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## Comments

on a draft Guidance for Industry  
Bioavailability and Bioequivalence Studies for Nasal Aerosols  
and Nasal Sprays for Local Action  
(Docket Number 99D-1738)

Submitted by  
IVAX Corporation

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99D-1738

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## **Introduction:**

IVAX Corporation develops proprietary and generic pharmaceutical products for marketing throughout the world. IVAX is primarily composed of Baker Norton Pharmaceuticals, Zenith Goldline Pharmaceuticals and Norton Healthcare Ltd. One area of our research and development involves the delivery of locally active drugs in nasal aerosols and nasal sprays.

We appreciate the opportunity to comment on this draft guidance. We have organized our comments into a technical section (for *in vitro* testing) and a clinical section.

## **Technical**

Section III. A. - Formulation: With regard to the following requirement: "Comparative information on the morphic form of the drug particles, and size and number of drug aggregates in the dosage form should be provided. In addition, documentation of the same anhydrous or solvate form should be provided." Much of this data may not be possible to determine, especially for nasal sprays, due to the large quantity of particulate excipients which may be present, thus making isolation of the drug substance difficult.

Section III. B. - Container Closure System: This section suggests that nasal actuators for comparative products should be similar in dimension and design. We argue that if the same dose, particle size distribution etc. are achieved for the finished product, then the actuator design is incidental. It would not be uncommon for a company to patent their actuator design, thus making direct comparison impossible without infringing on a patent. Reference is also made to comparability of orifice size. However, this will be dependent on the formulation characteristics. Different formulations may require different orifice sizes to achieve a comparative droplet distribution. We contend that the dose, particle size distribution, etc. are the important parameters to demonstrate equivalence.

Section V. B. - Tests and Metrics: This section suggests that automated actuation stations are recommended for all comparative *in vitro* BE tests to decrease variability and should be done in a blinded manner. The requirement for automated equipment requires extensive considerable capital investment and blinding may be difficult unless the actuators are identical in every way including color. We believe that well trained analysts, following predetermined procedures and test methods are capable of producing reliable independent results.

The apparatus suggested for unit spray content is the USP Unit Spray apparatus. This is appropriate for nasal aerosols (non-aqueous based formulations) but may not be appropriate for aqueous sprays which do not provide the same inherent pressure to dispel the contents into the apparatus. Also due to the angle of spray of most nasal actuators (i.e. upward) there would likely be drain back problems during testing.

In the subsection on droplet size testing, the application of CI or MSLI to measure drug particles size distribution needs to be assessed. As nasal product are designed to be retained in the nasal cavity following administration, a true indication of drug particle size distribution will not be obtained by firing the dose into an impactor unless a specially designed "nose" attachment is used in place of the USP "throat". For nasal sprays it is likely that the fine drug particles will be deposited with the bulk of the liquid medium in the upper stages of the impactor, thus not giving a true representation of the drug particle size distribution in the formulation. For pressurized nasal aerosols the local nasal action is provide by physical constraints (i.e. the spray deposits in the nose by impaction before it has a chance to be swept down the lungs by air flow). In a MI or MSLI this constraint will not exist and thus a typical MDI distribution profile may result. This will give a true indication of the drug particle size distribution but will not be indicative of the behavior of the product in the nasal cavity. Also the orientation of the impactor needs to be considered relative to the angle of discharge of the nasal aerosol spray.

In the light microscopy subsection, we do not believe that light microscopy will provide any useful information in either a solution product, due to recrystallization of large crystalline drug particles from the co-solvent or a nasal sprays due to particulate excipients from which the drug particles are indistinguishable.

In relation to spray pattern we also question the comparability between the behavior of a spray in totally unconfined airspace area to one that is sprayed into a small area (the nasal cavity) constrained in almost every dimension.

## CLINICAL

It is our contention that if the test and the reference products for nasal aerosols and sprays for local action are of equivalent formulation and have similar *in vitro* characteristics, then very limited, if any, *in vivo* studies should be performed.

Nasal formulations for local action, solutions or suspensions, are mostly retained in the nasal cavities upon administration (Newman, 1987; Newman, 1994; Schwab, 1998). It is generally considered that particles with aerodynamic diameters above 3 microns will be retained in the nose and only those below 3 microns will continue to the lower respiratory tract or be exhaled. Between 78% (Newman, 1987) and >95% (Newman, 1995) of the dose delivered into the nose is retained in the nasal passages depending on particle size distribution. Particle deposition efficiency in the nasal cavities is directly related to the logarithm of the impaction parameter. The impaction parameter is a function of particle size, particle density and respiratory flow (Yu, 1981). In addition, nasal deposition can be calculated for particle diameters of up to 100 microns (NCRP Report 125, 1997).

The nose is a very efficient aerosol filter, capable of removing respirable and non-respirable droplets from the inhaled air (Newman, 1994). It has also been suggested that aqueous spray formulations are better distributed and penetrate more in the nasal passages (i.e. greater nasal retention) than propellant driven aerosols (Thorsson, 1999). Once the drug settles in the nose, ciliary beating of the nasal mucosa moves the drug to the nasopharynx to be swallowed. The part of the dose that passes through the nasal passages without impacting the mucosa, contains the smallest particles which seems to be exhaled since very little is found in the lungs (Newman, 1995; Newman, 1994).

From the information available in the literature it seems appropriate to accept that the clinical efficacy of a locally administered nasal product will be therapeutically equivalent to a reference product if the *in vitro* characteristics are considered equivalent, be that for a solution or suspension formulation. Dose response is very difficult to demonstrate. The important clinical difference might be in the systemic bioavailability of the drug, which in turn affects the safety profile of the drug (Wilson, 1998). Since different formulations of the same active substance may have different systemic bioavailabilities (Thorsson, 1999), this approach is appropriate only for generic copies of a reference product. For drugs like steroids, where their systemic bioavailability may have an important effect on other organs and systems, the best way to evaluate their systemic safety is by determining the pharmacokinetics of the test product at the highest recommended dose and/or the effects on the HPA axis after nasal administration and compare it with those of the reference product.

Our proposal is then: first to demonstrate the *in vitro* equivalence of a generic test drug and the reference product. If this is demonstrated and the PK characteristics of the reference drug warrants it (i.e. low first pass metabolism with high bioavailability and potential for systemic adverse events), perform a PK study at the highest recommended dose including the effects on a pharmacodynamic marker (i.e. HPA axis) comparing the generic test product with the reference product. If the pharmacokinetics of the generic test drug and the reference product is different (a difference of >20% based on 90% confidence interval), further clinical work may be needed. On the other hand if the *in vitro* equivalence is demonstrated and the reference product has no or minimal systemic bioavailability, no further clinical work is necessary with the generic test product.

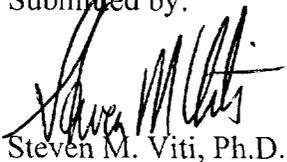
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## CONCLUSIONS

We thank the Agency for giving us the opportunity to comment on this important guidance. Technically, we agree it is important that several parameters of delivery must be equivalent between the test and reference products. However, if these parameters are equivalent, then it should not be necessary for the test and reference products to be chemically and physically identical. On the clinical front we believe that no *in vivo* work is necessary when *in vitro* equivalence has been demonstrated for a generic test drug and its reference product.

Submitted by:



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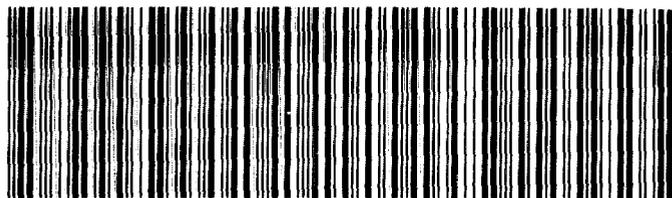
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