June 20, 2003

Via Fax and UPS

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

Re: Docket No. 99D-1738
Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action; 68 FR 16292 (April 3, 2003)

Dear Sir/Madam:

Aventis Pharmaceuticals is pleased to provide the following comments on the above-referenced draft guidance for industry entitled, *" Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action "*. This draft document provides recommendations to applicants planning product quality studies to document bioavailability (BA) or bioequivalence (BE) in support of new drug applications (NDAs), or abbreviated new drug applications (ANDAs) for locally acting drugs in nasal aerosols (metered-dose inhalers) and nasal sprays (metered-dose spray pumps).

Page 9 line 323
When three batches are studied, we recommend the batches be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch.

We believe that confusion is created by the addition of the second sentence indicating that the container (canister or bottle) can be from the same batch, whilst the previous sentence indicates that it is preferable to use different batches of drug, substance, critical excipients, and different container closure components. By stating 'preferable' it seems to permit the manufacturer the option of using the same batch of drug substance. Examples of situations when this could or could not apply would be useful to add to the text.

99D-1738 C19

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We have the following suggestion:

When three batches are studied, we recommend the batches be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. Where the same batch of drug, critical excipients or container or closure is used to manufacture the product batches, justification for use of the same batches should be provided.

Page 9 line 327

We prefer that the three batches be studied at the same time, if possible, to remove interstudy variation from the estimation of between batch means and variances.

We suggest that there are practical difficulties in studying these batches at the same time, as the time frame between manufacture of the pivotal clinical batch, primary stability batch and a production batch can be considerable and clearly testing would have been required with the first batch manufactured. If the methodology is validated this should ensure that interstudy variation is at an acceptably low level for batch comparative purposes.

Page 10 line 343

The recommended number of canisters or bottles of each batch to be used in the above studies, and recommendations for statistical analyses, are described in Appendix B.

We cannot comment on Appendix B as not yet available

Page 10 line 368

The recommended number of canisters or bottles of each product and batch to be used in the above studies, and recommended statistical approaches, are described in Appendices C, D and E.

We cannot comment on Appendixes C, D, and E as not yet available

Page 11 line 395

Actuation should be conducted in a manner that removes potential operator bias, either by employing automatic actuation, or by employing blinded procedures when manual actuation is used. However, we recommend automated actuation systems for all comparative in vitro BE tests.

We agree that the actuation should be conducted in a manner to remove operator bias, however we do not believe that blinding or automatic actuation are always required and that consistent data can be obtained by analyst alternatives.

Does the automatic actuation include any container shaking that is required or just the actuation?

Any automated system will have to be proven not to create it's bias on the product performance, especially through life and be similar to that achieved by an analyst. Similarly, blinding will

require unnecessary work (a third party to conduct the blinding, validation of blinding etc) for analytical work that can be conducted 'open'. Analytical sample randomization is useful to avoid analytical bias. Additionally, it may be useful for the analyst to know what the sample is during the analysis to enable decisions to be made on the quality of the analysis being performed and not to have to wait for the code to be 'opened'. This is an analytical study not a clinical study, where blinding is critical.

We suggest:

Actuation of the device should be conducted in a manner that removes potential operator bias. Container shaking and or automatic actuation employing blinded procedures, or when manual actuation is used, may be applied when operator bias is shown to be a problem.

Page 12 line 421

Supporting documentation for Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry would include representative copies, preferably electronic, of 20 percent of the total observations. For Spray Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic images rather than paper copies of 20 percent of the total observations would be submitted, as electronic files are definitive.

The provision of such a large amount of representative data is, we believe, unnecessary, and may be difficult to provide electronically, as the FDA would require the particular instrumental software to open the data. Further, there is no reason to consider electronic images more definitive than official paper copies of the data, unless you are referring to the raw data.

We suggest that representative sets of data are provided as paper copies (5%) and that the electronic and raw data are reviewed, as required, as part of a pre-approval inspection.

Lines 423, 425, 619, 1331, and 1342

There are typographical markings that obscure the text on printed copies of the guidance

Page 12 line 432

For noncomparative data, SAC through container life testing is used to characterize the delivery of drug discharged from the actuator of an aerosol or nasal spray relative to label claim through container life.

If, for example, a product delivers two actuations (minimum) to provide a label claim dose, then this test could be amended to take the two actuations as the unit assay through life to reflect the dose the patient receives. The product would then not require the single actuation through life assay.

We suggest:

For noncomparative data, SAC through container life testing is used to characterize the delivery of drug discharged from the actuator of an aerosol or nasal spray relative to label claim through container life. Where two actuations represent a dose, then two actuations can be combined to provide through life data.

Page 12 line 444

Because the data at beginning (B) lifestage will also be used for confirmation of priming (Section V.B.7), SAC through container life would be based on single actuation data per determination.

The requirement for Single Actuation Content is to base this analysis on single actuation data per determination. This may not be feasible for all products.

Page 13 line 457

Therefore, for aerosols, the test would be performed at such time that the product meets two conditions: (1) after the lagering period and (2) not less than one month after the last actuation conducted as part of batch release testing.

Could the term 'lagering' period be explained as this term is not commonly understood or an alternative used?

We do not understand the rationale for the testing after a minimum of a month storage after batch release testing. If this is to reflect a typical 'in-use' period (removal of primary packaging) then the guidance should make this clear and specific to the 'in-use' period of the product that may be more or less than one month.

We suggest:

Therefore, for aerosols, the test would be performed at such time that the product meets two conditions: (1) after the lagering period and (2) after a duration of room temperature storage that is not less than the in-use life period of the canister after the last actuation has been conducted as part of batch release testing.

Page 14 line 518

For increased ability to detect potential differences between products, it is recommended that the studies be performed within a range of 2 to 7 cm from the orifice, with the two distances separated by 3 cm or more.

We recommend setting standard distances for the study. It would be more appropriate for guidance purposes to use a set distance (i.e. 2.5 cm and 6 cm) and therefore make the test more uniform across users.

Page 16 line 587
In Agency experience, a two-liter or larger induction port (expansion chamber) is preferred to a one-liter chamber.

Can the agency add the supply source, material and dimensions of this induction port, as it is not a common induction port purchased with standard cascade impactors. Please provide information on how the induction port is interfaced with the impactor and nasal spray and provide references to the use of this induction port and the effect that it has on the retention of particles across the particle size range of interest. Given the large volume and possible flow rate of an impactor (28.3 l/min) what is the consequence on the time needed to pass air through the impactor, i.e. to ensure the large induction port has been properly sampled in to the impactor?

Page 16 line 594
The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.

This specification range for the label claim is not consistent with the specification approach being progressed for inhalation aerosols through the PQRI activity, which the FDA is active in.

We suggest that a mass balance value is not required as it is possible to have low as well as high deliveries on occasions, and that the data is equally valid. By eliminating data one, is providing a bias database. A consistent specification approach is required for these types of products.

Page 16 line 605
CI studies for nasal aerosols would use an induction port (expansion chamber) that maximizes drug deposition below the top stage of the CI. For this reason, a one-liter induction port is preferred to the USP 25 (<601>) induction port, although other sizes may also be appropriate.

Similar comments apply as for the 2-liter induction port. Additionally, it is expected that a 1-liter induction port would provide an environment where the amount of small particles is under-estimated due to the evaporation processes and retention time in the large volume. Therefore, the particles are captured in the induction port and are not drawn into the impactor.

Page 17 line 657
These data are supportive, and formal statistical testing is not applicable.

We suggest that more guidance is given on approaches that are preferred when reporting the results and what parameters should be included (e.g. longest axis length only, size ranges).

Page 30 line 1218
The Agency has determined that in lieu of the five-times-quantity requirement, the quantity of inhalant (nasal aerosol or nasal spray) test article (T) and reference standard (R) retained for testing and analyses be at least 50 units for each batch. For NDAs, three batches are needed for BA studies.

'R' is referred to as 'reference standard', whereas in line 54 'R' is formally defined as reference product. Apply a consistent definition to this abbreviation.

Page 31 line 1244

Recommendations are also provided for cases in which BA or BE is initially established on the low-strength product. No approved nasal aerosols are available in multiple strengths, thus BA and BE recommendations are not considered for these products.

In the event that multiple strength nasal aerosol products are approved, it is recommended to revise this sentence to clarify that BA/BE recommendations are not considered for multiple strength nasal aerosol products "at this time".

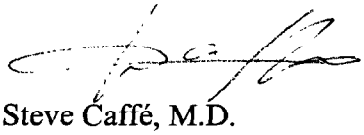
Page 36

Table 1. Recommended in vitro studies for BA and BE of Nasal Aerosols and Nasal Sprays

In the microscopy section please define the abbreviation CMD.

On behalf of Aventis Pharmaceuticals, we appreciate the opportunity to comment on the *Draft Guidance for Industry entitled " Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action"* and thank you for your consideration.

Sincerely,



Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs