IPAC-RS

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July 25, 2003

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BY COURIER

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

Re: IPAC-RS Comments to Docket No. 99D-1738

Dear Sir or Madam:

Please find enclosed two originals and one copy of the comments of The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) on the FDA Draft *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,* dated April 2003 (Docket No. 99D-1738). Please file the original copies and time/date stamp the photocopy and return it to the messenger.

We greatly appreciate the Agency's flexibility in allowing us extra time to review and comment on this Draft Guidance (as discussed via email on July 1, 2003 with Dr. Wallace Adams, Office of Pharmaceutical Science, CDER/FDA).

Thank you for your consideration.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi
IPAC-RS Legal Counsel and Secretariat

Enclosure
99D-1738

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IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation and Science

IPAC-RS COMMENTS

on the 2003 Draft Guidance for Industry
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

(FDA Docket No. 99D-1738)

24 July 2003

I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) is an association of companies that research, develop and manufacture aerosol drug products for oral inhalation or intranasal delivery. The importance of these drug products is growing with the expanding range of conditions they are used to treat, including asthma, chronic obstructive pulmonary disease (COPD), rhinitis, migraine, diabetes and others.

Current members of IPAC-RS are: Aradigm, AstraZeneca, Aventis, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, IVAX, Kos Pharmaceuticals, Nektar Therapeutics, Novartis, Pfizer, and Schering-Plough Corporation. IPAC-RS companies and the Food and Drug Administration (FDA) share a common goal: to meet the medical needs of patients in a timely manner by facilitating the arrival of new drug products to the market while maintaining scientifically justified standards of safety, efficacy and quality.

IPAC-RS commends the Agency for developing further and re-issuing for public comment the Draft Guidance for Industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. IPAC-RS appreciates the opportunity to offer the following comments on the Draft Guidance.

II. GENERAL COMMENTS

- We commend the Agency for the continuing effort to develop a scientifically-based and balanced approach to establishing bioavailability (BA) and bioequivalence (BE) of nasal therapies for local action. We particularly applaud the authors of the Draft Guidance for taking into consideration many of the public comments on the previous draft. We believe, however, that there still exist several key areas of the Draft Guidance that would benefit from further clarification or revision.

- The statistical information still under development comprises material information for BA and BE determinations. The import of the current Draft Guidance may change dramatically depending on the statistical approaches and criteria proposed by the Agency. We therefore strongly recommend that prior to the finalization of this Draft Guidance, the statistical appendices be issued as a draft with sufficient period for public consideration and comment. A public workshop on these issues may also be beneficial.

- We are encouraged by the Agency's recognition of the challenges in demonstrating equivalence of nasal sprays and aerosols for local action. We note, however, that over-reliance on the proposed in vitro tests, in the absence of their established predictive ability or in-vivo/in-vitro correlations, may lead, on the one hand, to undue hyper-sensitivity to differences between Test and Reference that are not clinically important, and on the other hand, to insufficient discrimination of differences that may potentially be important to the patients.

III. SPECIFIC COMMENTS

- We strongly support use of PK studies to assess systemic absorption, even when only a partial PK profile can be obtained. The Draft Guidance should mention that the most sensitive methodology should be used (sections II.A.2 and VII.A). A recommendation on the threshold for determining whether PK studies are feasible should be added. The PK study should be done with a dose no higher than the maximum approved dose.

- The particle size distribution of the drug substance, for suspension products, should be equivalent rather than *"comparable"* to that of the Reference (line 199).

- We agree that using *"the same brand and model of devices"* is the best way to assure equivalence (section III.B, lines 216-218).

- The requirement to submit "all raw data" (line 413) and also "20% percent of total observations" (line 423) seems contradictory and unnecessarily burdensome.

- The testing of drug content should be done on the minimum labeled dose (*e.g.*, on two actuations if the dose is one actuation per nostril) rather than on a single actuation as described in section V.B.1 entitled, "Single Actuation Content (SAC) Through Container Life."

  Furthermore, the requirement that *"the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-115 percent of the label claim"* (lines 843-845) is prohibitively strict, especially in light of the CMC quality requirement on the mean dose (85-115 percent of the label claim).

  We strongly recommend that the requirements for this new test be revised.

- Section V.B.2 presents recommendations for Droplet Size Distribution (DSD) data collection and reporting. We note that due to the variability of DSD laser diffraction measurements, the requirement for accuracy may be problematic and the value of single-sweep (line 499) or single-spray (line 512) data is questionable. The purpose of determining DSD at two life stages and at two distances is unclear.

- Section V.B.3.a explains that the purpose of cascade impaction (CI) testing of nasal sprays is *"to determine the amount of drug in small particles/droplets"* that *"may potentially be delivered to regions of the airways beyond the nose."* Using CI to achieve this goal, however, seems hardly necessary. The percentage of small droplets/particles could be determined from laser diffraction as part of DSD measurements. Moreover, the interpretation and consequently the value of CI results for nasal sprays is doubtful because of such factors as airflow, evaporation effects, design, sensitivity, *etc.*

- Section V.B.3.b recommends CI testing of nasal aerosols using an induction port *"that maximizes drug deposition below the top stage of the CI,"* such as a one-liter induction port. This configuration, however, has little resemblance to the geometry

of the nasal cavity, and the Draft Guidance should acknowledge that the CI data is NOT relevant for safety evaluations.

- The draft guidance should clarify the scientific reasoning behind the particular requirements recommended for plume geometry (lines 809-814) and priming/repriming (lines 843-845).

- In Section VI.C, the Draft Guidance recommends that seasonal allergic rhinitis be used as the indication for the clinical test of local delivery. We suggest that the Draft Guidance recognize that perennial allergic rhinitis could be a more appropriate model in some situations.

- The Draft Guidance may consider including *onset of action, time to maximal effect* and *duration of effect* (as defined in the April 2000 Draft Guidance *"Allergic Rhinitis: Clinical Development Programs for Drug Products"*) among the parameters of interest in clinical BE studies. These endpoints are likely to be important to patients and may show differences between Test and Reference.

- It is not clear why the efficacy analysis and equivalence analysis should be performed on different populations (Section VI.C), or why compliance with the study protocol should be part of the efficacy assessment (Section VIII.A). In general, the adequacy of the recommended PK, PD and BE studies is difficult to assess without the appendices.

- Especially in cases where the Draft Guidance recommends approaches that differ from past and established practices, it would be helpful if the text explained the rationale for such recommendations (*e.g.*, rationale for not using percent change from baseline (lines 990-992), or for not correcting the urinary free cortisol for creatinine (line 1197)).

- In keeping with the recommendation to use most sensitive methods, the Draft Guidance should make it clear that serum cortisol is a preferred PD measure (line 1186). The PD study should be done with a dose no higher than the maximum approved dose.

- A clear delineation of requirements for BA, BE and comparability should be added to the Draft Guidance.

- A glossary of key and new terms and abbreviations would be helpful.

IV. CONCLUSION

We thank the Agency for the development of this Draft Guidance and the opportunity to comment on the materials made available so far. We look forward to the issuance of draft statistical appendices and the public discussion of scientific approaches they will include.