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August 23, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room I-23
Rockville, MD 20857

RE: Docket #99D-1738
Draft Guidance for Industry'
Bioavailability and Bioequivalence Studies for Nasal Aerosols
and Nasal Sprays for Local Action

To Whom It May Concern:

Apotex Corp. has reviewed the above-listed draft guidance and proposes the following list of comments for your consideration.

Section II.A.2 Systemic Exposure and Systemic Absorption BA/BE Concepts

Page 4: The schematic representation referred to at the end of the first paragraph is on page 32 rather than page 35.

Section V.A.2 ANDAs

Page 8: It is difficult to obtain three lots of the brand product. Therefore, we would like to suggest testing only 2 batches of the brand.

Section V.B Test and Metrics

Page 10: The first sentence on page 10 should refer to Table 1 on page 33 rather than page 35.

Section V.B.I Dose or Spray Content Uniformity Through Container Life

Page 10: The guidance proposes using a stability indicating chemical assay for content uniformity. This is appropriate for suspension formulations. However, for a solution formulation a gravimetric approach should be able to be used instead, knowing the density of the product and the assay of the fill contents of the container.

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Page 11: At the end of this section there is a reference to section IX.A.1. This should be section IX.B.1.

Section V.B.2b Droplet and Drug Particle Size Distribution (PSD) – Instrumental Methods

Laser Diffraction, Page 12: FDA is requesting non-aerodynamic droplet size measurements of nasal solutions and suspensions by laser diffraction at the beginning, middle, and end of the plume (3 measurements per actuation), at three distinct distances from the **container** orifice and **at** multiple times throughout the container life (beginning, middle, and end). Given the anatomy of the nose (limited volume and distance from actuator to nasal cavity surface), we propose testing only 2 distances from the orifice and 2 different stages of the plume (2 measurements per actuation) when comparing droplet size between products.

Section V.B.3 Spray Pattern

Page 14: Once again, we propose that **two** distances from the actuator to the target would be acceptable, given the anatomy of the nose and the limited distances involved.

Based on our data, variability on the ratio of D_{max} / D_{min} is not high, but variability on either D_{max} or D_{min} is higher. Therefore, we would recommend performing confidence interval computations only on the ratio.

Section V.B.4 Plume Geometry

Page 15: We question the need for plume geometry measurements on solution formulations and would **recommend** performing plume geometry testing only on suspensions.

For suspensions, we question the need for 180 photographs each of test and reference (3 lots, 10 containers per lot, **2 angles** per measurement, 3 times throughout **actuation**). We propose this be reduced **significantly**, especially since this **is** supportive **data**.

Section V.B.6 Tail Off Profile

Page 18: We question the need for this study, as patients should not use the **products** after the end of the labeled number of actuations. Nevertheless, we propose **that the** criterion be that the test product should not be **significantly** more erratic **than the** reference.

Section VI.D. Clinical BE Study Designs and Subject Inclusion Criteria

Page 17: It is reasonable to try to obtain a dose-response 'relationship. However, what if such a relationship can not be established for a particular drug substance?

Section VII., Bioavailability and Bioequivalence: PK Systemic Exposure Studies

Page 19: If we aren't able to show equivalence of pharmacokinetic profiles due to poor absorption of the drug or analytical limitations, when can we switch to a PD assessment? In other words, at what point can we declare that a PK approach isn't feasible?

We would recommend that the ratio of means, not the confidence interval, be required to be within 80-125% for PK studies assessed using average BE.

Section VIII.D Clinical Study Designs and Subject Inclusion Criteria

Page 21: For some drugs, 14 days of dosing may not be necessary. The length of the study should depend on the potency of the drug on the suppression of the HPA axis.

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

Page 22: In section IX.B (statistical analysis), when evaluating laser diffraction and spray pattern data obtained from three distances from the actuator, should these results be averaged over distance or analyzed separately?

Page 23: In section IX.B.2.a, the term $(\mu_T - \mu_R)^2$ in the population BE criterion could penalize the test product even if its mean dose or spray content is closer to the 100% label claim.

Page 25: In section IX.B.2.c, "Variance Terms Offset!", the proposed variance terms offset of 0.0 is too stringent for variables such as D_{max} , D_{min} , and D_{50} . Even the proposal of 0.01 may still be too hard to meet.

Section IX.C In Vitro BE Data: Supportive Nonprofile and Profile Analyses

Page 26: The reference to IX.A.1 in the last sentence of this section should be IX.B.1.

Section X.A Solution Formulation Nasal Sprays

Page 29: We propose that in-vitro testing of lower strength solutions should not be required unless the surface tension is very different from the higher strength product (the product tested for in vitro equivalence).

Appendix A

There is no recommendation of what N should be and how different combinations of triplets should be selected. Depending on the choices, different results of calculation will be obtained. This means that one can potentially try to obtain a more favorable result by playing around with their choices: If N is to be fixed at 500 as indicated in Appendix B, one may ask if it is necessary to do 10 units from 3 lots. As shown in Appendix A, there are over millions of possible combinations with 10 units from 3 lots.

General

We believe that the requirements are too extensive for a solution formulation. The requirement of at least 30 units (10 from each of three batches) for each of the test and reference products is substantive, especially for spray pattern and particle size distribution.

Moreover, the clinical relevance of the in-vitro data is not clearly explained. In-vitro data can be overly discriminating between two products that are equivalent in-vivo. The in-vitro differences may not be clinically relevant.

We appreciate the opportunity to comment on this draft guidance.

Sincerely,



LuAnn Erlich, Ph.D.
Director
Pharmaceutical & Computer Services

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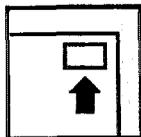
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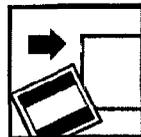
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