

GlaxoWellcome

September 9, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

**Re: Docket Number 99D-1738
Comments on Draft Guidance for Industry on Bioavailability and
Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action**

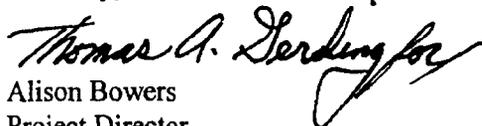
Dear Sir or Madam:

Glaxo Wellcome endorses the publication of the Draft Guidance for Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

We do, however, have concerns with some areas of the Draft Guidance and offer the following comments and recommendations for consideration by the Agency. Our comments are divided into two sections. The first section provides general comments applicable to the entire document. The second section presents specific comments identified by section number

Although we have recommended some revisions to the Guidance, we fully support this effort and look forward to working with the Agency to finalize a document which provides sponsors with a comprehensive, yet flexible approach to the development and subsequent registration of these intranasal formulations. Please contact me at (919) 483-4483 if you require clarification of any of these comments. Thank you for your consideration.

Sincerely,



Alison Bowers
Project Director
Regulatory Affairs

Attachments:
2 Copies of Docket Number 99D-1738 Comments

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99D-1738

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June 2, 2004

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**Re: NAS 0; Not Product Specific, General Correspondence: Other
Re. Attachment 6 to Citizen Petition 2004P-0239 to Issue a Final and Complete
Guidance Document to Determine Bioequivalence (BE) for Nasal Spray Products
and
FDA Docket No. 99D-1738: Comments on Draft Guidance for Industry on
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for
Local Action**

Dear Ms Ortega:

We are writing in response to your request for a written release regarding information marked "Confidential" in Exhibit 6 of the above-referenced petition submitted by GlaxoSmithKline on May 19, 2004. Please note that Exhibit 6 is a document that Glaxo Wellcome filed to the public docket on September 9, 1999 (FDA Docket No. 99D-1738: Comments on Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action). A copy of the document is already available to the public on FDA's website at <http://www.fda.gov/ohrms/dockets/dockets/99d1738/c000005.pdf>.

An erroneous document header was included on the Public Docket submission indicating that the documents were confidential. This letter confirms that the previous submissions to Public Docket Number 99D-1738 on September 9, 1999, and June 26, 2003, by Glaxo Wellcome and GlaxoSmithKline respectively, were not confidential, thus you are hereby authorized to release the documents in their current form as part of the Citizen Petition and the Public Docket.

Please let me know if you have any additional questions or concerns.

Sincerely,

Alison Bowers
Director, Policy, Intelligence, Education, Regulatory Affairs

Copy: C. Elaine Jones, William M Zoffer, GlaxoSmithKline
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From Alison Bowen

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Date June 2, 2004 Pages including cover 2

Subject Citizen Petition 2004 P-0239

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**COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY:
BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR NASAL
AEROSOLS AND NASAL SPRAYS FOR LOCAL ACTION (JUNE
1999)**

[DOCKET NO. 99D-1738]

We agree with FDA's recognition of the challenges/difficulties of demonstrating equivalence of nasal sprays/aerosols, particularly of corticosteroids intended for local action. Thus, in general, we support generation of this guidance. Our overall comments are shown below. Specific comments are organized under the same section headings as used in the draft guidance.

OVERALL COMMENTS

1. The same standards should apply to ANDAs and NDAs

We strongly support application of the same standards to ANDAs and NDAs, as product quality, safety and efficacy considerations are independent of the regulatory mechanism for approval. The public interest will be served by the adoption of scientifically appropriate equivalence criteria that will ensure that approved generic formulations of these products are interchangeable with the reference listed drug that has been proven safe and effective.

2. Significant portions of the guidance, particularly the statistical standards for bioequivalence, are incomplete, so a second period of public comment, and probably a public meeting, are required to finalize the guidance

The clinical components of the guidance are significantly less detailed than the *in vitro* aspects. This diminishes the value of a public review of the guidance at this time. In particular, it is premature to describe this guidance as relating to Bioavailability and Bioequivalence Studies, since no bioequivalence standards are provided. Section IX.E. is completely absent, and a significant portion of section IX (B)(2)(b) was not made available to industry until August 16. Thus we suggest that, as a minimum, a second period of public comment following publication of a complete draft will be required before this guidance may be finalized.

During the years 1988-1994 the Agency paid considerable attention to the issue of establishing bioequivalence standards for albuterol metered-dose inhalers, which work topically and for which conventional bioequivalence studies are inappropriate. The many variables associated with assessing the intra and inter-patient response to oral inhalation of

albuterol via metered-dose inhalers were discussed at a joint Pulmonary-Allergy and Office of Generic Drugs Advisory Committee meeting in September 1993. We recommend that an Advisory Committee be convened to discuss the bioequivalence issues that pertain to intranasal delivery systems intended to deliver drug topically to the mucous membranes. The need to establish standards for therapeutic equivalence of intranasal products provides a good opportunity to review the available scientific information in a public forum.

3. Demonstrating bioequivalence for these products is difficult

3.1 Bioequivalence standards to support substitution of Test and Reference intranasal corticosteroid products are not the same as comparability standards

At best, the studies proposed in the guidance describe an approach to examining the general comparability of products but they do not have the sensitivity to establish bioequivalence and substitutability, nor are any standards provided. The guidance seems to have been developed to match the replacement approach (as in the case of the Agency's Points to Consider: Clinical Development Programs for MDI and DPI drug products, September 19, 1994 which specifically addresses the switch from CFC products), instead of substitutability.

For example, the two-week "traditional treatment study" may provide confidence that the innovator and test formulations are statistically superior to placebo for efficacy endpoints, but the study would provide little confidence that the two products would perform similarly if one product were substituted for another; the study is not powered to demonstrate that the Reference and Test product would provide similar responses to treatment and no standards for determining bioequivalence are provided. Further, the additional studies described in the guidance document to assess PK and cortisol levels for corticosteroids have not been demonstrated as adequate markers to assess the potential for systemic effects. Thus, while the studies described in this guidance may demonstrate comparability in the broadest of terms, the studies would be inadequate to establish bioequivalence.

3.2 Efficacy studies are required to establish BE for locally-active compounds

The determination of bioequivalence of intranasal steroid formulations is complicated by the following considerations:

- 1) intranasal corticosteroids achieve therapeutic effects locally; therefore, systemic drug plasma concentrations do not correlate with therapeutic anti-inflammatory activity.
- 2) the lack of validated PD models to demonstrate bioequivalence between formulations.
- 3) systemic plasma levels of drug following administration of clinically effective doses are in the low ng/ml to pg/ml range, and current assays lack the sensitivity to establish meaningful drug plasma levels at clinically relevant doses.

- 4) the plasma concentration of such drugs following intranasal administration may reflect absorption of drug not only through the target tissues of the nasal mucosa but also from the oropharynx and gastrointestinal tract.

The guidance should include clinical protocols for *in vivo* tests in humans which have the sensitivity to discriminate between test and innovator products for determining the BA/BE of intranasal dosage forms intended to deliver the active moiety locally (21 CFR 320.24 (b)(3) and (4)). This philosophy is also outlined in the European Committee on Proprietary Medicinal Products Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents (CPMP/EWP/239/95 final, effective June 1996), which states that "in particular the relationship of the model with the therapeutic situation must be demonstrated". For intranasal corticosteroids a relationship between systemic exposure and systemic effects cannot be assumed, thus efficacy studies as well as studies of systemic markers are essential to establish therapeutic comparability or equivalence.

- 4. Glaxo Wellcome strongly supports the requirement for both *in vitro* and *in vivo* testing to establish BE for this group of products. The respective roles of PK, PD and clinical efficacy studies in the *in vivo* determination should be clarified**

4.1 PD/PK studies of clinical safety

We agree that pharmacokinetic (PK) data alone are not sufficient to permit a determination of bioequivalence for these locally active products. We believe that both efficacy studies and a study that provides a sensitive pharmacodynamic (PD) model of clinical safety to assess the effects on the HPA axis are required to characterize these products. The most clinically relevant methodology for determining HPA axis function is currently a matter of debate (Correspondence in J. Allergy Clin. Immunol. between Lipworth and Vargas, 1999). Further studies are needed to define the most appropriate and clinically relevant test for this determination. Effects on urinary free cortisol or serum cortisols may not be a sufficiently sensitive measure of HPA axis function for the purpose of making a determination of bioequivalence or interchangeability, as evidenced by the FDAs class labeling for inclusion in the Pediatric Use section of package inserts for intranasal corticosteroids i.e., "This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function". The appropriate substitution of one product for another would be of particular importance in children and adolescents when growth/laying down of bone is occurring and in the elderly where bone mass is decreasing.

4.2 Clinical studies for local delivery

With respect to clinical efficacy, we believe that it is appropriate for a Traditional Treatment Study, including a determination of onset of effect, to be conducted in all cases for corticosteroids and mast cell stabilizers. A “Days in the Park Study” or an “Environmental Exposure Unit Study” may provide an alternative method for generating supportive data relating to onset of effect. However, it is not appropriate to make a determination of therapeutic equivalence on the basis of a single Days in the Park Study or an Environmental Exposure Unit study for these products. Most corticosteroids and mast cell stabilizers (cromolyn) do not achieve their maximum therapeutic effect until after at least one to two weeks of treatment.

We welcome the inclusion of a Decision Tree but we believe that the guidance as written does not adequately address bioequivalence standards. The table below summarizes our impression of the information provided in the current draft guidance and highlights the areas where significant gaps exist.

Aspects Involved in a determination of BA/BE for nasal products intended for local action	Suggested study designs/methods for testing	Standards for bioequivalence
Q1	✓	✓
Q2	✓	✓
Container-closure system related characteristics – assessment of delivered spray	✓	Standards proposed but clinical relevance and discriminatory power unclear
PK measures of safety	Outline design only	No standards proposed
PD measures of safety	Outline design only – current area of scientific debate	No standards proposed
Clinical studies for local delivery	Three study designs for examining efficacy or comparability outlined; only the Traditional Treatment Study model offers a viable alternative to a complete clinical program.	No standards proposed

5. Glaxo Wellcome agrees with the Q1, Q2 and container closure system aspects of the *in vitro* requirements but the relevance and role of these *in vitro* tests in the assessment of Bioavailability and Bioequivalence warrants further discussion

We agree that these products should be qualitatively (Q1) and quantitatively (Q2) essentially the same, and match the container closure system of the innovator, before any assumption of comparable delivery to the nasal mucosa and GI tract can be made.

We understand that both the formulation and the delivery system (pump and actuator) may influence the delivery and absorption of drug. At the Pulmonary-Allergy Advisory Committee meeting in June 1990 a difference in serum potassium, finger tremor and heart rate effects associated with administration of two albuterol inhalers was linked to differences between the actuators fitted to the products. Thus we accept the need to establish common, stringent standards for *in vitro* properties as part of an overall determination of bioequivalence or substitutability but we do not agree that these standards, by themselves, establish BE. Thus we do not agree with use of the phrase "*in vitro* bioequivalence" in the context of these types of products. We recommend that the standards are limited to those with proven relevance and discriminatory power. Comparable *in vitro* performance cannot be extrapolated to *in vivo* bioequivalence at this time simply because the clinical models currently available are not sufficiently sensitive to discriminate between Test and Reference products.

6. The *in vitro* tests described in this guidance should be consistent with those proposed in the companion CMC guidance

We recommend that this guidance be clearly and consistently related to the *in vitro* tests described in the companion Chemistry, Manufacturing and Controls (CMC) Draft Guidances For Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, and Metered-Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. The BA/BE guidance should be consistent with the requirements, and refer to specific sections, of the two draft CMC guidance documents where appropriate unless there are differences in the tests which are necessary for Bioavailability/Bioequivalence (BA/BE). In these cases, an explanation of the reason for the difference is needed.

Examples include: 1) much more detail is provided in this guidance on priming/repriming than in the two CMC guidances 2) this guidance allows the grouping of stages of the Cascade Impactor for the purpose of comparing Test to Reference, while the Draft CMC guidance stresses the importance of evaluating individual stage data but does allow grouping of stages for the purposes of setting specifications. When the MDI/DPI guidance becomes final, we suggest that determinations of comparability or equivalence between Test and Reference should be made using the definition of significant change in the MDI/DPI guidance (if this section is retained). The linkage between development tests, specifications, stability testing and *in vitro* comparisons for BA/BE should be clear. The methodology described and the terminology used must be consistent.

7. The guidance should not address postapproval changes

Given the history of industry/Agency collaboration with respect to development of SUPAC guidances and the upcoming introduction of revisions to 21 CFR 314.70, we suggest that the Postapproval Change section is beyond the scope of this guidance and adds an unnecessary layer of confusion.

DETAILED COMMENTS, ANNOTATED BY SECTION OF THE DRAFT GUIDANCE

I. INTRODUCTION

We welcome the fact that this guidance applies equally to Nasal Aerosols (MDIs) and to Nasal Sprays (aqueous), and to NDA and ANDAs.

The third sentence of the first paragraph "Product quality BA and BE are reflective of potency.... a reproducibly potent product" is difficult to understand. We suggest that "criteria for" should be inserted before "BA". Footnote 2 in paragraph 3 should be moved to appear immediately after "OTC monograph".

II. BACKGROUND

A. Bioavailability and Bioequivalence Data

While the studies described in this guidance may demonstrate comparability in the broadest of terms, these studies would be inadequate to establish bioequivalence.

We recommend that this section is made consistent with the parallel statements in section IIA of the Draft CMC Guidance For Industry: Nasal Spray And Inhalation Solution, Suspension And Spray Drug Products, specifically the following statements (direct quotation plus additional text, which is underlined) "The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays depending on the intended site and mode of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical methods. Even where the pharmacokinetics of nasal doses can be measured, the measurements only allow a crude estimate of total nasal deposition. Moreover, bioequivalency studies are complicated by the fact that only a portion of the dose reaches the site of action. The remainder of the dose is swallowed and absorbed through the gastrointestinal (GI) tract. Thus, even if determination of blood or serum concentrations were possible, additional and more extensive studies would be necessary to distinguish the contributions of the drug absorbed from the nasal and GI routes. Importantly, blood levels are not necessarily correlated to pharmacodynamic effects if these drugs act locally and not systemically. Therefore, clinical studies are always required to establish BE."

It is extremely unlikely that an *in vitro* test for assessing the performance or quality characteristics of a new NDA or ANDA product can be correlated with and be predictive of human bioavailability data, therefore *in vivo* methodology for examining the bioequivalence of such products needs to be developed and included in this guidance.

We do not agree with the statement "A drug administered nasally and intended for local action is therefore likely to produce systemic activity, although plasma levels of the drug do not reflect the amount of the drug reaching nasal sites of action". There may be limited systemic exposure with some products, but this is no guarantee of systemic activity.

1. Local delivery BA/BE concepts

We are not aware of any evidence to support the statement in paragraph 1 that "*in vitro* methods are less variable, easier to control, and more likely to detect differences between products if they exist". We do agree that "the clinical relevance of these tests, or the magnitude of the differences in the tests, is not established".

In vitro methods can only be relied upon for solution products if the formulations are identical and the Q1, Q2 and mirrored container-closure system standards are fully met. If they are not, the formulation may affect permeability of the membrane and availability of the drug for absorption at the site of action. The clinical relevance of the proposed *in vitro* tests for nasal products has not been established.

There is no evidence given to support the "assumption [in paragraph 2] that *in vitro* studies would be more sensitive indicators of drug delivery to nasal sites of action than would be clinical studies". For suspensions it is stated that it is not possible "to adequately characterize PSD" (drug particle size distribution). In section V.B.2 it is noted that present agency experience suggests that drug and drug aggregate PSD characterization cannot be acceptably validated for nasal aerosols and nasal sprays. This leaves the value of *in vitro* specifications for droplet size distribution and PSD as controls from a bioavailability perspective in question. There is no reason why well designed pharmacokinetic and pharmacodynamic studies, or clinical trials, should be given less weight than *in vitro* experiments.

We agree that *in vivo* studies are essential for suspension products. In section VI.D. it is implied that one of 3 *in vivo* designs might be acceptable. It is our opinion that option IV.D.1: Traditional Treatment Study would always be required to support approval of a new suspension corticosteroid product NDA or ANDA, although other study options could provide supportive or complimentary data.

2. Systemic exposure and systemic absorption BA/BE concepts

We agree that it is more desirable to measure pharmacokinetics (PK) when possible and to use pharmacodynamic (PD) measures when this is not possible. However, in the case of inhaled and intranasal products, inclusion of measures of PD, e.g. serum cortisol for corticosteroid products, in PK studies can be helpful in providing clinical perspective. Thus, PD should also be measured if it is quantifiable. An efficacy study for intranasal and inhalation products is also necessary because direct relationships between efficacy and systemic exposure have not been established.

We disagree that the clinical endpoints defined in the present guidance would be adequate to measure systemic absorption - these measures lack sensitivity and no standards for bioequivalence were provided for review.

It is not clear what the threshold is for determining whether PK studies are feasible. PK measures are not predictive of efficacy for these products. In order to obtain measurable levels of systemic drug, it may be necessary to administer therapeutically irrelevant doses. A discussion of using multiples of the therapeutic dose and the volumes of the intranasal doses needed should be included. Generation of PD or PK data at higher than therapeutic doses would provide valuable information for safety purposes, but will not contribute to an assessment of therapeutic equivalence.

We welcome the inclusion of a Decision Tree but we recommend that it include a determination of Q1, Q2, confirmation of matching container closure systems, and clarification of the role of PD systemic exposure studies. The reference to "local delivery" should be clarified to represent "therapeutic equivalence".

B. CMC Tests and *In Vitro* BA Tests (Noncomparative) versus BE Tests (Comparative)

We understand the distinction made between CMC tests and *in vitro* BA tests, however, for solution and suspension nasal sprays/aerosols, the CMC tests for content uniformity through life and particle/droplet size distribution are designed to ensure accurate/reproducible dosing and thus "release" of drug substance from the drug product. Therefore, the Test product should be required to meet the same CMC test specifications as the Reference product.

The guidance states that BE limits may be based on *a priori* judgements. We agree that these limits should be established *a priori* and believe that they should be standardized across the industry for a single product, based on the variability of the Reference product. A determination of substitutability of each Test product with the Reference product should be dependent on compliance with the same BE limits. For this reason, since no bioequivalence standards are provided in Section IX.E, a second draft with a period of public comment will be required before this guidance may be finalized.

The guidance states "When conducted premarket for an NDA, some of the *in vitro* BA tests described in this guidance can be noncomparative and serve primarily to document (benchmark) the product quality BA of a pioneer product". This is interesting information, but more appropriate for a CMC guidance.

III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM

A. Formulation

We request that the Guidance define what is meant by "For an ANDA of a suspension formulation, the PSD of the active drug in the dosage form **should be the same** as that of the reference listed drug... Section V.B. is referenced but this section does not define sameness. When the MDI/DPI guidance becomes final, we suggest that determinations of comparability between Test and Reference should be made using the definition of significant change in the MDI/DPI guidance (if this section is retained).

The final sentence of the first paragraph is confusing. It could be interpreted to mean "that the PSD of the drug in the emitted dose, determined by *in vitro* test X, should be identical for all strengths of finished product", or that "the PSD of the bulk drug **used in each product strength** should be identical". We agree with the latter interpretation. Additionally, each strength of generic product PSD should match the innovator product PSD at the corresponding strength.

B. Container and Closure System

While we agree with the requirement that generic container-closure systems match that of the innovator product, there are likely to be some differences in the materials of construction of the container closure system between ANDAs and the reference listed drug. Therefore, ANDAs should be required to provide sufficient data to demonstrate that the level of extractives has reached equilibrium and assure that Test and Reference product container-closure systems are comparable.

In the second paragraph, it is suggested that “*In vitro* tests alone may be appropriate” for demonstrating equivalence. We do not agree with this statement. If the final determination is that *in vitro* tests alone are permissible for solutions, the first sentence/second paragraph should be rewritten as follows: “For nasal aerosols and nasal sprays approved under an ANDA, BE should be documented on the basis of validated *in vivo* and *in vitro* tests, or, in the case of solutions, validated *in vitro* tests alone may be appropriate.”

The penultimate sentence of this section requires the Test product to attain prime within the same number of actuations as the Reference product. There is value in this requirement if products can be substituted and the patient considers the product will work in an identical way without reference to the instructions for use, but this could be considered to be beyond the scope of establishing bio-equivalence. If, for example, the pack size was increased and the Test product had a longer dip tube, more priming shots might be needed.

IV. DOCUMENTATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

A. INDs/NDAs

We suggest that the first sentence be reworded as follows: “*In vitro* BA studies should be provided in INDs/NDAs for solutions and suspensions. NDAs (for suspensions) must also include *in vivo* studies”. The sentence as currently written implies that *in vivo* studies could be required in order to progress IND studies, which is inaccurate.

B. ANDAs

1. Solution formulations

We agree that these products should be qualitatively (Q1) and quantitatively (Q2) essentially the same, and match the container closure system of the innovator in order to support a basic assumption of comparable delivery to the nasal mucosa and GI tract.

2. Suspension formulations with PK systemic exposure data

We agree that these products should be qualitatively (Q1) and quantitatively (Q2) essentially the same, and match the container closure system of the innovator in order to support a basic assumption of comparable delivery to the nasal mucosa and GI tract. We agree in principle with the statements in this section but note that it is not clear whether the “meaningful” AUC and Cmax data need to be generated at therapeutically relevant doses or not.

3. Suspension formulations without PK systemic exposure data

The studies suggested in this section only describe comparability studies. There is a reference to *in vivo* bioequivalence, but no statistical standards for BE are provided in Section IX.E. The methods described do not include sufficiently sensitive standards upon which to reach a determination of bioequivalence. The next draft of this guidance should include clear discussion of the approach for determination of bioequivalency between formulations that would permit substitution of one product for another.

C. Postapproval Change

The *in vitro* sections of this guidance (sections V and IXA-D) seem to reflect a philosophy of "identify, describe and control all possible measures " without thought to the end use of the product. This gives cause for concern should these requirements become mandatory for characterizing and demonstrating equivalence of innovator products subject to minor change, e.g., excipients, site of manufacture of drug product, drug substance, etc.

Given the history of industry/Agency collaboration with respect to development of SUPAC guidances and the upcoming introduction of revisions to 21 CFR314.70, we suggest that the Postapproval Change section is beyond the scope of this guidance and adds an unnecessary layer of confusion. If this section is retained, guidance regarding the circumstances when *in vitro/in vivo* bioequivalence studies need to be repeated should be circulated for public comment prior to finalization.

V. BIOAVAILABILITY AND BIOEQUIVALENCE: *IN VITRO* STUDIES

A. Batches and Drug Product Sample Collection

1. INDs/NDAs

We understand this to mean that a second clinical batch can be substituted for a production batch for *in vitro* quality BA studies provided that the clinical batch is fully representative of the to-be-marketed product. We believe a second stability batch would also serve this purpose. The batches selected should be representative of the production scale and include different batches of input drug substance, pumps and actuators.

The opening paragraph of this section implies that it is necessary to conduct three *in vitro* BA studies for an IND; later sections of the guidance provide extensive details of the batches to be evaluated, testing to be conducted and the statistical evaluation required. We agree that BA studies are required for an NDA or ANDA and that comparisons (or full BE studies) would be appropriate to compare products that changed during development, however the need for three *in vitro* BA studies is considered excessive for early INDs (e.g. Phase 1, Phase 2).

B. Tests and Metrics

Section V.B. introduces the concept of blinding an *in vitro* analysis. This suggests that such studies should have a protocol containing pre-defined criteria for randomization, batch selection, variability, replicate analyses for each test and a determination of BA/BE. While the tests are the standard *in vitro* tests, the results are certainly not evaluated in the conventional fashion, e.g. against the regulatory specification.

The level of detail regarding method development included in Note 6 is inappropriate for a guidance of this type.

We note that automated actuation stations are recommended, but maintain that manual actuation methods may be permitted providing appropriate validation data are available.

1. Dose or spray content uniformity through container life

We do not agree that a single dose represents the minimum number of sprays **per nostril** described in the product labeling. It should represent the usual or minimum dose described in the product labeling, i.e., if the dose is one spray per nostril, a single dose is two sprays, one in each nostril.

Content uniformity should be assessed by an appropriate assay. As when testing to specification, there is no need for this assay to be stability-indicating. An explanation for the difference in approach to assessment for solutions and suspensions should be provided, i.e., uniformity is assessed within and between units for solutions but within and between units and also between batches for suspensions.

We support footnote 7 regarding definition of the middle of unit life (corresponding to 50 per cent of the labeled number of medicated doses). We note that this contradicts the statement relating to priming in the Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (Lines 554-557). The MDI guidance should be modified to match footnote 7 of the current guidance. The final sentence of this section: "Analytical data should be validated" should read "Analytical methods should be validated".

2. Droplet and drug particle size distribution (PSD)

Considering the shortcomings of all available PSD test methods, the assumption that any of the proposed PSD *in vitro* tests could characterize the actual *in vivo* particle size distribution of a nasal solution or suspension product and fully support a determination of substitutability is inappropriate.

In the first paragraph the sentence: "Droplet size distribution measurements are thus critical to delivery of drug to the nose" should read "droplet size distribution is thus critical.... etc."

a. Particle size distributions

Drug and aggregate PSDs

While it is difficult to validate a visual PSD test for a suspension product formulated with excipients, we note that it is a requirement of the CMC Guidance's on MDIs/DPIs and Nasal Spray and Inhalation Solution/Suspension/Spray Products, where no allowance is made for this to be supportive characterization data.

The first sentence of this paragraph should say, "partially dissolved" not "partially undissolved".

b. Instrumental methods

Laser diffraction

The laser diffraction and light microscopy tests are severely limited in their ability to produce accurate results. Both of these *in vitro* PSD methods may provide supportive information on the particle size characteristics of the product, but these tests do not have the sensitivity and selectivity to serve as BE measures. Thus collection of Laser Diffraction measurements at three distances from the delivery orifice and at different delay times, and the submission of all the data listed in paragraph 2, seems excessive in the absence of any evidence of clinical relevance. As a minimum, the third sentence of the second paragraph should be modified to "Copies of all instrumental..." since the originals and raw data would be retained by the sponsor.

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

It appears that for BA/BE comparisons it is permitted to pool 3 size range groups of results. We assert that for BA/BE purposes, the comparison of T to R should be based on an assessment of individual stages and accessories, not groupings, as this can mask shifts in the PSD. The concept of grouping stages is allowed by the two draft CMC guidances for the purpose of establishing control specifications, but the application must provide an evaluation of the PSD by individual stages (7) and accessories to provide a baseline against which future changes may be evaluated.

3. Spray pattern

Spray pattern and plume geometry testing in an unconstrained environment are indirect measures of reproducibility of dosing and the clinical relevance of these tests is uncertain.

The guidance claims that "Comparable spray pattern and plume geometry data for T and R, combined with other *in vitro* tests (and *in vivo* studies for suspensions), ensure equivalent drug deposition patterns, resulting in equivalent delivery of drug to nasal sites of action and equivalent systemic exposure or absorption". This is a very bold statement and should be supported by references.

We do not believe that there is a need to test spray pattern at 3 distances from the actuator – this also contradicts the companion CMC document that references 2 distances. The requirement to test at different distances should not be necessary, provided that during method development multiple distances were evaluated to determine the optimal distance to obtain a spray pattern that is of uniform density and reproducible. Also, if the intent were to develop representative *in vitro* studies, the most appropriate distances would be 1, 2, and 3 cm, all of which are practically immeasurable when 0.1ml of an aqueous product is sprayed onto a surface. We suggest that spray pattern should only be assessed at 1 distance.

A new test description "ovality ratio" is introduced in this guidance. This is not consistent with the terminology used in the companion CMC guidance, which includes a description of the spray image and the ratio of the longest to shortest axes. Ovality ratio is more appropriate than a specification for description of the spray image (e.g. ellipsoid). The two guidances must use consistent terminology.

4. Plume geometry

The value of conducting plume geometry testing as part of a BA/BE *in vitro* assessment is not clear. The final sentence of this section notes that this test provides supportive comparability data. It is not clear from Table 1 what part “supportive characterization” data will play in a determination of *in vitro* comparability or BE. This should be explained in the next draft of the guidance.

5. Priming and repriming

Priming and repriming data should always be required for an ANDA. We note that this section provides much more detail than the two draft CMC guidances. These documents must be consistent. We suggest that methodology is more appropriately addressed in the CMC guidance and that this guidance should concentrate on standards for *in vitro* comparability and equivalence.

6. Tail Off Profile

Provided the sponsor can show that the product can deliver the labeled number of sprays to specification, the contribution of these data to a determination of substitutability and applicability of the same labeling to both the Test and Reference product is questionable.

VI. BIOAVAILABILITY AND BIOEQUIVALENCE: CLINICAL STUDIES FOR LOCAL DELIVERY

A. General Information

The clinical studies described in this section might be appropriate to demonstrate comparability but they would not demonstrate bioequivalence. The methods are not sufficiently sensitive and no bioequivalence standards or power calculations are provided.

We are not aware of the existence of a validated pharmacodynamic effect bioassay which is illustrative of a dose-response relationship between delivered dose and systemic concentrations for corticosteroids, where dose-response relationships have typically been difficult to establish.

B. BE Clinical Study Endpoints

We support the use of patient-rated total nasal symptom score as the primary efficacy endpoint. However it is not exactly clear which aspect of the TNSS results are primary, since statistical determinations of significance could differ depending upon whether absolute units or percent change from baseline is used. We propose that mean change should be the primary efficacy variable. The protocol should clearly state whether the contributing symptoms are primary or secondary endpoints and the time interval to which the primary endpoint refers. The products should be comparable at all timepoints. The difference between treatments used to establish statistical significance must have been shown to be clinically meaningful.

D. Clinical BE Study Designs and Subject Inclusion Criteria

It is difficult to demonstrate a dose-response relationship with some of these products. We recommend that the guidance include clinical protocols for *in vivo* tests in humans which have proven sensitivity to discriminate between test and innovator products for determining the bioavailability and bioequivalence of an intranasal dosage form which is intended to deliver the active moiety locally (21 CFR 320.24 (b)). Until a sensitive method has been determined and validated, this guidance should not be finalized.

We welcome the development of guidance on clinical development programs for allergic rhinitis drug therapy. We note that the Division of Pulmonary Drug Products issued a Points to Consider document on January 23, 1996 which described the clinical development programs for new nasal spray formulations, and would appreciate information about the current status of that document. We suggest that much of the information about seasonal allergic rhinitis studies in the current draft is more appropriate to the general guidance than a BA/BE guidance, especially since this guidance does not include any *in vivo* bioequivalence standards.

If suitable standards are established and true bioequivalence and therapeutic equivalence criteria met, it is our understanding that the guidance is intended to indicate that a local delivery study conducted in seasonal allergic rhinitis would support approval of a Test product for all related indications e.g. perennial allergic rhinitis, pediatric age groups. The guidance must include true bioequivalence and therapeutic equivalence standards before such a determination can be made.

We concur that a 2-week treatment period is the minimum period of study for a comparability study with a corticosteroid. It is more important to include a second dose of the Test product in the study than the second dose of the Reference product.

Each sponsor, whether innovator or generic, should agree to a program of work for a comparability program *a priori* on a compound by compound basis. The guidance does not make it clear whether all three study types would be required to establish comparability or whether one model is preferred over the others for a particular class of compound. We consider that a Traditional Treatment Study would always be required as one component of such a clinical program.

1. Traditional treatment study

We do not believe a long placebo run-in is appropriate for the following reasons. The vehicle placebo has some therapeutic properties and has been shown to produce variable degrees of improvement as large as 35%. It is important to establish that patients have a suitable degree of symptomatology prior to being assigned to treatment, and a placebo run-in will underestimate the severity of the patient's symptoms. Furthermore, since patients are improved as a result of the vehicle placebo run-in, there will be less opportunity for improvement once patients are assigned to treatment. This will inappropriately underestimate the degree of improvement of the active drugs compared to the placebo and increase the likelihood that significant differences between treatments will not be observed, i.e., that they are comparable. Additionally, to address this risk, a post-treatment run-out without use of test article or placebo would establish that symptoms are still possible. Additionally it is not clear whether the study design proposed should include predosing the drug to support a prophylaxis claim, or only to treat patients who present with symptoms.

Use of the phrase "instantaneous" is unclear. Because of potential differences in time to onset and time to maximum effect, we believe that it is important that the products be comparable over the entire period of the study. We believe the primary endpoint should be based on mean scores over periods of time throughout the study period and not on a single diary card entry or physician assessment. It should be stated whether the end of the dosing interval result is intended to represent a single diary card entry or pooled data over several days or weeks of treatment. It will be difficult to generate onset, reflective and instantaneous data in a single study.

It is not clear whether it is considered that 12 lead ECGs are needed for all these studies or only for certain classes of compound e.g. antihistamines, which we would consider to be more appropriate.

2. Day(s) in the park study

This is not a sufficiently sensitive study method for establishing equivalence between Test and Reference products. The low level of symptomatology required to enter a Park study affects the outcome. Park studies can show differences between active and placebo, but are not sensitive enough to show differences between actives, thereby increasing the likelihood that significant differences between treatments will not be observed, i.e. that they are comparable.

3. Environmental exposure unit (EEU) study

The chamber studies have no clinical relevance to real life exposure and do not provide a sufficiently sensitive study method for establishing equivalence between Test and Reference products. While one- or two-day park or environmental exposure unit studies (Exposure Studies) may be a good source of supplemental data to support the onset of effect of a generic product, they do not address maximum effect, which can be different from product to product, and it will be important to establish this for generic nasal corticosteroids. Furthermore, Exposure Studies are limited by design to a small number of relatively mild allergic rhinitis patients, whereas traditional rhinitis studies used to gain approval for innovator products were conducted with larger numbers of moderate to severe rhinitis patients. Limited exposure to study drug and mild patient populations are likely to result in different drug profiles compared to those found in the innovator approved labeling, especially with respect to adverse events.

VII. BIOAVAILABILITY AND BIOEQUIVALENCE: PK SYSTEMIC EXPOSURE STUDIES

At present this section only addresses study designs for investigating comparability – no BE standards are provided. If it is possible to conduct a study with PK endpoints, it is recommended that relevant PD endpoints are included as secondary endpoints. In this example, the study should be powered to reflect the PK endpoint in order to improve study sensitivity. If a PD primary endpoint is more appropriate, the study should be powered to reflect the inherent variability of that endpoint. For example, if urinary cortisol was selected as a PD endpoint, a clinically relevant difference should be prospectively determined and the study powered on that basis. We note that the value of PD or safety-related endpoints was recognized during development of the guidance relating to albuterol MDIs, when tremor was noted to be a valuable indicator of systemic exposure during studies of the Gentlehaler.

We acknowledge the desirability of using plasma concentration-time profiles from BA and BE studies to evaluate systemic exposure for suspension drug products. In order to obtain measurable levels, it may be necessary to select multiples of the therapeutic doses. Some guidance on the appropriateness of this approach would be helpful. For example, it is accepted that several actuations in each nostril may be required to deliver systemically detectable levels. It would be helpful if FDA included advice regarding how many more sprays than the therapeutic dose are appropriate in order to satisfy "attempts to minimize loss of drug dose due to excess fluid drainage into the nasopharynx or externally from the nasal cavity" when the next draft of this guidance is circulated for comment.

Clearly, for a drug for which therapeutic doses yielded systemic levels that were around or just below the limit of quantification, determination of comparable systemic exposure would not be meaningful evidence upon which to make a determination of bioequivalence. Again, this section references statistical analyses that are not included in the guidance, which undermines the value of public comment at this time.

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

A. General Information

This guidance should include clear discussion of the relative standards for determination of comparability between formulations, and the bioequivalence standards that would permit substitution of one product for another. The methods described do not include sufficiently sensitive standards upon which to reach a determination of bioequivalence.

B. BE Study Endpoints for Corticosteroids

We believe that the most clinically relevant methodology for determining HPA axis function is currently a matter of debate (Correspondence in J. Allergy Clin. Immunol. between Lipworth and Vargas, 1999). Further studies are needed to define the most appropriate and clinically relevant test for this determination. When analyzing the results of HPA axis suppression associated with exogenous corticosteroids, it is important to take into consideration the clinical implications of the findings.

The safety of corticosteroid products and the interchangeability between innovator and generic formulation are paramount. Effects on urinary free cortisol or serum cortisols may not be a sufficiently sensitive measure of HPA axis function for the purpose of making a determination of bioequivalence or interchangeability, as evidenced by FDAs class labeling for inclusion in the Pediatric Use section of package inserts for intranasal corticosteroids i.e., "This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function". Additionally, if these pharmacodynamic measures are to be used as study endpoints, an adequate number of subjects should be enrolled to provide sufficient discriminatory power between treatments.

D. Clinical Study Designs and Subject Inclusion Criteria

We are not aware that these study designs have been validated as PD models of systemic exposure for patients with rhinitis. For BE to be established, pharmacodynamic endpoints must be clinically relevant and the length of the studies has to be sufficiently long to result in exogenous steroid exposure, should it exist. A crossover design is not suitable where the allergen load is not constant as in a seasonal situation. A crossover study will need to include extensive washout periods if onset of effect is a desired endpoint. Finally, crossover studies in people who are sensitized to allergen (season or challenge) in the first part of the study would be fraught with challenges due to the "priming" of the nasal mucosa and the potential protection from this by an active drug.

IX. STATISTICAL ANALYSES

A. *In Vitro* BA Data

We do not agree that "The overall means for the formulation should be averaged over all bottles or canisters, life stages and batches..." in order to document bioavailability. This is inconsistent with the companion CMC guidance.

We do not agree with looking at overall means for Content Uniformity. Content Uniformity should be evaluated using separate means at beginning-of-use, middle-of-use (aerosols) and end-of-use as it is important to compare the dosing profile from beginning to end. For Particle Size Distribution, individual stages should be evaluated, not groupings.

Considerable emphasis is being placed on the value of *in vitro* equivalence. It would be helpful if the next draft of this guidance included reference to the supportive data for these conclusions. We wish to confirm that this approach is based upon actual data.

The guidance does not clearly state how these noncomparative BA *in vitro* data analyses are intended for use during the review of these products. Both profile and nonprofile data are to be collected and reported - this may simply be intended to provide population means in order to assess the performance of the product – if so this should be explained.

B. *In Vitro* BE Data: Nonprofile Analyses Using a Confidence Interval Approach

Samples should be selected in a randomized fashion, consistent with that described on page 10 of the guidance.

The relationship between statistical determinations and specification limits should be explained in the next draft of this guidance.

A significant portion of section IX (B)(2)(b) was not made available to industry until August 16. There should be an opportunity for public comment on the values for average BE limit, variance terms offset, scaling variance and upper limit.

D. *In Vitro* BE Data: Profile Analyses Using a Confidence Interval Approach

A better explanation of the “average BE limit” is required.

We do not agree with looking at overall means for Cascade Impactor or Multi-Stage Liquid Impinger data for the purpose of making an *in vitro* bioequivalence determination.

E. *In Vivo* BE Data: Categorical Endpoints

This guidance should not be finalized until the proposed standards and endpoints to be included in this section have been released for public comment. Bioequivalency determinations should be based on the currently acceptable approach. The individual/population bioequivalence approach currently under discussion has generated much controversy and concern. It should only be considered after it has been accepted by the scientific community.

X. MULTIPLE STRENGTHS

A. Solution Formulation Nasal Sprays

All *in vitro* tests should be performed for low (indeed all) strength products.

B. Suspension Formulation Nasal Sprays

We do not agree that *in vivo* studies should be waived for documentation of BE of lower strength products. Each strength of product should be fully characterized and different strengths of these products should be assessed *in vivo*, and preferably within the study designs described in section IV.D. No assumptions can be made with respect to dose linearity or proportionality between different strengths of these suspensions, given the difficulties in differentiation of clinical effects (or systemic exposure) of different doses, as evidenced in the medical officer's review of Vancenase Double Strength, NDA 20-469 (Summary Basis of Approval, 1996, overview of efficacy, page 125: "...these studies were not able to differentiate a fourfold difference in dose exposure between active formulations...not considered adequate to determine equivalence of two formulations with the same total dose exposure"). We note also that the guidance in this section appears to contradict the statement on page 17 that "Doses may differ by two or fourfold".

XI. SMALLER CONTAINER SIZES

This section indicates that smaller container sizes should use the same "components". This implies that the same container should contain a smaller volume of product. This is unnecessarily restrictive, there may be several advantages associated with use of a smaller container, including increased convenience to the patient, improved stability from a smaller headspace and reduced environmental impact. The sentence beginning, "Smaller container sizes ... documented (ANDA)" in the first paragraph appears twice.

DECISION TREE

This decision tree is helpful, however each sponsor, whether innovator or generic, should agree to a program of work for a bioequivalence program *a priori* on a compound by compound basis. We recommend that the decision tree include a determination of Q1, Q2, matched container closure system, and clarification of the role of PD systemic exposure studies. The reference to "local delivery" should be clarified to represent "therapeutic equivalence".

GLOSSARY

Provision of a glossary of terms, especially relating to the statistical methods, e.g., profile data, non-profile data, would be helpful.

References

Lipworth B. Effect of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal axis. Correspondence in J Allergy Clin Immunol, March 1999; 537.

Vargas R. Reply. Correspondence in J Allergy Clin Immunol, March 1999; 537-8.

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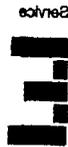
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