug Metab Pharmacokinet* 2000;25:7-12.



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

TEST <sup>1</sup>	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 <sub>10</sub> , D <sub>50</sub> , D <sub>90</sub> , span at 2 distances	D <sub>50</sub> , 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 <sub>max</sub> , ovality ratio at 2 distances	Qualitative – shape comparison Quantitative - Same as previous column	B	PBE for area and ovality ratio (automated analysis) or D <sub>max</sub> 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

1356 <sup>1</sup> Although alternate test methods may be appropriate for certain tests, if validated, we recommend sponsors planning to use such methods contact the appropriate reviewing  
1357 division prior to use.

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