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# ITFG/IPAC Collaboration

## BA/BE Technical Team

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***Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting***

30 August 2000

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# I. EXECUTIVE SUMMARY

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In this paper, the BA/BE Team of the ITFG/IPAC Collaboration provides responses to the questions raised by the FDA during the 26 April 2000 OINDP Subcommittee meeting in regard to the draft Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (the draft BA/BE Guidance).

The ITFG/IPAC Collaboration encourages the Agency to solicit additional scientific discussion on BA/BE studies before issuing further guidance in this area. To resolve the outstanding issues expeditiously, the ITFG/IPAC Collaboration strongly recommends that the Agency pursue existing avenues for scientific collaboration between the Agency and outside interested parties, such as the Orally Inhaled and Nasal Drug Products Subcommittee (OINDP) of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), or another AAPS/FDA/USP workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery.

To support the efforts of the OINDP Subcommittee, the ITFG/IPAC Collaboration has prepared the enclosed paper summarizing the perspectives of its membership on the BA/BE questions presented by the Agency during the OINDP Subcommittee meeting.

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## II. BACKGROUND

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- Between October 1998 and June 1999, the FDA issued the following draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*; 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*; and 3) *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.
- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft Guidances for Orally Inhaled and Nasal Drug Products (OINDP).
- In October 1999, The Inhalation Technology Focus Group (ITFG) supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge and address key issues in the draft OINDP Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration. The BA/BE Team is formed to address BA/BE issues of OINDP.
- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.
- At the 26 April 2000 OINDP Subcommittee meeting, the BA/BE Technical Team of the ITFG/IPAC Collaboration reported that it has developed position statements on in vitro and in vivo testing in the FDA's draft BA/BE Guidance.
- During the 26 April meeting, the Agency presented several BA/BE questions to the OINDP Subcommittee. Many of these questions were left unanswered due to lack of available data.
- At the 26 April meeting, the BA/BE Team committed to providing the Agency and the OINDP Subcommittee with its perspectives on the BA/BE questions presented by the Agency during the OINDP Subcommittee meeting. This is the topic of the present paper.
- The Team also committed to provide the Agency and the OINDP Subcommittee a technical review of the in vitro and in vivo tests in the FDA's draft BA/BE Guidance. The companion paper addressing the Team's position statements on the in vitro and in vivo tests in the draft Guidance is being submitted to the Agency simultaneously with this paper.

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## **III. INTRODUCTION**

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### **A. Background on ITFG/IPAC Collaboration**

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease, rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes. The Inhalation Technology Focus Group (ITFG) of the AAPS is comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes. The ITFG and members of IPAC share common views on chemistry, manufacturing and controls (CMC) documentation and bioavailability (BA) and bioequivalence (BE) issues in the FDA's draft Guidances for orally inhaled and nasal drug products (OINDP) published in 1998-1999. ITFG and IPAC also share the Agency's goals of developing scientifically justified guidance for OINDP and making generic copies of these drug products available to patients in an expeditious manner, while maintaining appropriate standards of safety, efficacy and quality.

In October 1999, ITFG scientists and representatives of IPAC companies initiated the ITFG/IPAC Collaboration, a joint, data-driven scientific effort. The objective of the ITFG/IPAC Collaboration is to combine the scientific expertise, industrial experience and regulatory knowledge of both organizations to address specific CMC and BA/BE issues in a manner that most effectively contributes to the Agency's development of Orally Inhaled and Nasal Drug Products (OINDP) Guidance documents.

### **B. Agency Questions on the Draft BA/BE Guidance**

In October 1999, the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research at FDA created the Expert Panel on Orally Inhaled and Nasal Drug Products (later becoming the OINDP Subcommittee of the Pharmaceutical Sciences Advisory Committee) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft BA/BE and CMC Guidances. On 26 April 2000, the FDA held a meeting of the OINDP Subcommittee during which the Agency presented several BA/BE questions. The Subcommittee members and invited guests addressed these questions, but in many cases the participants could not provide any definitive answers to the Agency's questions at that time. Consequently, the BA/BE Technical Team offered to research and submit to the Agency and OINDP Subcommittee its responses to these questions. Conversations with Dr. W. Adams (Office of Generic Drugs) indicated Agency support for this undertaking. During the past several months, Team members have worked together to develop responses to the Agency's questions.

### **C. Assumptions of BA/BE Technical Team**

In preparing this paper, the BA/BE Technical Team used the following working assumptions:

- Our specific BA/BE recommendations apply to locally acting drugs per the current draft BA/BE Guidance for nasal aerosols and sprays, and should apply, as appropriate, to orally inhaled drug products in the anticipated forthcoming BA/BE Guidance for orally inhaled drugs;
- Our conclusions apply to both orally inhaled and nasal drug products, but these dosage forms should be treated in separate Guidances;
- Scientific and clinical bases for developing BA/BE Guidance are evolving; and
- Our BA/BE working propositions reflect only the current state of knowledge.

### **Reference**

*Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation; Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation; and Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.* These draft Guidances are available at <http://www.fda.gov/cder/guidance/index.htm>

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## IV. RESPONSES TO AGENCY'S IN VITRO BA/BE QUESTIONS

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### IN VITRO BA AND BE TESTING

#### A. Profile Analysis

#### QUESTION:

1. *Should all stages, including the inlet (throat) of the cascade impactor (CI) be considered in a comparison of test and reference products?*

#### ANSWER:

##### Summary of Position

Yes, in general, all stages, including the throat of the CI should be considered in a comparison of Test and Reference products having polydisperse particle size distributions in order to achieve a discriminating test.

##### Discussion

In general, all stages, including the throat of the CI should be considered in a comparison of Test and Reference products having polydisperse particle size distributions in order to achieve a discriminating test. The elimination of the mass collected by the throat in a comparative assessment will result in an underestimation of the coarse component of the dose that may vary significantly from the Test to the Reference formulation. It is important to quantify this coarser portion and determine information on its particle size distribution because even though coarser particles are unlikely to reach receptors in the lower respiratory tract, they will deposit in the oropharyngeal region (unless a spacer or holding chamber is used) and consequently may impact systemic absorption or potentially cause local adverse events. In cases where a pre-separator is used, the mass collected from the pre-separator should be grouped with that collected from the throat because these two components do not have sufficiently separate collection efficiency characteristics to be treated as isolated components.

If the Test and Reference products produce monodisperse aerosols, it is appropriate to consider only those stages on which analytically significant mass is collected.

The Team cautions that there are no published data that demonstrate unequivocally that combinations of CI stages can be reliably used to predict in vivo BA/BE.

## **QUESTION:**

- 2. *Should a statistical approach rather than a qualitative comparison be used for profile comparisons? If yes, does the chi-square comparative profile approach seem appropriate?***

### **Summary of Position**

Yes, a statistical approach should be used for particle size profile comparisons. The chi-square (multivariate) comparative approach may be appropriate for particle size comparisons; however, further assessment is needed to determine the discriminatory capabilities of the test. Further, the Guidance should define “equivalence limits” (*i.e.*, the extent to which two profiles can differ and still be considered equivalent).

### **Discussion**

Yes, a statistical approach, rather than a qualitative comparison, should be used for particle size profile comparisons. The chi-square (multivariate) comparative approach, currently proposed by the FDA (Tsong, 2000) may be appropriate for particle size comparisons; however, further assessment is needed to determine the power, sensitivity and discriminatory capabilities of the test. An issue that needs resolution involves the determination of the “equivalence limit” needed for a specific comparative profile assessment. This equivalence limit is dependent upon the number of impactor stages used, whether any stages are combined, and whether different weighting factors are used.

In order for the BA/BE Team or any interested party to perform an adequate assessment of this statistical test, further instruction in the Guidance is needed regarding the pre-specified equivalence limit for a particular impactor configuration. Adequate sets of actual data are needed to create large simulated data sets. The simulated data can be used not only for the determination of these equivalence limits, but also for evaluating the discriminatory capabilities of the chi-square comparative profile test.

It is recognized that in addition to the profile comparison, assessment of other univariate measures, such as total drug recovery, are also required to determine equivalence.

### **Reference**

Tsong, Yi, *Comparative Statistics for Assessing In-Vitro Equivalence Based on Profile Measures*. OINDP Advisory Subcommittee Meeting on FDA Guidance on Drug Products for Oral Inhalation and Nasal delivery, April 26, 2000 available at

<http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1e/index.htm>

## **B. In Vitro Tests for DPIs: Comparability**

### **QUESTION:**

- 1. Prior to doing in vivo studies to establish equivalence of a test DPI product, a firm would need to design its product to have the best likelihood of being found equivalent in these in vivo studies.**
  - a. What design features of the device and formulation and what parameters should be considered in determining pharmaceutical equivalence?**

### **ANSWER:**

#### **Summary of Position**

We agree with the Agency's views that in vitro testing of the following characteristics of a Test Product would be appropriate prerequisite for further characterization by in vivo studies. The factors that could influence the qualities of the delivered dose are complex, and not all are well understood at present. Accordingly, no sufficiently predictive or convincing in vitro/in vivo relationship has yet been demonstrated for products intended for local action. Nonetheless, we agree with the Agency's views that suitably demonstrated equivalence between a Reference and a Test DPI product in all categories should maximize the likelihood of being found equivalent by in vivo studies.

#### **Assumptions**

Two assumptions are implicit in the Agency's question. These are that:

- 1) a generic device can be developed and approved that is not identical to the original device (*i.e.*, not the same device), but can be made to be essentially the same, and
- 2) there are only three major aspects of the DPI system that need to be considered in assessing pharmaceutical equivalence:
  - the formulation;
  - the device elements; and
  - the chemical, physical and in-vitro characteristics that demonstrate the performance of the assembled system.

## **Discussion**

With regard to the **formulation**, the following features should be examined:

- inactive ingredients must be qualitatively (Q<sub>1</sub>) the same and quantitatively (Q<sub>2</sub>) essentially the same as the inactive ingredients in the Reference product;
- the proportion of active ingredient in the formulation relative to the inactive components must be essentially the same as the Reference product;
- the active ingredient should have essentially the same qualitative pattern of impurities, although a different pattern may be accepted depending on toxicological assessment. These impurities should be restricted by specifications to the same degree as the Reference product;
- the active ingredient should have the same physical characteristics with respect to:
  - solvate or hydrate form;
  - crystalline and morp hic form;
  - particle size distribution;
  - surface topology; and
  - surface charge;
- the excipient materials should have the same physical characteristics with respect to:
  - crystalline and morp hic form;
  - particle size distribution;
  - moisture sorption profile;
  - surface topology; and
  - surface energy, surface charge, or force of adhesion between the active ingredient and excipient;
- if the active ingredients and excipient materials undergo special processing to form a stable secondary structure (*e.g.*, agglomerates), these should have the same physical characteristics with respect to:
  - particle size distribution;
  - moisture sorption profile;
  - surface topology; and
  - surface charge.

With regard to the **device**, the following design features should be examined:

- the dimensions of the device, especially the primary air passageways, should be essentially the same;
- the materials of construction should be similar with regard to chemical, physical and engineering properties such as:

- thermal expansion coefficient;
  - response to thermal stress;
  - propensity to accumulate or dissipate static charge;
  - extent to which moisture sorption or relative humidity affect static charging;
  - adhesion forces between formulation and surfaces other than those related to static charging;
  - suitability for contact with the oral mucosa;
  - suitability for contact with the product formulation (where there is direct contact); and
  - stability against deterioration or corrosion during the intended life of the device;
- the air flow path should be identical or demonstrated to be functionally equivalent in flow resistance and dispersive energy imparted by the passing air stream. If the Test device is not dimensionally equivalent, the demonstration of functional equivalence should include a comparative analysis of curves for flow resistance and dispersive energy throughout a dynamic airflow range consistent with the inhalation capabilities of the patient population using the device;
  - the design and mechanism for metering the dose of medication should be the same. The reliability of the metering mechanism should be demonstrated:
    - for the labeled number of metered doses to be delivered by the device during its expected use period (especially for the case where a drug containing reservoir can be replaced in the device when exhausted); and
    - in response to normal handling including minor, accidental stresses, *e.g.*, drop, vibration; and
  - the design and reliability of features for protecting the formulated powder from chemical, physical or microbiological compromise should be adequately demonstrated.

**QUESTION:**

- b. What comparative in vitro tests should be conducted to help support bioequivalence?***

**ANSWER:**

**Summary of Position**

The following comparative in vitro tests should be conducted to help support BA/BE. The draft BA/BE Guidance should specify those aspects of any of these tests that are considered to be critical for proper execution and interpretation. For example, it

may not be sufficient to show equivalent performance under one test condition, but over a range reflecting clinical usage.

### **Discussion**

Comparative in-vitro tests should be conducted to demonstrate equivalence in **performance** features that affect the efficacy of the pharmaceutical agent and the safety profile of the delivery system. These features have been mentioned in the response to Part a of the question and can be summarized as follows:

- delivered dose amount;
- delivered dose uniformity;
- aerodynamic particle size distribution of the delivered dose;
- aerodynamic particle size distribution of the carrier or excipient materials;
- microbiological burden in the powder formulation;
- chemical, physical and microbiological stability of the contained formulation;
- chemical and physical composition of the device, including extractive materials;
- plume characteristics, kinetics of plume formation and kinetics of dispersing the formulated powder to the desired particle size distribution across a physiologically relevant range of airflows and environmentally realistic range of temperatures and humidities; and
- reliability of the device throughout the defined use period.

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## V. RESPONSES TO AGENCY'S IN VIVO BA/BE QUESTIONS

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### IN VIVO BA AND BE TESTING

#### A. Clinical Studies for Local Delivery of Nasal Aerosols and Sprays

##### QUESTIONS:

1. *Three study designs have been proposed in the draft guidance for drugs intended to have local action; traditional treatment study; day(s) in the park study, and environmental exposure unit study. These study designs are based on seasonal allergic rhinitis (SAR).*

*Is it feasible to demonstrate a dose-response for locally acting nasal drugs? If not, what other approaches can be relied upon to establish equivalent local delivery?*

##### ANSWER:

#### Summary of Position

At present, the studies proposed in the draft BA/BE Guidance for nasal aerosols and nasal sprays describe studies that are useful for determining the comparability of products. However, their value for establishing clinical equivalence and substitutability is unproven. The traditional treatment study offers the most appropriate study design for assessing nasal drug products intended for local delivery. There is a need for the draft Guidance to further develop the statistical requirements for this study if it is to be used for equivalence testing. However, given the utility of this study design, it is not adequate to confidently establish dose-response relationships for locally acting nasal drugs nor is there an alternative method that can be relied upon to establish equivalent local delivery.

#### Assumptions

Prior to clinical testing, the test and reference intranasal drug products have met all the in vitro equivalence criteria that are specified in the draft BA/BE Guidance for nasal drug products intended for local delivery and comply with the defined Q1, Q2 and container-closure system standards. Clinical studies are intended to assess local efficacy and systemic safety.

## **Discussion**

We agree with the points made by Dr. Roman at the April 26, 2000 OINDP Subcommittee meeting about the relative merits of the Traditional Treatment study for measuring dose-response compared with the other proposed models (Roman 2000). The traditional treatment study offers the best model for establishing efficacy of corticosteroids in a real world situation using well established endpoints and methodology which is reproducible at many investigational locations. Weaknesses of the traditional study design include its dependence on seasons and measurable placebo effect. We concur that a 2-week treatment period is the minimum period of study to establish comparability between two intranasal corticosteroid products but do not believe the design is adequate to establish BA/BE between locally acting nasal drug products (Test and Reference) of this kind. There is a need to develop the draft Guidance further to address statistical power in the context of an equivalence-based Traditional Treatment study that would provide assurance that comparisons between the Reference and Test product would demonstrate similar responses to treatment.

We suggest that the results of a Days-In-The-Park study or environmental exposure unit study may provide additional valuable information to allow comparisons between products during the first few days of therapy. It would be appropriate for the draft BA/BE Guidance to discuss this utility for these study designs.

The draft BA/BE Guidance has much in common with the replacement approach described in the Points to Consider: Clinical Development Programs for MDI and DPI drug products, September 19, 1994; Points to Consider: Clinical Development Programs For New Nasal Spray Formulations, January 23, 1996; and draft Guidance for Industry - Allergic Rhinitis: Clinical Development Programs for Drug Products, April 2000, which specifically address changes to formulations and/or devices, and most specifically the switch from CFC to HFA or dry powder products. The draft BA/BE Guidance should include more specific advice regarding the appropriate SAR clinical protocols or cross-reference the Guidance relating to studies in allergic rhinitis.

The draft BA/BE Guidance must include statistical standards for tests that have the sensitivity to establish equivalence and discriminate between Test and Reference products intended to deliver the active moiety locally (21 CFR 320.24 (b)(3) and (4)). For inhaled products, it is widely accepted that the appropriate way to demonstrate the suitability of the clinical test to determine local delivery bioequivalence is to show a dose-response relationship, at least for the Reference product. The draft Guidance must address the issue of substitutability and not confuse this with comparability.

We are not aware of the existence of a validated pharmacodynamic effect bioassay that can be used to establish a dose-response relationship between delivered dose and effect. In studies of recently approved corticosteroids for intranasal use, comparisons of the consistency of effect and degree of improvement in the first few days of therapy have proved useful in developing an appropriate dose regimen even when differences between doses could not be separated by more conventional approaches (Meltzer *et al*, 1990, Medical Review in SBA for Nasonex, 1997). The approach to collection and presentation of data, and selection of primary and secondary endpoints described in draft Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000) may be an appropriate model for

differentiating between several doses of Test/Reference product in a 2 week clinical study using endpoint comparisons of time to maximum effect, end of dosing interval (snapshot before next dose), and onset of action, as well as the mean change from baseline for the patient-rated total nasal symptom score over the entire double-blind period. Replication or substantiation of these results in either an Environmental Exposure Unit or Days-In-The-Park study may be appropriate. The products should be equivalent at all pre-defined timepoints. The standards used to establish statistical equivalence must have been shown to be of some clinical relevance.

We support inclusion of at least two doses of the Reference and Test product in the dose-ranging study, and at least one of these doses should be representative of the currently approved dosage regimen for the Reference product.

It is our view that the Traditional Treatment study for establishing equivalence between Test and Reference product offers the best model for investigating and establishing appropriate standards for bioequivalence between intranasal corticosteroids. This study design does have some limitations and further work is needed to prove the usefulness of this study design for BE purposes. After demonstrating in vitro equivalence and systemic equivalence via a pharmacokinetic study and HPA axis suppression study of appropriate design and sensitivity, a clinical study (Traditional Treatment) with two doses of each product (including the recommended dose for the Reference product) is likely to fulfil the need for a study of local delivery, providing statistical standards that have the sensitivity to establish equivalence and discriminate between Test and Reference products can be devised.

## **References**

- Roman I, Clinical Studies for Local Delivery of Nasal Aerosols and Sprays, available at <http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1s/index.htm> (2000).
- Points to Consider: Clinical Development Programs for MDI and DPI drug products, September 19, 1994, FDA.
- Points to Consider: Clinical Development Programs For New Nasal Spray Formulations, January 23, 1996, FDA.
- Draft Guidance for Industry - Allergic Rhinitis: Clinical Development Programs for Drug Products, April 2000, FDA. 21 CFR 320.24 (b)(3) and (4).
- Meltzer, EO, Orgel HA, Bronsky EA *et al.* A dose-ranging study of fluticasone propionate aqueous nasal spray for seasonal allergic rhinitis assessed by symptoms, rhinomanometry, and nasal cytology. *J. Allergy Clin Immunology* 1990;86: 221-230.
- Summary Basis of Approval (Nasonex Nasal Spray, NDA 20-762). Medical Officers Review. 1997: 60-64.

## QUESTION:

2. ***Can bioequivalence established based on SAR assure bioequivalence for other indications such as recurrence of nasal polyps, or other non-SAR conditions?***

## ANSWER:

### **Summary of Position**

A pre-existing indication for PAR, PNAR or nasal polyps at the same dose should be transferable from the Reference product to the Test product if the Q1, Q2 and container-closure standards are met and bioequivalent performance in terms of efficacy, onset of effect, duration of action, systemic and local safety have been clearly demonstrated in SAR. In order to transfer a pre-existing indication for use in children from Reference to Test product, care should be taken to ensure that the studies conducted to assess systemic safety are predictive of all potential patient subgroups.

### **Assumptions**

Prior to clinical testing, the Test and Reference intranasal drug products have met all of the in vitro equivalence criteria specified in the draft BA/BE Guidance and comply with the defined Q1, Q2 and container-closure system standards. Clinical studies are intended to assess local efficacy and systemic safety.

### **Discussion Case 1: Adult Patients**

If suitable standards are established and bioequivalence criteria met, it is our understanding that the draft Guidance is intended to indicate that a local delivery study conducted in SAR would support approval of a Test product for all related indications. In our opinion, demonstration of equivalent efficacy (within defined standards) in a SAR model would be transferable to a perennial allergic (PAR) or perennial nonallergic rhinitis (PNAR) indication, if these indications are already approved for the Reference product at the same dosage regimen as proven for SAR. As acknowledged in the draft Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000), SAR and PAR are closely related indications.

We believe that transfer of previously approved other non-SAR indications (nasal polyps) to a new strength of an Innovator product has been permitted by FDA in prior actions (SBA for Vancenase AQ 84mcg, 1995). A comparison of the onset of effect of the two formulations appears to have played an important role in this determination. Based on this precedent, in the absence of data, we support the transfer of other previously approved non-SAR indications (nasal polyps) to a Test product showing local delivery bioequivalence in SAR.

## **Discussion Case 2: Pediatric Patients**

Recent studies with intranasal and inhaled corticosteroids examining pediatric growth have led to concerns that traditional measures of HPA axis function were not sufficiently predictive of this aspect of safety in the pediatric patient subgroup. This is evidenced in the FDA class labeling required for the Pediatric Use section of package inserts for intranasal corticosteroids *i.e.*, “*This effect [on growth] 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*”.

As the draft Guidance already states, studies of local delivery will not be sufficient to establish BE for these products – studies of systemic safety are required. Therefore we propose that the revised Guidance address the relative merits of various approaches to assessing systemic safety in the context of their predictive power for different patient subgroups, particularly children. This will serve to address the particular situation for intranasal and inhaled corticosteroids. For example, timed serum cortisol assessments or 12-24 hour urinary cortisol measurements, if carefully conducted, may be sufficiently sensitive and predictive of systemic equivalence. These tests of systemic safety will be required before a Test product can be considered equivalent to a Reference product in pediatric patients, regardless of whether a long-term growth study has previously been conducted with the Reference product, to ensure that the systemic exposure is equivalent from Test and Reference product in this potentially vulnerable patient subgroup.

## **References**

Summary Basis of Approval (Vancenase AQ 84mcg, NDA 20-469) Medical Officers Review. 1995: 53.

Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products, available at <http://www.fda.gov/cder/news/cs-label.htm>

## **B. Clinical Studies for Local Delivery of Orally Inhaled Corticosteroids (ICS)**

### **QUESTION:**

- 1. A number of approaches have been proposed to assess bioequivalence of ICS (e.g., clinical trials, bronchoprovocation tests, steroid reduction model, trials with surrogate measures such as exhaled nitric oxide (eNO), etc.**

**Are any of these study designs proven to offer better discrimination in terms of dose-response sensitivity?**

- 2. What other in vivo approaches (e.g., surrogate markers) might be sufficiently sensitive and validated to establish in vivo BA and BE for inhaled corticosteroids?**

### **ANSWER:**

#### **Summary of Position**

To assess the local delivery bioequivalence of two oral inhalation corticosteroid products, the comparative dose-response trial with pulmonary function measurements as the primary analysis parameters remains the method of choice.

However, variability is large, and metrics sensitive enough for establishing local delivery bioequivalence with trial designs that are practical from both a subject number and length of study perspective are not yet available. Further, although desirable, no alternative design has been sufficiently validated that will meet this need. One exciting possibility that may offer both a more sensitive method and a simpler clinical study for inhaled corticosteroids is the cross-over design suggested by Ahrens at the April 26 OINDP Subcommittee meeting. We recognize that this concept must be appropriately tested in the clinic and hope that sufficient funds can be found to permit this analysis in the near future.

#### **Assumptions**

Prior to clinical testing, the test and reference ICS drug products have met all the in vitro equivalence criteria that are specified in the draft BA/BE Guidance for nasal drug products intended for local delivery. The recommended dose range, dosage regimen, and available strengths of the Reference product should be taken into account in selecting the doses to be studied. It is assumed that at least a four-fold dose range is included in the dosing recommendations of the reference product to allow an adequate dose-response study to be conducted. If multiple strengths of Reference product are available, interchangeability should be established for each corresponding strength.

#### **Discussion**

Inhaled corticosteroids have a broad spectrum of therapeutic effects in asthma. They affect smooth muscle as well as the recruitment and release of many inflammatory

mediators in both circulating and structural cells within the airways. The likelihood of finding pharmacological markers that reflect a certain aspect of the inflammation is therefore potentially large. However, the methodology to assess these markers is not standardized or validated. The surrogate marker should ideally be an objective measurement, which is causally and statistically associated with the clinical outcome. The marker should be specific, validated, practical, proximal to the disease outcome and should show little variability.

It is widely accepted that the appropriate way to demonstrate the suitability of the clinical test to determine local delivery bioequivalence of an ICS is to show a dose-response relationship, at least for the Reference product. While it has been possible to demonstrate the response of a number of potential surrogate markers to changes in the asthmatic condition, it has only been possible in a few cases to demonstrate a dose-response relationship with any of the markers. One potential surrogate marker that has attracted much attention is exhaled nitric oxide. The scientific understanding of the role of exhaled nitric oxide in asthma is still being defined and it would be premature to pursue the use of this marker as a bioequivalence surrogate at this time. The situation is confounded by conflicting reports about the sensitivity of this marker to predict asthma (Marshall *et al.*, 2000; Hunt *et al.*, 2000; Deykin *et al.*, 2000; Henriksen *et al.*, 2000; Silvestri *et al.*, 2000; Lim *et al.*, 2000; Jatakanon *et al.*, 2000).

Cell counts in BAL or sputum have also been examined as surrogate markers. One of the most promising cell count markers is that of eosinophils. Relationships have been found between eosinophil count and lung function in asthmatics (Lim *et al.*, 2000; Jatakanon *et al.*, 2000; Pizzichini *et al.*, 1996; Louis *et al.*, 2000). Eosinophil counts in sputum have been found to be reproducible and to be sensitive to corticosteroids in the majority of patients (Louis *et al.* 2000; Hargreave 1998). Thus far, research has focused on the suitability of eosinophil counts to predict asthma severity. Information is limited on the sensitivity of this marker to differentiate two different formulations for a given corticosteroid by frequent sputum sampling, or even to demonstrate a dose-response for a given product. Additionally, the influence of different technicians and laboratory procedures on the precision of this method should not be discounted.

So far, no surrogate marker has yet been shown to be able to replace the accepted pulmonary function measures of the standard comparative clinical trial. Some researchers have attempted to use pulmonary function measures, but to modify the clinical trial design for increased sensitivity and/or simplicity. Standardization of pulmonary function equipment is also important. Success has been reported for designs that use the inhibition of the allergen-induced late asthmatic response or the increase in histamine or methacholine airway responsiveness (Wong *et al.*, 1992; Cockcroft and Murdock, 1987; Krann *et al.*, 1988). An apparently sensitive but complex study design which required over 300 patients was able to differentiate between CFC and HFA formulations of beclomethasone dipropionate, but with a large confidence interval that would not have been acceptable for traditional bioequivalence testing (Busse *et al.*, 1999).

Regardless of the study design, it has proven exceedingly difficult to draw conclusions about the comparative efficacy between different formulations for a given inhaled corticosteroid. The primary reasons for this are poor dose-response relationships and lack of control over confounding factors.

An additional area of uncertainty is the choice of patient for a bioequivalence trial. It is recognized that the patient selection criteria are extremely important factors in the study. What severity of asthma should be tested? Should patients be steroid dependent or not? Does previous treatment confound the readout or does it aid, as in step down trials? Bronchial hyperreactivity must be tested in hyperreactive patients – if some enrolled patients happen to be non-reactive, will the results be inconclusive? Is it enough to select stable symptomatic patients, or does one need to provoke asthma by allergen challenge or cold air to amplify readout? If allergen provocation is selected as the model, are effects on late reaction satisfactory or is a dual reaction (*i.e.*, early and late) desirable? Are the two products fulfilling the criteria for local delivery bioequivalence in adult asthmatics also equivalent in terms of local delivery for other patient populations, such as children? Resolution of these questions is not possible without further discussion between the Agency and outside groups.

With the current state of understanding, it is premature for the Agency to suggest methods other than the standard comparative clinical dose-response trial for local delivery bioequivalence testing. A flexible position on patient selection criteria is also warranted.

The BA/BE Team strongly recommends that the Agency foster research on local delivery bioequivalence testing of inhaled corticosteroids through an appropriate forum (*e.g.*, PQRI, academic research grants, etc.). The crossover study design suggested by Ahrens during the April 26 OINDP Subcommittee meeting is particularly promising and should be tested in the clinic. Other approaches that should be considered include a classic comparative parallel-group dose-response (Busse *et al.*, 1999) or dose-reduction (Gibson *et al.*, 1992, Agertoft *et al.*, 1993, Agertoft *et al.*, 1997, Selroos *et al.*, 1994) design. Dose response studies may need to include a dose range in a ratio of at least 4:1 or 8:1 to have any chance of providing adequate data to support BE.

Given the current state of the art, another and more radical approach would be a stand-alone documentation of dose-response coupled with traditional equivalence testing of *in vitro* performance and systemic PK/PD. This approach would give the sponsor, the Agency and the prescribing physician the greatest benefits in terms of patient safety and development cost, and least risks in terms of failures of not living up to dubious local delivery BE criteria. It would also reflect the prevailing dosing recommendations for inhaled glucocorticoids, where individual dose titration to the lowest effective dose is an important feature.

The Agency should also consider appropriate metrics to determine local delivery bioequivalence. The BA/BE Team urges the Agency to consider several procedures that have recently been suggested, including the Finney Bioassay (Busse *et al.*, 1999) and testing for therapeutic equivalence (Källén *et al.*, 2000). The traditional confidence interval approach with predetermined acceptance limits may need to be reconsidered, given the large variability and poor dose response observed with inhaled glucocorticoid. However, with refinement of the method, the traditional approach could offer valuable data of clinical significance in determining the appropriate standards for BE.

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## C. PK or PD Studies for Systemic Exposure of Locally Acting Drugs

### QUESTION:

***Are there situations where in vitro data plus systemic PK and systemic PD data can be relied on to assure local drug delivery for either nasal or inhaled drugs?***

### ANSWER:

#### **Summary of Position**

Yes, there could be situations where in vitro data plus systemic PK and systemic PD data may be relied upon to assure BE of two products of the same formulation for nasal and/or inhaled drugs. If a predictive in vitro/in vivo correlation can be documented from the literature or from experimental clinical data, the sponsor should have the opportunity to discuss the possibility of waiving clinical studies with the Agency. At present this is not the case for intranasal or inhaled corticosteroids. Post-approval changes to manufacture of approved Reference or approved Test products may not require extensive testing, but such changes are outside the scope of this draft Guidance.

#### **Assumptions**

The two formulations that are being compared for bioequivalence meet *all* the in vitro criteria that have been proposed in the draft BA/BE Guidance for nasal products: Q1 the same; Q2 essentially the same; container and closure system essentially the same; equivalence using a confidence interval approach (nonprofile analysis) for dose or spray content uniformity through container life, droplet size distribution, spray pattern, and priming and/or repriming when this information is specified in the reference product labeling; equivalence using a confidence interval approach (profile analysis) for particle size distribution data (cascade impactor or multistage liquid impinger); comparative data for plume geometry, tail off profile, priming data when reference product labeling does not specify priming information, and drug count median diameter and drug and aggregate particle size distribution data from microscopic analyses.

#### **Discussion Case 1: Need to Establish Bioequivalence for Formulation Changes with the Same Manufacturer**

In the new drug development process and at submission of an NDA, a battery of in vitro studies is undertaken. These studies are described in the Chemistry, Manufacturing and Controls section of the NDA. This battery of information will later serve as a database for the product specifications, against which all subsequent production batches will be compared prior to sale and against which changes in the manufacturing process can be evaluated.

There are many in vitro parameters that go into making a finished product and each company develops an in vitro test history of their product throughout all the development stages. If these variables do not change in production, then adequate

reassurance of product quality can be obtained from these in vitro tests because of the established in vitro test history. Also if small changes are made in the manufacturing process or manufacturing site of the same finished product, such that only a few variables are changed, then the established in vitro test history of the product is still adequate to assure maintenance of the product's quality, safety and efficacy after evaluation of the changes.

The large number of in vitro tests that are used to characterize the product development are impractical for routine production batch release. From historical and scientific data, several tests are selected for batch release. Tests that are thought to best assure the consistency of the in vitro properties of the drug formulation are carefully chosen from the evaluation of the overall manufacturing process through the final drug product. The NDA process should fully characterize the in vitro performance of the product and this may permit links to be established between the in vitro tests and the in vivo PK/PD and clinical safety and efficacy properties of the drug product.

Any changes in the formulation or in the production process will always require an evaluation of how the change will affect the clinical outcome, and what kind of analyses are required to ascertain that the clinical performance of the product will still be the same. The necessary undertakings will vary relative to the importance of the performed change. A sliding scale may be appropriate. At one end of the scale is a minor change that can be handled as a technical note and, thus, no in vitro and no in vivo investigations need to be done. At the other end of the scale is a major change in formulation (outside defined Q1, Q2 and container-closure system limits) and/or in the manufacturing process where in vivo PK/PD and clinical studies, as well as in vitro testing, need to be performed.

Situations where an in-vitro analysis, complemented with systemic PK and PD studies, to ascertain that the clinical performance of a modified product will not be affected can, thus, occur.

### **Discussion Case 2: Need to Establish Bioequivalence for Formulations from Different Manufacturers**

When a different manufacturer makes a similar formulation (as outlined in the Assumptions), no links between the in vitro test history, in vivo PK/PD results, and clinical properties are available. In such cases, the need for and scope of clinical trials have to be determined based on whether a predictive correlation has been documented between the results of in vitro tests and PK/PD studies and clinical outcomes.

Rather than having the Agency prepare specific guidances that could anticipate all the possible testing scenarios, discussions on when the clinical testing program can be abbreviated are best left to the sponsor and the Agency. It is appropriate that the sponsor be given the opportunity to present the strongest case for an abbreviated clinical program. If a predictive in vitro/in vivo correlation can be documented from the literature or from experimental clinical data, the sponsor should even have the opportunity to request waiving all clinical studies.

## **Discussion Analysis**

To address the difficulty of determining appropriate in vitro and in vivo standards for establishing bioequivalence between Test and Reference products, the draft bioequivalence Guidance for nasal and oral inhalation products for local delivery should recommend in vitro testing and in vivo PK/PD and clinical performance documentation for all drug products in this category. However, the Guidance should further recommend that the sponsor and the Agency establish a dialogue to determine if and how the clinical program can be modified or waived, *e.g.*, if a predictive in vitro/in vivo correlation can be documented. It is anticipated that there could be situations where only PK/PD testing will fulfill the clinical bioequivalence requirement. At present this is not the case for intranasal or inhaled corticosteroids. Post-approval changes to manufacture of approved Reference or approved Test products may not require extensive testing, but such changes are outside the scope of this draft Guidance.

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## **VI. CONCLUSION**

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The questions posed by the FDA on the draft BA/BE Guidance have underscored a number of open issues. The accompanying paper prepared by the BA/BE Technical Team of the ITFG/IPAC Collaboration highlight even more issues in need of resolution. It seems reasonable to conclude that more scientific discussion is needed on the appropriate BA/BE requirements for OINDP.

The BA/BE Team encourages the FDA to speedily utilize one or more of the options that the Agency has available to help resolve these issues in a prompt manner. The Product Quality Research Institute (PQRI) may be a good vehicle to bring the FDA and other interested parties together to discuss these issues, as well as to conduct new research studies. Consultation with the OINDP Subcommittee or the Advisory Committee for Pharmaceutical Science may also be helpful. Federal grants may be suitable means to foster research on any one of these key issues, while an AAPS/FDA/USP workshop may provide for broad industry and academic discussion of the issues. The ITFG/IPAC Collaboration encourages the Agency to utilize existing avenues for further scientific collaboration and consideration of key BA/BE issues. We hope that the Agency is receptive to our comments and continues to dialogue with the public.