
Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

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
March 2003

Guidance for Industry

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

Additional copies are available from:

*Division of Drug Information (HFD-240)
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane,
Rockville, MD 20857 (Tel) 301-827-4573
Internet at <http://www.fda.gov/cder/guidance/index.htm>*

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

TABLE OF CONTENTS

1
2
3 **I. INTRODUCTION..... 1**
4 **II. BACKGROUND 2**
5 **A. BA and BE Data 2**
6 1. *Local Delivery BA/BE Concepts..... 3*
7 2. *Systemic Exposure and Systemic Absorption BA/BE Concepts..... 4*
8 **B. CMC and In Vitro BA Tests (Noncomparative) Versus BE Tests (Comparative)..... 5**
9 **III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM 5**
10 **A. Formulation 5**
11 **B. Container and Closure System..... 5**
12 **IV. DOCUMENTATION OF BA AND BE 6**
13 **A. NDAs..... 6**
14 **B. ANDAs..... 6**
15 1. *Solution Formulations..... 7*
16 2. *Suspension Formulations with PK Systemic Exposure Data..... 7*
17 3. *Suspension Formulations without PK Systemic Exposure Data..... 7*
18 **C. Postapproval Change 8**
19 **V. IN VITRO STUDIES..... 8**
20 **A. Batches and Drug Product Sample Collection 8**
21 1. *NDAs 8*
22 2. *ANDAs..... 9*
23 **B. Tests and Metrics..... 9**
24 1. *Single Actuation Content (SAC) Through Container Life..... 11*
25 2. *Droplet Size Distribution by Laser Diffraction..... 12*
26 a. *Nasal sprays..... 12*
27 b. *Nasal aerosols..... 13*
28 3. *Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor... 14*
29 a. *Nasal sprays: Drug in Small Particles/Droplets 14*
30 b. *Nasal aerosols: Particle/Droplet Size Distribution..... 15*
31 4. *Drug Particle Size Distribution by Microscopy..... 15*
32 5. *Spray Pattern..... 16*
33 a. *For nonimpaction systems 17*
34 b. *For impaction systems 17*
35 c. *For both nonimpaction and impaction systems..... 17*
36 6. *Plume geometry..... 18*
37 7. *Priming and Repriming..... 19*
38 **VI. CLINICAL STUDIES FOR LOCAL DELIVERY..... 20**
39 **A. General Information 20**
40 1. *NDAs 20*
41 2. *ANDAs..... 21*

42 B. Clinical Study Batches..... 21

43 C. Clinical BE Study Design and Subject Inclusion Criteria..... 21

44 D. Clinical BE Study Endpoints..... 23

45 VII. PK STUDIES FOR SYSTEMIC EXPOSURE..... 24

46 A. General Information 24

47 B. Study Batches..... 24

48 C. Study Design and Subject Inclusion Criteria..... 25

49 D. Study Measures..... 25

50 VIII. PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION 26

51 A. General Information 26

52 B. Clinical Study Batches..... 27

53 C. Clinical BE Study Designs and Subject Inclusion Criteria..... 27

54 D. Clinical BE Study Endpoints for Corticosteroids 28

55 IX. NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING..... 28

56 X. MULTIPLE STRENGTHS..... 29

57 A. Solution Formulation Nasal Sprays 30

58 B. Suspension Formulation Nasal Sprays 30

59 XI. SMALLER CONTAINER SIZES 31

60 REFERENCES..... 32

61 TABLE 1 33

62

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

64

65 APPENDIX A: DECISION TREE FOR PRODUCT QUALITY STUDIES

66 APPENDIX B: STATISTICS FOR IN VITRO BA DATA

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

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

69 APPENDIX E: STATISTICS FOR IN VITRO PROFILE COMPARISONS

70 APPENDIX F: STATISTICS FOR ALLERGIC RHINITIS STUDIES

71 APPENDIX G: STATISTICS FOR SYSTEMIC EXPOSURE AND ABSORPTION

Guidance For Industry¹

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.

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 monograph² 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.

The first draft of this guidance was issued in June 1999 for comment. Because of changes made as a result of comments received to the docket, internal discussions, and deliberations of the Advisory Committee for Pharmaceutical Science, we have decided to issue the guidance once

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

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

again in draft. A series of attachments are being developed and will be posted with this draft guidance as stand alone documents on the Internet as soon as they have been completed.

II. BACKGROUND

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

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

Note: Detailed CMC information relevant to nasal aerosols and nasals sprays is presented in the final guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*.⁴ The document provides complementary information on the BA/BE testing methods recommended in this guidance.

A. BA and BE Data

Bioavailability is defined at 21 CFR 320.1 as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be

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

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

147 assessed by measurements intended to reflect the rate and extent to which the active ingredient or
148 active moiety becomes available at the site of action." *Bioequivalence* is defined as "the absence
149 of a significant difference in the rate and extent to which the active ingredient or active moiety in
150 pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug
151 action when administered at the same molar dose under similar conditions in an appropriately
152 designed study." BA and BE are closely related, and the same approach used to measure BA in
153 an NDA can generally be followed in establishing BE for an NDA or ANDA. Although BA may
154 be comparative, establishing BE specifically involves a comparison of the BA of one product
155 with the BA of another product. BE is usually established using (1) a criterion to allow the
156 comparison, based on means and/or variances for BA measures, (2) a confidence interval for the
157 criterion, and (3) a BE limit (goalpost) for the criterion.

158
159 BA and BE data must be provided in accordance with the regulations.⁵ BA and BE can be
160 established using in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in
161 vitro studies, or, in certain cases, using in vitro studies alone.⁶ BA and BE assessments for
162 locally acting nasal aerosols and sprays are complicated because delivery to the sites of action
163 does not occur primarily after systemic absorption. Droplets and/or drug particles are deposited
164 topically. The drug is then absorbed and becomes available at local sites of action. A drug
165 administered nasally and intended for local action has the potential to produce systemic activity,
166 although plasma levels do not in general reflect the amount of drug reaching nasal sites of action.
167 Systemic exposure following nasal administration can occur either from drug absorbed into the
168 systemic circulation from the nasal mucosa, or after ingestion and absorption from the
169 gastrointestinal tract (Daley-Yates et al., 2001). For these reasons, BA and BE studies generally
170 would consider both local delivery and systemic exposure or systemic absorption.

171 172 1. *Local Delivery BA/BE Concepts*

173
174 For local delivery, BA is a function of several factors, including release of the drug
175 substance from the drug product and availability to local sites of action. Release of the
176 drug from the drug product produces droplet or drug particle sizes and distribution
177 patterns within the nose that are dependent upon the drug substance, formulation, and
178 device characteristics. Availability to local sites of action is usually a function of droplet
179 or drug particle sizes and distribution patterns, as well as drug dissolution in the case of
180 suspension products, absorption across mucosal barriers to nasal receptors, and rate of
181 removal from the nose. From a product quality perspective, the critical issues are release
182 of drug substance from drug product and delivery to the mucosa. Other factors are of
183 lesser importance.
184

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

⁶ In addition to pharmacokinetic studies, in vivo studies that can be submitted in support of an ANDA include tests in humans in which an appropriate acute pharmacological effect is measured as a function of time and appropriately designed comparative clinical trials for demonstration of BE (Types of evidence to establish bioavailability or bioequivalence, 21 CFR 320.24).

185 A critical question in assessing product quality BA and BE is the extent to which one can
186 rely on in vitro methods alone, or upon in vitro methods plus clinical endpoints, to
187 measure (benchmark) BA and/or establish BE. In vitro methods are less variable
188 (Newman et al., 1995; Borgstrom et al., 1996; Suman et al., 2002), easier to control, and
189 more likely to detect differences between products if they exist, but the clinical relevance
190 of these tests, or the magnitude of the differences in the tests, can not always be clearly
191 established. Clinical endpoints may be highly variable (Welch et al., 1991; Meltzer et al.,
192 1998) and relatively insensitive to dose differences over an eightfold or higher dose range
193 (Advisory Committee for Pharmaceutical Science, 2001), thus insensitive in detecting
194 potential differences between products. However, clinical studies can unequivocally
195 establish effectiveness of the drug product.

196
197 In this guidance, the recommended approach for solution formulations of locally acting
198 nasal drug products, both aerosols and sprays, is to rely on in vitro methods to assess BA.
199 To establish BE, the recommended approach relies on (1) qualitative and quantitative
200 sameness of formulation of test and reference products, (2) comparability in container and
201 closure systems, and (3) in vitro methods that demonstrate equivalent performance. This
202 approach is based on the premise that in vitro studies would be more sensitive indicators
203 of drug delivery to nasal sites of action than would be clinical studies. For solution
204 formulations, see Section IV.B.1.

205
206 The recommended approach for establishing BA and BE of suspension formulations of
207 locally acting nasal drug products, both aerosols and sprays, is to conduct in vivo studies
208 in addition to in vitro studies. As with the solution formulation aerosols and sprays, to
209 establish BE, the approach also relies on qualitative and quantitative sameness of
210 formulation of test and reference products and comparability in container and closure
211 systems. We recommend that in vitro studies be coupled with a clinical study for BA, or
212 a BE study, with a clinical endpoint (Section VI), to determine the delivery of drug
213 substance to nasal sites of action. In vivo studies are recommended because of an
214 inability at the present time to adequately characterize drug particle size distribution
215 (PSD) in aerosols and sprays (Sections V.B.3, 4). Drug PSD in suspension formulations
216 has the potential to influence the rate and extent of drug availability to nasal sites of
217 action and to the systemic circulation.

218 219 2. *Systemic Exposure and Systemic Absorption BA/BE Concepts*

220
221 Locally acting drugs are intended to produce their effects upon delivery to nasal sites of
222 action without relying on systemic absorption. Although systemic absorption may
223 contribute to clinical efficacy for certain corticosteroids and antihistamines, the
224 consequences of systemic absorption (e.g., hypothalamic-pituitary-adrenal (HPA) axis
225 suppression by corticosteroids) are generally undesirable. In the absence of validated in
226 vitro methodology for characterizing drug PSD for suspension products and when
227 measurable plasma levels can be obtained, this guidance recommends PK studies to
228 measure systemic exposure BA or to establish systemic exposure BE (see Section VII).
229 For suspension products that do not produce sufficient plasma concentrations to allow

230 assessment of systemic exposure, clinical studies or BE studies with a pharmacodynamic
231 or clinical endpoint are recommended to measure systemic absorption BA and establish
232 systemic absorption BE, respectively (Section VIII). For a schematic representation of
233 recommended studies, see Appendix A: Decision Tree.

234
235 **B. CMC and In Vitro BA Tests (Noncomparative) Versus BE Tests**
236 **(Comparative)**
237

238 Generally, CMC tests help characterize the identity, strength, quality, purity, and potency of the
239 drug product and assist in setting specifications (tests, methods, acceptance criteria) to allow
240 batch release. These tests have a different purpose than do BA/BE tests, which focus on the
241 release of the drug substance from the drug product. Some of the in vitro BA/BE tests described
242 in this guidance may be the same as CMC tests for characterization and/or batch release. CMC
243 and in vitro BA tests have acceptance criteria. In vitro BE tests have BE limits. A specification
244 (test, method, acceptance criterion) for a CMC test for batch release or an in vitro BA test is
245 usually based on general or specific manufacturing experience. For example, a CMC test such as
246 dose content uniformity has acceptance criteria based on repeated manufacturing of batches. In
247 contrast, BE tests have limits that are not usually based on manufacturing experience, but are part
248 of equivalence comparisons between test and reference products. BE limits may be based on a
249 priori judgments and may be scaled to the variability of the reference product (see Appendices C,
250 E). When conducted premarket for an NDA, some of the in vitro BA tests described in this
251 guidance can be noncomparative and serve primarily to document (benchmark) the product
252 quality BA of a pioneer product.
253

254
255 **III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM**
256

257 **A. Formulation**
258

259 Particle size, morphic form, and state of solvation of an active ingredient have the potential to
260 affect the BA of a drug product as a result of different solubilities and/or rates of dissolution. We
261 recommend for an ANDA of a suspension formulation, data demonstrating comparable PSD and
262 morphic form of the drug particles, size and number of drug aggregates in the dosage form, and
263 hydrous or solvate form of the active drug in the dosage form to the reference listed drug, be
264 provided, where possible. Where impossible, the rationale for not providing this full set of
265 comparative data is requested. For suspension formulations marketed in more than one strength,
266 we recommend that the drug substance in each strength product be micronized under identical
267 parameters, and the PSD of the resultant bulk drug used in each product strength be identical.
268

269 **B. Container and Closure System**
270

271 Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated
272 accessories, and protective packaging, which together constitute the drug product. Similarly,
273 nasal sprays usually consist of the formulation, container, pump, actuator, protection cap, and
274 protective packaging, which together constitute the drug product.

275
276 For nasal aerosols and nasal sprays approved under an ANDA, we recommend BE be
277 documented on the basis of validated in vitro and vivo tests, or, in the case of solutions, validated
278 in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is
279 greatest when the test product uses the same brand and model of devices (particularly the
280 metering valve or pump and the actuator) as used in the reference product. If this is infeasible,
281 we recommend that valve, pump, and actuator designs be as close as possible in all critical
282 dimensions to those of the reference product. We recommend that metering chamber volumes
283 and actuator orifice diameters be the same. For a nasal spray, spray characteristics can be
284 affected by features of the pump design, including the precompression mechanism, actuator
285 design, including specific geometry of the orifice (Kubic and Vidgren 1998), and the design of
286 the swirl chamber. The external dimensions of the test actuator are expected to ensure
287 comparable depth of nasal insertion to the reference actuator. A test product is expected to attain
288 prime within the labeled number of actuations for the reference product. We recommend you
289 consider the volume of components of the device that must be filled to deliver an actuation,
290 including the internal diameter and length of the diptube because this volume can influence the
291 number of actuations required to prime a spray pump.
292
293

294 IV. DOCUMENTATION OF BA AND BE

295 A. NDAs

296
297 For product quality, we recommend that in vitro BA studies be provided in NDAs for solution
298 and suspension products, and in vivo BA studies be provided for suspension products. These
299 data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the
300 in vivo performance of the product. Where the formulation and/or method of manufacture of the
301 pivotal clinical trial product changes in terms of physicochemical characteristics of the drug
302 substance, the excipients, or the device characteristics, BE data using in vitro tests (for solution
303 and suspension products) and in vivo tests (for suspension products) may be useful in certain
304 circumstances to ensure that the to-be-marketed product (T) is comparable to very similar clinical
305 trial batches and/or to batches used for stability testing (R) (Section V.A.1). We recommend
306 sponsors discuss the usefulness of these BE approaches with the appropriate CDER review staff.
307
308

309 B. ANDAs

310
311 For product equivalency, we recommend that the drug concentration in the test and reference
312 product formulations not differ by more than ± 5 percent. In addition, we recommend that the
313 inactive ingredients in the test product formulation be qualitatively (Q_1)⁷ the same and
314 quantitatively (Q_2) essentially the same as the inactive ingredients in the formulation of the
315 reference listed drug, and the container and closure recommendations of Section III be followed.
316 Quantitatively *essentially the same* has been determined by CDER to mean that the concentration
317 or amount of the inactive ingredient(s) in the test product would not differ by more than ± 5

⁷ See 21 CFR 314.94(a)(9)(v).

318 percent of the concentration or amount in the reference listed drug. We recommend a side-by-
319 side Q₁ and Q₂ comparison of the compositions of the test and reference listed drug formulations
320 be provided. Please also provide a side-by-side comparison of the components of the container
321 and closure system, listing brand and model, dimensions of critical components (Section IIIB),
322 and engineering drawings if possible.

323
324 1. *Solution Formulations*

325
326 We believe in vitro tests alone can be relied on to document BE for nasal solution
327 formulation products intended for local action. This approach is based on an
328 understanding that for solution products, equivalent in vitro performance and adherence
329 to Q₁ and Q₂ recommendations and to container and closure recommendations will ensure
330 comparable delivery to the nasal mucosa and to the respiratory and gastrointestinal tracts.
331 Suggested methodology and validation approaches for the recommended tests are
332 provided in Section V. Suggested statistical methods to allow comparisons will be
333 discussed in the appendices to this document. When in vitro data fail to meet acceptance
334 criteria, the applicant is encouraged to modify the test product to attain equivalent in vitro
335 performance. Because of insensitivity to potential differences between T and R, in vivo
336 studies would not be sufficient in the face of failed in vitro studies.

337
338 2. *Suspension Formulations with PK Systemic Exposure Data*

339
340 To document BE for suspension formulation products intended for local action, we
341 recommend both in vitro and in vivo data be used. In vivo studies would include both a
342 BE study with a clinical endpoint (local delivery) and a pharmacokinetic study (systemic
343 exposure). This approach is only applicable for those suspension formulation products
344 that produce sufficiently high plasma concentrations of the moiety(ies) to be measured to
345 allow reliable analytical measurement for an adequate length of time after nasal
346 administration. Suggested methodology and validation approaches for the recommended
347 tests are provided for in vitro studies in Section V, and for in vivo studies in Sections VI
348 and VII. As with solutions, in vivo studies would not be sufficient in the face of failed in
349 vitro studies (i.e., in vitro BE studies that fail to meet the statistical tests) even though the
350 BE study with a clinical endpoint or the PK study meets the statistical test. Conversely,
351 ANDAs with acceptable in vitro data, but with in vivo data that fail to meet the statistical
352 tests, would be insufficient to establish BE.

353
354 3. *Suspension Formulations without PK Systemic Exposure Data*

355
356 For those products intended for local action that produce blood or plasma levels that are
357 too low for adequate measurement, given current assay constraints, a BE study with a
358 clinical endpoint to establish equivalent local delivery to nasal sites (Section VI) and a
359 study with a pharmacodynamic or clinical endpoint to establish equivalent systemic
360 absorption (Section VIII) are recommended. In vivo studies that meet the statistical test
361 would not be sufficient in the face of in vitro studies that fail to document BE. As for

362 suspensions with PK data, ANDAs with acceptable in vitro data, but with in vivo data
363 that fail to meet the statistical tests, would be insufficient to establish BE.

364
365 **C. Postapproval Change**
366

367 This document does not cover postapproval changes. Sponsors planning such changes can
368 consult the guidance for industry *Changes to an Approved NDA or ANDA* and contact the
369 appropriate review division prior to instituting the change.
370

371
372 **V. IN VITRO STUDIES**
373

374 **A. Batches and Drug Product Sample Collection**
375

376 **1. NDAs**
377

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

390
391 The BA batches to be studied would be equivalent to the to-be-marketed product and
392 representative of production scale. The manufacturing process for these batches would
393 simulate that of large-scale production batches for marketing (additional information on
394 large-scale batches is provided in the International Conference on Harmonisation (ICH)
395 guidance for industry *Q1A Stability Testing of New Drug Substances and Products*,
396 Section II.B.3). Complete batch records, including batch numbers of device components
397 used in the batches, would accompany the BA submission.
398

399 In vitro BA studies are intended to characterize the means and variances of measures of
400 interest for canisters (nasal aerosols) or bottles (nasal sprays) within a batch and between
401 batches, where applicable. However, under 21 CFR 320.1 and 320.21, the studies can be
402 noncomparative to other formulations or products. The in vitro tests and metrics are
403 described in Section V.B of this guidance. The recommended number of canisters or
404 bottles of each batch to be used in the above studies, and recommendations for statistical
405 analyses, are described in Appendix B.
406

2. *ANDAs*

In vitro BE studies for nasal aerosols and sprays would generally be performed on samples from each of three or more batches of the test product and three or more batches of the reference listed drug. Test product samples would be from the primary stability batches used to establish the expiration dating period. When three batches are studied, we recommend the test product be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. For nasal sprays formulated as solutions, in vitro BE tests can alternatively be performed on three sublots of product prepared from one batch of the solution.⁸

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

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

B. Tests and Metrics

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

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

⁸ 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.

446 These tests are relevant to all nasal aerosols and nasal sprays, whether formulated as solution or
447 suspension products, with the exception of drug particle size distribution by microscopy, which
448 applies only to suspension products. The in vitro tests are summarized in Table 1.
449

450 We recommend you validate all in vitro tests for accuracy and precision prior to the study. For
451 applicable studies, instrument settings established during prestudy validation would be used in
452 the study. For comparative studies, use of the same settings will ensure that T and R are studied
453 under the same instrumental conditions. The in vitro tests would be conducted on canisters or
454 bottles selected in a random manner from the test batch, including units from the beginning,
455 middle, and end of the production run. Actuation should be conducted in a manner that removes
456 potential operator bias, either by employing automatic actuation, or by employing blinded
457 procedures when manual actuation is used. However, we recommend automated actuation
458 systems for all comparative in vitro BE tests. These systems are expected to decrease variability
459 in drug delivery due to operator factors, thereby increasing the sensitivity for detecting potential
460 differences between products in the above tests.⁹ In addition, it is important that the analyst
461 performing the postactuation evaluations of the collected data be blinded to the identity of the
462 samples. We recommend analytical methods used for analysis of samples from the in vitro tests
463 be validated.¹⁰ Unexpected results and deviations from protocol or SOPs, with justification for
464 deviations, would be reported. Examples include, but are not limited to, canisters or bottles
465 replaced during in vitro analyses, failure to use the specific actuations required by the protocol,
466 and experiments rejected due to assignable causes (e.g., instrument failure, sample collection, or
467 processing errors). The original and reanalyzed data, with the reason for reanalysis, would be
468 tabulated in the study report. The validation reports for the in vitro tests and analytical methods,
469 the randomization procedure, and all test methods or SOPs for each test would accompany the
470 data in the submission. When appropriate, we recommend the test method or SOP include a
471 standardized shaking procedure prior to testing, following labeled instructions, if any.
472

473 In addition to submission of all raw data, the agency would like to see supporting documentation
474 for the following tests: Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume
475 Geometry. Documentation includes instrument output reports and photographic or graphic
476 material as applicable. We recommend that documents be clearly labeled to indicate the product
477 (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as
478 appropriate. For Droplet Size Distribution by Laser Diffraction, profiles of droplet size and
479 obscuration or percent transmission over the complete life of the single sprays would be
480 submitted. For Spray Pattern and Plume Geometry, we recommend each image display the
481 relevant BA/BE measures described in this guidance. Supporting documentation for Droplet

⁹ 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.

¹⁰ A draft guidance for industry entitled *Analytical Procedures and Methods Validation* was issued in August 2000.

482 Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry would include
483 representative copies, preferably electronic, of ≥ 20 percent of the total observations. For Spray
484 Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic
485 images rather than paper copies of ≥ 20 percent of the total observations would be submitted, as
486 electronic files are definitive. For automated image analysis of Spray Pattern and Plume
487 Geometry, in addition to the electronic images, we recommend paper copies of a few screen
488 images be submitted as reference samples.

489

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

491

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

498

499 The dosage unit sampling apparatus for collection of an emitted dose from an aerosol is
500 described in *U.S. Pharmacopeia* (USP) 25, <601>. We recommend a suitable apparatus
501 be used for collecting an emitted dose from a nasal spray. For both solution and
502 suspension formulations of nasal aerosols and nasal sprays, the mass of drug per actuation
503 would be based on a stability-indicating chemical assay unless use of a nonstability-
504 indicating method is justified. Because the data at beginning (B) lifestage will also be
505 used for confirmation of priming (Section V.B.7), SAC through container life would be
506 based on *single actuation data per determination*. For BA and BE submissions, the tests
507 would determine delivered (emitted or ex-actuator) drug mass from primed units at the
508 beginning of unit life, at the middle of unit life, and at the end of unit life¹¹ for nasal
509 aerosols, and at beginning and end of unit life for nasal sprays. The delivered mass of
510 drug substance would be expressed both as the actual amount and as a percentage of label
511 claim. We recommend that mean and variability in SAC through container life be
512 determined based on within and between unit (container) data and between batch (or
513 subplot) data. For BE data, equivalence of T and R data would be based on the statistical
514 methodology of Appendix C.

515

516 To use the SAC through container life data for priming studies, we recommend aerosols
517 and sprays be unprimed prior to the conduct of the tests. Therefore, for aerosols, the test
518 would be performed at such time that the product meets two conditions: (1) after the
519 lagging period and (2) not less than one month after the last actuation conducted as part
520 of batch release testing. During the time period between batch release and SAC through
521 container life testing, the aerosol product would not be actuated. Also, during this one

¹¹ 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).

522 month period, both T and R aerosols would be stored in the valve upright position, unless
523 labeling indicates that the product be stored in the valve down position, in which case the
524 test would be conducted on products stored in the valve down position. For sprays, the
525 SAC through container life test would be conducted not less than one month after
526 completion of batch release testing. During the time period between batch release and
527 SAC testing, the product would not be actuated.

528
529 2. *Droplet Size Distribution by Laser Diffraction*
530

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

533
534 a. Nasal sprays
535

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

538
539 Laser diffraction is a nonaerodynamic optical method of droplet sizing that
540 measures the geometric size of droplets in flight. Modern laser diffraction
541 instrumentation can provide plots of obscuration (optical concentration) or percent
542 transmission (%T) and droplet size distribution (D_{10} , D_{50} , D_{90}) over the entire life
543 of a single spray. Span $((D_{90} - D_{10})/D_{50})$ can be computed from these data. These
544 profile data indicate that each plume can be characterized by three phases:
545 formation, fully developed, and dissipation. For nasal sprays, the general profile
546 for obscuration or percent T versus time can be characterized by a rapid increase
547 in obscuration, or decrease in percent T, early in the life of the spray (formation
548 phase), followed by attainment of a plateau (fully developed phase), then a rapid
549 decrease in obscuration, or increase in percent T, late in the life of the spray
550 (dissipation phase). Changes in droplet size occur coincident with the changes in
551 obscuration or percent T, with droplet sizes attaining plateau values within the
552 same approximate time period as the plateau in obscuration or percent T. Profiles
553 of the droplet size and obscuration or percent T over the complete life of the
554 single sprays are recommended to be determined at each of two distances (see
555 below) to establish the fully developed phase during which data would be
556 collected. Droplet size distribution and span during the fully developed phase are
557 requested. The sponsor's protocol or SOP would state the criterion selecting the
558 region of the plateau at which droplet size data will be determined (e.g., the
559 average of all scans over the entire plateau, the data of a single scan (sweep) only
560 at the maximum obscuration (or minimum percent T), or the average of a
561 specified range of scans around this obscuration or percent T). This criterion
562 would be established prior to the study for each of the two distances and
563 implemented consistently during the study.

564
565 We would also like to see instrument setup and operation conditions. We
566 recommend the instrument be operated within the manufacturer's recommended

567 obscuration or percent T range, which would be stated in the submission, to avoid
568 or minimize multiple scattering (due to high droplet concentration). Avoidance of
569 multiple scattering is preferred to use of a correction algorithm that compensates
570 for this effect.

571
572 Single spray droplet size distribution and span would be reported based on volume
573 (mass) rather than count (number of droplets). We would like to request data be
574 provided for nasal sprays at:

- 575
- 576 • Fully developed phase only
- 577 • B and E lifestages
- 578 • Two distances from the actuator orifice. For increased ability to detect
579 potential differences between products, it is recommended that the studies be
580 performed within a range of 2 to 7 cm from the orifice, with the two distances
581 separated by 3 cm or more.

582
583 b. Nasal aerosols

584
585 Droplet size distribution can be determined using laser diffraction or appropriately
586 validated alternate methodology.

587
588 We would like to see instrument setup and operation conditions. We recommend
589 the instrument be operated within the manufacturer's recommended obscuration
590 or percent T range, which would be stated in the submission, to avoid or
591 minimize multiple scattering (due to high droplet concentration). Avoidance of
592 multiple scattering is preferred to use of a correction algorithm that compensates
593 for this effect.

594
595 Beam steering resulting from refractive index effects due to evaporation of
596 propellant is an additional concern for nasal aerosols. Droplet size distribution
597 would be characterized at distances from the actuator that eliminate or minimize
598 beam steering, if possible. If a correction algorithm is used, we recommend an
599 explanation of the corrections be provided.

600
601 We ask that single-spray droplet size distribution and span be reported based on
602 volume (mass) rather than count (number of droplets). Data would be provided
603 for nasal aerosols at:

- 604
- 605 • Fully developed phase only
- 606 • B and E lifestages
- 607 • Two distances from the actuator orifice

608
609 For both nasal sprays and nasal aerosols, mean D_{10} , D_{50} , D_{90} values for a given bottle or
610 canister can be computed from the mean of up to three consecutive sprays from that unit

611 at each lifestage. However, to assess precision, the data of each spray would also be
612 reported.

613
614 3. *Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by*
615 *Cascade Impactor*

616
617 Sizing of droplets or particles by multistage cascade impactor (CI) measures
618 aerodynamic diameter based on inertial impaction, an important factor in the
619 deposition of drug in the nasal passages. Analytical data should be based on a
620 validated chemical assay.¹⁰ We recommend that analytical runs include at least
621 three or more concentrations of quality control samples that represent the entire
622 range of the standard curve or the expected concentration range of samples from
623 the various stages of the CI. An analytical validation report would accompany the
624 CI data report. The SOP or validation report would indicate the minimum
625 quantifiable mass of drug deposited on each location reported.

626
627 a. Nasal sprays: Drug in Small Particles/Droplets

628
629 For nasal sprays, the majority of the emitted dose is deposited prior to or on the
630 first stage of the CI test. Small droplets, for this test and dosage form defined as
631 smaller in size than the nominal effective cutoff diameter (ECD) of the top stage
632 of a suitable CI, may potentially be delivered to regions of the airways beyond the
633 nose. This test is intended to determine the amount of drug in small
634 particles/droplets. For example, for USP 25 Apparatus 1 (<601>), an eight stage
635 CI operated with the standard 28.3 liter per minute configuration, small droplets
636 are those under 9.0 microns. For BA, the CI test is intended to quantify the mass
637 of drug in small droplets. For BE, the mass of drug in small droplets for the T
638 product would be less than or equivalent to the corresponding mass of drug from
639 the R product. The comparative test addresses a potential safety concern — an
640 excess of small droplets due to T relative to R might deliver to regions beyond the
641 nose excipients with possible adverse pulmonary effects. The CI test for nasal
642 sprays is not intended to provide PSD of drug or aerosolized droplets.

643
644 Measurable levels of drug below the top stage of the CI would be a function of the
645 specific drug product and the experimental setup and procedure, including the
646 number of actuations and assay sensitivity. Thus, we recommend a validated,
647 highly sensitive assay be used. In Agency experience, a two-liter or larger
648 induction port (expansion chamber) is preferred to a one-liter chamber. We prefer
649 studies use the fewest number of actuations (generally not exceeding 10) justified
650 by the sensitivity of the assay, to be more reflective of individual doses. Drug
651 deposition would be reported in mass units. Mass balance accountability would
652 be reported. Mass balance would be based on drug deposition on each of
653 valvestem, actuator, adapters, induction port, any other accessories, the top stage,
654 and all lower stages to the filter. The total mass of drug collected on all stages
655 and accessories is recommended to be between 85 and 115 percent of label claim

656 on a per actuation basis. The total mass of drug below the top stage is of primary
657 interest. Therefore the pooled mass of drug deposited on all lower stages and
658 filter can be reported.

659
660 For BA and BE, CI test would be data requested only at the beginning lifestage.
661 Statistical approaches will be provided in Appendices B and D, respectively.

662
663 b. Nasal aerosols: Particle/Droplet Size Distribution

664
665 CI studies for nasal aerosols would use an induction port (expansion chamber)
666 that maximizes drug deposition below the top stage of the CI. For this reason, a
667 one-liter induction port is preferred to the USP 25 (<601>) induction port,
668 although other sizes may also be appropriate. Agency experience indicates that
669 with a suitable induction port and CI, the amount of drug deposited below the top
670 stage from nasal aerosols formulated with either chlorofluorocarbon or
671 hydrofluoroalkane propellants is of the same order of magnitude as from orally
672 inhaled aerosols. Therefore, unlike for nasal sprays in which the total mass of
673 drug below the top stage is of interest, we recommend a particle/droplet size
674 distribution be provided for this dosage form. Selection of the most suitable CI
675 may be influenced by the effective cutoff diameters (ECDs) of stages of various
676 brands of cascade impactors, the geometry of the induction port, and other factors.

677 The number of actuations recommended for the CI study of aerosols is described
678 in the draft guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI)*
679 *Drug Products - Chemistry, Manufacturing, and Controls Documentation*. Drug
680 deposition would be reported in mass units. Mass balance accountability would
681 be reported.

682
683 For BA and BE, CI data would be requested only at the beginning lifestage. At
684 this time, it is recommended that studies of nasal aerosols use USP 25 Apparatus
685 1 (<601>) operated at the standard 28.3 liter per minute configuration. We
686 recommend determination of a profile based on drug deposition at 11 sites: (1)
687 sum of valve stem plus actuator; (2) induction port; (3 - 10) eight individual
688 stages; and (11) filter. Deposition in the valve stem plus actuator would be
689 included to provide a profile of drug deposition ex-valve rather than ex-actuator.
690 It should be noted that the in vitro BE limit for the profile comparison depends on
691 the number of stages and other accessory deposition sites. Statistical approaches
692 for BA and BE will be provided in Appendices B and E, respectively.

693
694 4. Drug Particle Size Distribution by Microscopy

695
696 For suspension products, drug particle size may be important for rate of dissolution and
697 availability to sites of action within the nose. Therefore, drug particle size distribution
698 (PSD) and extent of agglomerates would be characterized in the spray or aerosol
699 formulation prior to actuation, and in the spray following actuation. Determination of
700 PSD and agglomerates in both the formulation and following actuation are intended to

701 characterize the potential influence of the device on deagglomeration. Determination in
702 the spray is only requested at the beginning lifestage. Nasal spray formulations frequently
703 contain suspended drug substance in the presence of insoluble suspending agent, which
704 complicates the particle size characterization. When examining formulations containing
705 suspending agents, and currently available technology cannot be acceptably validated to
706 determine drug particle size, a qualitative and semi-quantitative method for examination
707 of drug and aggregated drug particle size distribution can be used. We recommend
708 studies of nasal sprays include placebo product to provide an estimate of the occurrence
709 of apparent drug particles (*false positives*) due to excipient. Evaluation may use light
710 microscopy or other appropriate means.

711
712 For NDAs and ANDAs of both sprays and aerosols, we recommend drug PSD and
713 agglomerates data be provided in the BA or BE submission, along with a description of
714 the test method. Sponsors can submit representative photomicrographs, if desired. For
715 BE, PSD by light microscopy, even if qualitative or semi-quantitative, can be useful to
716 the applicant to estimate particle size relative to the precursor product prior to further
717 product development and testing. These data are supportive, and formal statistical testing
718 is not applicable.

719 720 5. *Spray Pattern*

721
722 Spray pattern studies characterize the spray either during the spray prior to impaction, or
723 following impaction on an appropriate target such as a thin-layer chromatography (TLC)
724 plate. Spray patterns for certain nasal spray products may be *spoked* or otherwise
725 irregular in shape.

726
727 Spray patterns can be characterized and quantitated by either manual or automated image
728 analysis, if validated. Both analyses will allow shape and size to be determined.
729 Automated analysis systems may also allow determination of center of mass (COM;
730 unweighted for image intensity) and/or center of gravity (COG; weighted for image
731 intensity) within the pattern to be determined. COG is of greater interest and is preferred
732 in the automated analyses of spray patterns. Automated image analysis is expected to
733 increase objectivity in spray pattern measurement. The technology enables the perimeter
734 of the true shape of the spray pattern to be determined, identifies COM and/or COG, and
735 enables the area within the perimeter to be quantitated, thus its use is encouraged.

736
737 Equivalence of spray patterns between T and R products can be established based on a
738 combination of qualitative and quantitative measures:

- 739
740 • Comparative visual inspection for shape. For the automated analyses, the true shapes
741 identified by the software serve as the basis of comparison (qualitative).
742 Establishment of qualitative sameness of T and R spray pattern shapes is a
743 prerequisite to the quantitative analyses in the following two bullets.
- 744 • Equivalent area within the perimeter of the true shape for automated analysis, or
745 equivalent D_{\max} for manual analysis (quantitative)

746 • Equivalent ovality (ellipticity) ratio (quantitative)

747
748 a. For nonimpaction systems

749
750 Spray patterns can be visualized using a system based on a laser light sheet and
751 high-speed digital camera that enables visualization of a pattern perpendicular to
752 the axis of the nasal spray. The perimeter of the true shape, area within the
753 perimeter (to include a high proportion, e.g., $\geq 95\%$ of the total pattern), COG,
754 and D_{\max} (longest diameter) and D_{\min} (shortest diameter) that pass through the
755 COG and extend to the perimeter of the true shape, can be determined based on
756 automated analysis using time-averaged images over the duration of a single
757 spray. Software settings can be established during prestudy validation and the
758 settings should be used consistently in the study. Statistical analysis at each
759 distance would be based on equivalence of area within the perimeter and ovality
760 ratio (D_{\max} divided by D_{\min}).

761
762 b. For impaction systems

763
764 The number of sprays per spray pattern would preferably be one. We recommend
765 that the visualization technique be specific for the drug substance. If exploratory
766 studies document that a drug-specific reagent cannot be found, a nonspecific
767 visualization reagent can be used. We recommend that application of the reagent
768 be controlled to maintain the details of the image intensity of the pattern.

769
770 Manual analysis

771
772 The approximate COM would be identified, and D_{\max} and D_{\min} drawn through this
773 center. The two lines may not be orthogonal to each other. Representative plots
774 can be submitted, and each figure can be marked with the COM, D_{\max} and D_{\min} ,
775 each based on visual analysis. The ovality ratio would be provided for each spray
776 pattern. Statistical analysis at each distance would be based on equivalence of
777 D_{\max} and ovality ratio.

778
779 Automated analysis

780
781 The automated image analysis software can define the perimeter of the true shape
782 of the spray pattern to include a high proportion (e.g., $\geq 95\%$) of the total pattern.
783 T and R would both be sprayed on each TLC plate to ensure measurement of the
784 spray pattern at the same intensity range for a given plate. D_{\max} and D_{\min} would
785 pass through the COM or the COG, as appropriate, and extend to the perimeter of
786 the true shape. Statistical analysis at each distance would be based on equivalence
787 of area within the perimeter and ovality ratio.

788
789 c. For both nonimpaction and impaction systems

791 The information above would apply to spray patterns in which the COM or COG
792 falls within the perimeter of the image of the actual spray pattern, and the D_{\max}
793 axis doesn't extend outside of the perimeter. Infrequently, the COM or COG may
794 fall outside the perimeter of the spray pattern, and/or the D_{\max} axis may cross the
795 perimeter. Horseshoe-shaped and certain other patterns may cause such an effect.

796 When this occurs, automated analysis using a system that has the capability of
797 fitting the perimeter with an appropriate geometric shape is recommended.
798 Statistical analysis at each distance would be based on equivalence of area within
799 the perimeter of the *true shape* of the spray pattern (not within the fitted
800 geometric shape), and ovality ratio, where D_{\max} and D_{\min} are computed from the
801 *fitted geometric shape* (e.g., ellipse).

802
803 For all cases above, we recommend spray patterns be determined based on:

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

811
812
813 For manual quantitation of spray patterns based on impaction studies such as TLC
814 plate methodology, we recommend the submission include copies, preferably
815 electronic, of images of representative spray patterns at two distances, and each
816 figure would clearly indicate the estimated COM (manual analysis), D_{\max} and
817 D_{\min} . When automated image analysis software is used for impaction studies, data
818 would be presented in electronic files. For automated image analysis of either
819 impaction or nonimpaction studies, electronic files would be definitive.
820 Submission of electronic files is recommended to avoid printer-dependent
821 variations in spatial calibration of images. These files would contain the images,
822 showing the COG or COM and the perimeter of the true shape of the spray
823 pattern, and the accompanying quantitation reports. Each image would also
824 include a legible scale used for measurement.

825
826 Some automated image analysis software may not include automated quantitation
827 of spray pattern images. For such cases, the analyst would determine and display
828 the quantitative parameters on the electronic image. As mentioned above,
829 quantitation of electronic images would be definitive.

830 831 6. *Plume geometry*

832
833 Plume geometry describes a side view of the aerosol cloud parallel to the axis of the
834 plume, and we recommend it be based on high-speed photography, a laser light sheet and

835 high speed digital camera, or other suitable methods. The image would be *snapshot*, not
836 time-averaged. Quantitation can be by manual analysis or automated image analysis.

837
838 During the very early life of an aqueous nasal spray plume, formulation may exit the
839 actuator orifice as a narrow stream that subsequently forms a relatively stable, fully
840 developed, conical plume prior to separating from the orifice. We recommend plume
841 angle, width, and height, all quantitated by the same analytical method, be reported at a
842 single delay time while the fully developed phase of the plume is still in contact with the
843 actuator tip. The applicant would provide documentation that the plume is fully
844 developed at the selected delay time. The angle would be based on the conical region of
845 the plume extending from a vertex that occurs at or near the actuator tip. Plume angle
846 based on spray pattern dimensions and distance from actuator tip to an impaction surface
847 is not appropriate. For this guidance, the recommended plume width would be the width
848 at a distance equal to the greater of the two distances selected for characterization of the
849 spray pattern. Plume width data would thus complementary to spray pattern data
850 obtained at the same distance. Plume height would be the distance from the actuator
851 orifice (sprays) or end of the inhaler tube (aerosols) to the leading edge of the plume. We
852 request that the criteria for defining the plume angle, width, and height borders be
853 provided.

854
855 Plume geometry would be performed at:

- 856
- 857 • Beginning lifestage only
- 858 • One side view only
- 859 • A single delay time
- 860

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

867
868 We recommend plume geometry measurements be summarized as mean, geometric mean,
869 and %CV. Comparative data would be supportive, thus for BE studies, the ratio of the
870 geometric mean of the three batches of T to that of the three batches of R, based on log
871 transformed data, would fall within 90 – 111% (point estimates) for plume angle and
872 width. Due to subjectivity in the measurement of plume height, point estimates would
873 not be applicable.

874 7. *Priming and Repriming*

875
876
877 Priming and repriming data will ensure delivery of the labeled dose of drug following
878 labeled instructions for use. Priming would be established based on the same B lifestage
879 data obtained for the single actuation content (SAC) through container life study (Section

880 V.B.1). For products approved under an NDA, priming and repriming data based on
881 single actuations would be provided in the CMC portion of the submission.
882

883 For products approved under an ANDA, the labeling would be the same as that for the R
884 product, except for specific changes described in the regulations (21 CFR
885 314.94(a)(8)(iv)). For nasal sprays and some nasal aerosols, the R product labeling
886 (package insert and/or patient package insert) describes the number of actuations to prime
887 the product on initial use and on repriming following one or more periods of nonuse (e.g.,
888 24 hours and 7 days following last dose). For these products, we request priming and
889 repriming data for T and R products. Studies would follow the recommended time
890 periods described in Section V.B.1 between lagging and/or batch release testing and
891 conduct of the priming test. Priming and/or Repriming studies would not be requested
892 when the R product lacks priming and/or repriming instructions, respectively.
893

894 We recommend that priming and repriming data for T in multiple orientations be
895 provided in the CMC portion of the ANDA submission. Therefore, for the BE
896 submission, studies can be based on products stored in the valve upright position, with
897 the exception of nasal aerosols in which R labeling recommends storage in the valve
898 down position. For the latter products, priming data, and repriming data when applicable,
899 would be provided following storage in the valve down position. Priming studies would
900 be based on the emitted dose of the single actuation at B lifestage immediately following
901 the specified number of priming actuations in the R product labeling. For ANDAs,
902 priming would be established providing that the geometric mean emitted dose of the 30
903 canisters or bottles calculated from the SAC data at B lifestage falls within 95 – 105
904 percent of label claim. Repriming would be similarly established based on a single
905 actuation following the specified number of repriming actuations in the R product
906 labeling. Although noncomparative to R, the priming studies would be essential to the
907 BE submission to document that each product delivers the labeled dose within the
908 number of actuations stated in the R product labeling, thus ensuring that the SAC through
909 container life studies are conducted on primed T and R products.
910

911 VI. CLINICAL STUDIES FOR LOCAL DELIVERY

912 A. General Information

913 1. NDAs

914 At the present time, of the classes of drugs covered in this guidance, only certain
915 corticosteroids are formulated as suspension formulation nasal aerosols and nasal sprays
916 and require in vivo studies as a component of the BE or BA submission (21 CFR 320.21).
917 The same adequate and well-controlled clinical trials in humans conducted under an
918 authorized IND, used to establish the safety and effectiveness of a drug product in support
919 of a forthcoming NDA (21 CFR 314.126), can be used in some cases to establish BA or,
920 when comparative, BE (21 CFR 320.24).
921
922
923
924

925
926 2. *ANDAs*
927

928 Clinical studies are at times incapable of showing a dose-response relationship and may
929 not be consistently reproducible. However, a showing of dose-response is not necessary
930 for BE studies with a clinical endpoint, as these studies are intended only to confirm the
931 lack of important clinical differences between T and R suspension formulation nasal
932 aerosol and nasal spray products (Advisory Committee for Pharmaceutical Science,
933 2001). For an ANDA, an authorized Bio-IND will be needed for the conduct of a BE
934 study with a clinical endpoint.¹²
935

936 A determination of bioequivalence of a rhinitis BE study with a clinical endpoint for
937 locally acting nasal suspension drug products would be based on the following premises
938 for T relative to R products:
939

- 940 • Qualitative and quantitative sameness of formulation
- 941 • Comparability in container and closure systems
- 942 • Equivalence of in vitro tests
- 943 • Equivalence of systemic exposure or systemic absorption
- 944 • Equivalence of the local delivery study.
945

946 A number of FDA guidances provide information about the general conduct of clinical studies,
947 including clinical studies to document BA and BE: *General Considerations for Clinical Trials*
948 (International Conference on Harmonisation (ICH) E8); *Structure and Content of Clinical Study*
949 *Reports* (ICH E3); *Good Clinical Practice: Consolidated Guidance* (ICH E6); *Statistical*
950 *Principles for Clinical Trials* (ICH E9), and *Choice of Control Group and Related Issues in*
951 *Clinical Trials* (ICH E10).
952

953 **B. Clinical Study Batches**
954

955 We recommend that the batch used for the BA study be the same pivotal clinical trial batch used
956 in the in vitro BA studies (Section V.A). Where BE studies are conducted for an NDA, the
957 batches of test and reference products would be the same batches employed in the in vitro testing.

958 Each of the T and R batches used to establish local delivery BE for an ANDA would be one of
959 the three batches used for the in vitro BE studies. We recommend that the inactive ingredients of
960 the placebo (P) product meet Q₁ and Q₂ recommendations relative to the R product (Section
961 IV.B); the P container and closure would meet the recommendations of Section III.B.
962

963 **C. Clinical BE Study Design and Subject Inclusion Criteria**
964

965 The study design would be the traditional treatment study in which T and R are assessed for a
966 two-week duration. The two-week duration, in addition to allowing a comparison of equivalent

¹² 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.

967 efficacy, will also allow for an assessment of safety and tolerability over a reasonable period of
968 use. We recommend the study be conducted at the lowest labeled adult recommended dose in an
969 attempt to optimize study sensitivity. Primed products according to labeling instructions prior to
970 dosing. Ensure that priming occurs out of range of the patients, to avoid inhalation of drug fired
971 to waste. Documentation would rely on the inclusion of a test product placebo (P) dosed at the
972 same frequency and number of actuations per nostril as T and R.

973
974 A study population consisting of seasonal allergic rhinitis (SAR) patients will allow
975 documentation of BE, which may extend to all indications in product labeling for locally acting
976 nasal corticosteroids. In addition to a history of SAR, we recommend patients have a positive
977 test for relevant specific allergens (e.g., allergen skin test) and be experiencing a defined
978 minimum level of symptom severity at the time of study enrollment. We discourage the
979 inclusion of patients with other significant diseases including asthma, with the exception of mild
980 intermittent asthma.

981
982 The recommended design for this study is a randomized, double-blind, placebo-controlled,
983 parallel group study of 14 days duration, preceded by a 7-day placebo run-in period to establish a
984 baseline and to identify placebo responders.¹³ We recommend placebo responders be excluded
985 from the study to increase the ability to show a significant difference between active and placebo
986 treatments (efficacy analysis), and to increase sensitivity to detect potential differences between
987 T and R products (equivalence analysis). The protocol would define *placebo responders* a priori.
988 Whether the drug is labeled for once or twice daily dosing, clinical evaluations would be made
989 twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo
990 run-in period and the 14-day randomized treatment period. Scoring should be made immediately
991 prior to each dose, to reflect the previous 12 hours (*reflective* scores) and how the patient is
992 feeling at the time of evaluation (*instantaneous* or *snapshot* scores). Because the primary BE
993 endpoint would be based on reflective symptom scores, placebo responders should be identified
994 based on reflective scores, although BE endpoints would include both reflective and
995 instantaneous scores.

996
997 We recommend baseline scoring preferably consist of reflective AM and PM scoring on Days 5,
998 6, and 7 of the placebo run-in period, and AM scoring (prior to drug dosing) on Day 1 of the 14
999 day randomized treatment period, resulting in 7 total AM and PM ratings. Placebo responders
1000 would be identified based on the mean total nasal symptom score (TNSS) over the 7 total AM
1001 and PM ratings. The study protocol would state the minimum qualifying reflective TNSS for
1002 enrollment at screening, and the same minimum qualifying TNSS would be met based on the
1003 mean of the 7 total AM and PM ratings prior to each patient's participation in the randomized
1004 portion of the study. We recommend randomization occur after evaluation of the 7 total AM and
1005 PM ratings, and the randomized portion of the study can start in the morning of Day 1 after the
1006 AM baseline scoring.
1007

¹³ 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.

1008 Symptom scores during the randomized treatment period would consist of the PM score on Day
1009 1, and the 26 AM and PM ratings on Days 2 to 14, resulting in 27 total ratings. We recommend
1010 the study be multicenter to avoid potential investigator bias. A double dummy design is not
1011 recommended for study blinding of aqueous nasal sprays due to a concern that the doubled fluid
1012 volume may result in washing the drug from its nasal deposition sites, potentially resulting in an
1013 altered safety and efficacy profile. However, study blinding is a critical consideration, and we
1014 recommend a description of how the T, R and P products are to be masked be carefully described
1015 in the study protocol.

1016
1017 We recommend the *equivalence analysis* be conducted as an evaluable (per protocol) analysis
1018 rather than an intent-to-treat analysis. The evaluable population would consist of compliant
1019 patients who missed no more than a specified number of days of symptom scores, took no
1020 contraindicated concurrent medications, and had no protocol violations. The protocol would
1021 describe the specific criteria used to exclude randomized subjects, resulting in the reduced subset
1022 of subjects for analysis (*FDA Guideline for the Format and Content of the Clinical and*
1023 *Statistical Sections of an Application*, Section III.B.9). In addition to the equivalence analysis, an
1024 *efficacy analysis* would be conducted to demonstrate study sensitivity to the T and R products.
1025 The efficacy analysis would be conducted as an intent-to-treat analysis, and the intent-to-treat
1026 population would be clearly defined. Because specific study recommendations are not provided
1027 in this guidance, we recommend a protocol for a BE study with a clinical endpoint for a specific
1028 suspension drug product be submitted prior to the conduct of the study to the appropriate review
1029 division at FDA.

1031 D. Clinical BE Study Endpoints

1032
1033 The endpoints for the *equivalence* and *efficacy analyses* should be patient self-rated *TNSS*.
1034 These most often include a composite score of runny nose, sneezing, nasal itching, and
1035 congestion, although addition of non-nasal symptoms to the composite score maybe pertinent for
1036 certain drug products.¹⁴ *TNSS* is a categorical variable, classified into a number of discrete
1037 categories, as opposed to a continuous variable. A common allergic rhinitis rating system uses a
1038 four-point scale with signs and symptoms ordered in severity from 0 (no symptoms) to 3 (severe
1039 symptoms), as follows¹⁵:

- 1041 • 0 = absent symptoms (no sign/symptom evident)
- 1042 • 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily
1043 tolerated)
- 1044 • 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but
1045 tolerable)
- 1046 • 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with
1047 activities of daily living and/or sleeping)

¹⁴ 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.

¹⁵ 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.

1048
1049 We recommend the endpoints for the equivalence and efficacy analyses be expressed as mean
1050 change from baseline (pretreatment) of the TNSS, expressed in absolute units, rather than percent
1051 change from baseline. The study report would include the daily AM and PM 12-hour reflective
1052 symptom scores. In addition, the report would include the mean symptom score over the 7 total
1053 AM and PM ratings of the placebo run-in period and the mean symptom score over the 27 ratings
1054 of the randomized treatment period. For the equivalence and efficacy analyses, the *primary*
1055 endpoint would be reflective scores for the 12-hour pooled TNSS over the two-week randomized
1056 portion of the study. However, instantaneous scores would also be provided as a *secondary*
1057 endpoint. Statistical approaches for analysis of the rhinitis study data are provided
1058 in Appendix F.

1059
1060 Safety assessments would be made before (at screening or baseline) and at end-of-treatment.
1061 Adverse events would be reported daily.

1062
1063

1064 VII. PK STUDIES FOR SYSTEMIC EXPOSURE

1065
1066
1067

A. General Information

1068 The Agency recommends that plasma concentration-time profiles from BA and BE studies be
1069 used to evaluate systemic exposure for suspension drug products that produce sufficiently high
1070 concentrations of the moiety(ies) to be measured to allow reliable analytical measurement for an
1071 adequate length of time after nasal administration. The recommended moiety(ies) to be
1072 measured in the BA and BE studies are described elsewhere.¹⁶

1073

1074 Systemic drug levels that occur with locally acting drug products are generally in the low ng/mL
1075 or low pg/mL range, depending on the drug and the drug product. Validated bioanalytical
1076 methodology may be available for many of the nasal corticosteroid drugs. For these drugs, pilot
1077 studies are not needed prior to conducting the full-scale PK study. If validated methodology is
1078 unavailable, a small-scale, single-dose pilot study, or when appropriate, a small-scale, multiple-
1079 dose pilot study, may be helpful in assessing the proposed analytical methodology and
1080 determining whether sufficiently high drug concentrations are attained. A PK study for systemic
1081 exposure would be preferred to a PD or clinical study for systemic absorption (Section VIII). If a
1082 sponsor has convincing data based on unsuccessful attempts to conduct the PK study in order for
1083 a PD or clinical study for systemic absorption could be used. If systemic exposure were
1084 established based on a PK study, a PD or clinical study for systemic absorption (Section VIII)
1085 would not be requested.

1086
1087

B. Study Batches

1088
1089
1090

The Agency recommends that the BA batch used for the PK systemic exposure study be a pivotal clinical trial batch. Alternatively, a PK batch similar to the batch used in a pivotal clinical trial

¹⁶ *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.

1091 can be used, in which case we recommend that any differences between the PK batch and the
1092 pivotal clinical trial batch be discussed with the appropriate CDER review division prior to the
1093 study. If the PK batch is not one of the three batches used for the in vitro BA studies (Section
1094 V.A.1), make sure that in vitro BA data are provided for the PK batch using the same protocols
1095 as for the three batches.

1096
1097 For a BE study, the batches of T and R would be the same batches used for the clinical study for
1098 local delivery, and each of these batches would be one of the three batches used for the in vitro
1099 BE studies.

1100 **C. Study Design and Subject Inclusion Criteria**

1101
1102
1103 The BA study to characterize systemic exposure can be one of the same PK studies conducted to
1104 address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA
1105 study can be conducted in healthy subjects or allergic rhinitis (AR) patients. Where appropriate,
1106 the BA study would include a reference product that may be an oral or intravenous solution, oral
1107 suspension, or other nasal product. Consultation with the appropriate review division is
1108 recommended regarding whether a comparative or noncomparative BA study is appropriate.

1109
1110 For an NDA or an ANDA, the in vivo BE study would be conducted with a replicate or
1111 nonreplicate randomized crossover design. For aqueous nasal sprays, the study would be
1112 conducted at the maximum labeled adult dose to maximize plasma drug levels, while avoiding
1113 the possibility of alteration of the drug deposition pattern within the nose at higher volumes when
1114 dosed above label claim. The deposition pattern could be altered due to loss of drug from the
1115 nasal cavity at these higher volumes, due either to drainage into the nasopharynx or externally
1116 from the nasal cavity. Although alteration of the deposition pattern may be less likely for a nasal
1117 aerosol when dosed above the maximum labeled number of actuations, the same study design
1118 and dose as for aqueous nasal sprays would be followed. We recommend that subjects for the
1119 study be healthy, with exclusions primarily for reasons of safety. The study protocol would
1120 include information regarding time interval between doses to each nostril and subject head
1121 position during dosing.

1122
1123 This guidance recommends that the PK study generally be conducted as a single-dose study.
1124 Such studies are more sensitive than multiple dose studies in assessing rate of release of the drug
1125 substance from the drug product into the systemic circulation. In addition, the nasally dosed
1126 corticosteroids tend to have biologic half-lives ranging from less than one hour up to about eight
1127 hours. For these products, when dosed either once or twice daily, systemic accumulation is
1128 expected to be relatively low, thus a multiple dose study may not result in a more reliable
1129 analytical measurement. However, there may be drugs that, due to pharmacokinetic
1130 characteristics, yield higher concentrations in a multiple-dose study, enabling the drug
1131 moiety(ies) of interest to be measured more reliably than in a single-dose study. For these drugs,
1132 a multiple-dose PK study would be preferred to a single-dose study.

1133 **D. Study Measures**

1134
1135

1136 The following BA and BE measures are considered pivotal¹⁶ in a single-dose study: $AUC_{0-t_{last}}$ (a
1137 measure of total exposure); $AUC_{0-\infty}$ (a measure of total exposure); and C_{max} (peak exposure). If
1138 $AUC_{0-\infty}$ cannot be determined reliably due to inability to estimate k_{el} accurately, total exposure
1139 would be based only on $AUC_{0-t_{last}}$. The following BA and BE measurements and plasma
1140 concentrations provide supportive PK characterization: plasma concentrations at each sampling
1141 time; T_{max} ; and k_{el} . The following BA and BE measurements are considered-pivotal for a
1142 multiple-dose study: $AUC_{0-\tau}$ (total exposure), where τ is the dosing interval; and C_{max} (peak
1143 exposure). T_{max} data should also be provided as supportive characterization.

1144
1145 Statistical analysis information is provided in Appendix G.

1146 1147 1148 **VIII. PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION**

1149 1150 **A. General Information**

1151
1152 As stated in Section VI.A, at present only certain corticosteroids are formulated as suspension
1153 products and require product quality in vivo studies. For those suspension drug products for
1154 which the moiety(ies) to be measured in the blood or plasma (Section VII) are too low to allow
1155 reliable analytical measurement for an adequate length of time, PD or clinical endpoint studies
1156 serve as measures of systemic absorption (Section II.A.2). However, *PK studies as measures of*
1157 *systemic exposure are preferred if at all possible*. As stated in Section VII, if a sponsor has
1158 convincing data based on unsuccessful attempts to conduct the PK study a PD or clinical study
1159 would be used in lieu of the PK study. The BA study to characterize systemic absorption may be
1160 one of the same clinical studies conducted to establish the safety of the drug product. The study
1161 would be conducted under an authorized IND in support of a forthcoming NDA (21 CFR
1162 314.126).

1163
1164 If a PD or clinical study is to be conducted (see previous paragraph), the recommended systemic
1165 absorption BE study design for nasal corticosteroids would be assessment of the HPA axis. The
1166 study would be conducted at the maximum labeled adult dose of the nasal aerosol or nasal spray
1167 to maximize study sensitivity. However, the study design would be based on an understanding
1168 that the maximum labeled dose over a 6-week period (Section VIII.C) may not result in
1169 detectable adrenal suppression by T and R because this dose may be at or near the bottom of the
1170 adrenal suppression dose-response curve. In addition to a test product placebo (P), we
1171 recommend an active control such as prednisone be included to ensure that the study is
1172 sufficiently sensitive to detect a drug effect (sensitivity analysis). Ensure that the active control
1173 dose is sufficiently large and the duration sufficiently long to produce a statistically significant
1174 response relative to placebo, with a duration sufficiently short to minimize undue exposure or
1175 risk to subjects. Determination of the optimum active control dose and dosing regimen may call
1176 for a pilot study by the sponsor. The pilot study may determine that an initial phase of the
1177 6-week study period may use a matching active control placebo, with active control given over
1178 the remainder of the study period, in an effort to reduce patient exposure to the active control.
1179 The pilot study can also provide an estimate of the number of subjects to be included in the
1180 pivotal study to yield a statistically significant difference in the HPA axis endpoint between the

1181 active control and the test product placebo (i.e., the aerosol or spray placebo). It may also allow
1182 estimation of the number of subjects to be included to characterize any HPA axis effects or lack
1183 thereof and to allow conclusions about any relative effects of T versus P and R versus P
1184 (“relative assessment of the HPA axis”; Appendix G.B). Conduct of the study in allergic rhinitis
1185 (AR) patients will allow an efficacy assessment to evaluate compliance with the study protocol
1186 (efficacy analysis). Therefore, AR patients, rather than healthy, non-allergic patients are
1187 recommended as the study population. We also recommend that other measures of compliance
1188 be instituted, including before and after weighing of the aerosol or spray container and diary
1189 entry of drug use.

1190
1191 Because this section does not provide specific recommendations, we recommend sponsors
1192 submit prior to the conduct of the study a protocol for a BE study with a PD or clinical endpoint
1193 for a specific drug product to the appropriate review division at FDA. For an NDA, the same
1194 adequate and well-controlled clinical trials in humans conducted under an authorized IND, used
1195 to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21
1196 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR
1197 320.24). For an ANDA, if the maximum single or total daily dose of the active control in the
1198 pilot or full-scale study exceeds that specified in the labeling of the selected active control drug
1199 product, an authorized Bio-IND will be needed.¹²

1200 1201 **B. Clinical Study Batches**

1202
1203 The Agency recommends the BA batch used for the study be a pivotal clinical trial batch used in
1204 the in vitro BA studies (Section V.A). For BE studies for an NDA, the batches of T and R would
1205 be batches used in in vitro testing. For an ANDA, the batches of T and R used for the systemic
1206 absorption study would be the same batches used for the clinical study for local delivery. Each
1207 of these batches would be one of the three batches used for the in vitro BE studies. Formulation
1208 and device recommendations for the P are described in Section VI.B. An active control such as
1209 prednisone is recommended. For blinding, matching active control placebo (identical in
1210 appearance to the active control) is also recommended.

1211 1212 **C. Clinical BE Study Designs and Subject Inclusion Criteria**

1213
1214 We recommend the study be conducted as a placebo and active-controlled, randomized, double-
1215 blind, parallel design comparing T and R for a 6-week duration. The study would not be
1216 conducted as a subset of the 2-week local delivery rhinitis study (Section VI). Subjects would be
1217 patients with a history of AR. The *relative assessment of HPA axis suppression* would be
1218 conducted as an evaluable (per protocol) analysis. The sensitivity analysis and efficacy analysis
1219 would be conducted as intent-to-treat analyses. The protocol would specify whether placebo
1220 responders will or will not be excluded from the analysis. We recommend that subjects be
1221 domiciled within the clinical study center during the days of HPA axis assessment. Domiciling
1222 the subjects during the 24-hour urine or plasma collection periods can help to conduct the study-
1223 related procedures reliably and completely. T and R would be dosed at the maximum labeled
1224 adult dose. P would be dosed at the same frequency and number of actuations per nostril as T
1225 and R. As stated above, the study would include an active control such as prednisone. Four

1226 study arms would be included: T, R, P, and the active control. The randomized portion of the
1227 study would be conducted according to a double-blinding design (i.e., all subjects would receive
1228 both the active control (either the active control itself or a matching placebo of the active control)
1229 and a spray or aerosol (either active or placebo)). The four treatment groups would be T plus
1230 matching active control placebo, R plus matching active control placebo, P plus matching active
1231 control placebo, and P plus active control. The matching active control placebo would be dosed
1232 on days when the active control is not taken, including the placebo run-in period. We
1233 recommend the number of centers conducting the HPA assessment be kept to a minimum to
1234 avoid center-to-center variability. A double-dummy design is not recommended for aqueous
1235 nasal sprays, as explained in Section VI.C. However, study blinding is a critical consideration,
1236 and we recommend a description of how the T, R and P products are to be masked be carefully
1237 described in the study protocol.¹⁷
1238

1239 The expected effect for the active control would be far larger than that for the T and R products.
1240 The sample size of the active control arm group may therefore be smaller in size than for the
1241 other study arms. We recommend the sample size for the T and R study arms be sufficient to
1242 characterize any HPA axis effects or lack thereof to allow conclusions about any relative effects
1243 of T versus P and R versus P, as stated in Section VIII.A.
1244

1245 We recommend timed urine or plasma samples for determination of 24-hour urinary free cortisol
1246 (UFC) or 24-hour plasma cortisol levels, respectively, be collected. Collections would be made
1247 prior to dosing (baseline) and during the last 24 hours of the 42 days of dosing (i.e., over the day
1248 41 – 42 period) while the drug is being actively dosed.
1249

1250 **D. Clinical BE Study Endpoints for Corticosteroids**

1251

1252 Whether the drug is labeled for once or twice daily dosing, the endpoint can be either 24-hour
1253 urinary free cortisol (UFC), based on a full 24-hour urine collection, or plasma cortisol levels
1254 collected every 4 hours over a 24-hour period, with exclusion of the middle of the night sample.
1255 For the UFC endpoint, urinary creatinine would also be measured to confirm completeness of the
1256 24-hour collection. The UFC value would not be corrected for creatinine. We recommend for
1257 the plasma cortisol endpoint, both AUC(0-24) and the trough (maximum effect) concentration
1258 during the dosing interval should be determined. The sensitivity analysis endpoint would be
1259 baseline-adjusted prior to analysis. Raw data would be provided for the relative assessment of
1260 HPA axis suppression. Efficacy analysis TNSS data would be expressed as change from
1261 baseline.
1262

1263 Statistical approaches for each of the analyses are provided in Appendix G.B.
1264

1265 **IX. NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING**

1266
1267

¹⁷ 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.

1268 Reserve samples must be retained for BA and BE studies (21 CFR 320.38 and 320.63) conducted
1269 in vivo or in vitro. The regulations state that each reserve sample must consist of a sufficient
1270 quantity of samples to permit FDA to perform five times all of the release tests required in the
1271 application or supplemental application. Dose content uniformity or spray content uniformity
1272 release tests alone usually require 30 units (canisters or bottles) per batch. Performance of other
1273 release tests requires additional units. The number of reserve sample units required for three
1274 batches of T and R could exceed 1000 units (up to 250 units for each batch of T and R) based on
1275 the *five-times-quantity* requirement.

1276
1277 The Agency has determined that in lieu of the *five-times-quantity* requirement, the quantity of
1278 inhalant (nasal aerosol or nasal spray) test article (T) and reference standard (R) retained for
1279 testing and analyses be at least 50 units for each batch.¹⁸ For NDAs, three batches are needed for
1280 BA studies. Thus, we recommend at least 50 units from each of the three batches of nasal spray
1281 or nasal aerosol be retained. However, where the reference product is another nasal aerosol or
1282 nasal spray, at least 50 units of that batch would also be retained. For ANDAs, at least 50 units
1283 of each of three batches would be retained for each of T and R used in in vivo or in vitro BE
1284 studies. For NDAs and ANDAs, if the in vivo or in vitro studies include placebo aerosols or
1285 sprays, at least 50 units of each placebo batch would also be retained. These recommendations
1286 apply only to nasal aerosols and nasal sprays for local action covered in this guidance and which
1287 are marketed as multiple dose products, typically labeled to deliver 30 or more actuations per
1288 canister or bottle. The number of reserves for nasal aerosols and nasal sprays delivering less than
1289 30 actuations per canister or bottle is not addressed in this guidance. Additional information
1290 regarding retention of BA and BE testing samples is pending.¹⁹

1291

1292

1293 X. MULTIPLE STRENGTHS

1294

1295 A small number of nasal sprays for local action are available in two strengths. Current examples
1296 are (1) ipratropium bromide nasal spray, a solution formulation, and (2) beclomethasone
1297 dipropionate nasal spray, a suspension formulation. Lower strengths of a product ordinarily
1298 would achieve the lower dose per actuation using a lower concentration formulation, without
1299 changing the actuator and metering valve or pump (other than diptube due to different volumes
1300 of product or other factors) used in the higher strength product. The following sections describe
1301 recommended BA and BE studies for low strengths of nasal sprays for which BA or BE for the
1302 higher strengths has previously been established. Recommendations are also provided for cases
1303 in which BA or BE is initially established on the low-strength product. No approved nasal
1304 aerosols are available in multiple strengths, thus BA and BE recommendations are not considered
1305 for these products.

1306

¹⁸ Quantity of Reserve Samples, Preamble to final rule, Retention of Bioavailability and Bioequivalence Testing Samples, 58 FR 25918-26, 1993, IIC21.

¹⁹ 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.

1307 **A. Solution Formulation Nasal Sprays**

1308
 1309 We recommend the BA of lower or higher strength solution formulation nasal sprays be based on
 1310 conduct of all applicable in vitro tests described in Section V. These studies are generally
 1311 noncomparative in character. Documentation of BE between T and R products would follow the
 1312 recommendations described in Section III regarding formulation and container and closure
 1313 system. Abbreviated in vitro testing, as follows, is recommended to document BE of the low-
 1314 strength T product to the low-strength R product, provided BE of the high-strength product has
 1315 been documented.

In vitro test	High Strength	Low Strength
Single Actuation Content		
Through Container Life	B, E ^a	B, E
Priming and Repriming	Yes	Yes
Droplet Size Distribution		
by Laser Diffraction	B, E	B
Drug in Small Particles/Droplets		
by Cascade Impactor	B	No
Spray Pattern	B	B
Plume Geometry	B	No

1328
 1329 ^a Beginning (B), Middle (M), End (E)

1330
 1331 With the exception of the reduced testing, the Agency recommends the same protocols and
 1332 acceptance criteria used to establish BE of the high-strength products be used for the low strength
 1333 products. In vivo studies are not needed for documentation of BA or BE of solution formulation
 1334 nasal sprays. Initial documentation of BE of the low-strength product would be based on all
 1335 applicable in vitro tests described in Section V. For subsequent documentation of BE for the
 1336 high-strength product, all applicable in vitro tests described above for the high-strength product
 1337 would be conducted.

1338
 1339 **B. Suspension Formulation Nasal Sprays**

1340
 1341 We recommend BA of lower strength suspension formulation nasal sprays be based on conduct
 1342 of all applicable in vitro tests described in Section V and systemic exposure studies, assuming
 1343 availability of bioanalytical methodology to allow measurement of systemic concentrations. In
 1344 the absence of this methodology, we suggest BA for systemic absorption be documented through
 1345 pharmacodynamic or clinical studies.

1346
 1347 BE conditions for the lower strength product would include:

- 1348
 1349 1. Documentation of BE for the high-strength test and reference products, based on
 1350 acceptable comparative formulations and container and closure systems,
 1351 comparative in vitro data, and comparative in vivo data

- 1352
1353 2. Acceptable comparative formulations and container and closure systems for the
1354 low-strength test and reference products
1355
1356 3. Acceptable comparative studies for low-strength test and reference products for
1357 all applicable in vitro tests in Section V
1358
1359 4. Proportionally similar Single Actuation Content Through Container Life between
1360 high- and low-dose test product and high- and low-dose reference product
1361

1362 In vivo studies would not be needed for documentation of BE of the lower strength products.
1363

1364 For cases in which an ANDA applicant initially documents BE on the low-strength suspension
1365 formulation product, and subsequently submits an ANDA for the high-strength product, full in
1366 vitro and in vivo documentation of BE would be provided for the high-strength product.
1367

1368 **XI. SMALLER CONTAINER SIZES**

1370
1371 Nasal aerosols and nasal sprays may be available in two container sizes. Current examples are:
1372 (1) beclomethasone dipropionate nasal aerosol, a suspension formulation; (2) fluticasone
1373 propionate nasal spray, a suspension formulation; and (3) cromolyn sodium nasal spray, a
1374 solution formulation. Smaller container sizes of nasal aerosols would be formulated with the
1375 same components and composition, metering valve, and actuator as the large container size that
1376 was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA).
1377 Smaller container sizes of nasal sprays would be formulated with the same components and
1378 composition, pump, and actuator as the large container size that was studied in pivotal clinical
1379 trials (NDA) or for which BE has been documented (ANDA). Where this is the case, no further
1380 documentation of either BA or BE is necessary. However, reestablishing proper priming, given a
1381 change in the volume of components of the device that will be filled in order to deliver an
1382 actuation, may in some cases be appropriate (Section V.B.7).

1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414

REFERENCES

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

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

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

1415 ¹ Although alternate test methods may be appropriate for certain tests, if validated, we recommend sponsors planning to use such methods contact the appropriate reviewing
1416 division prior to use.

1417