AstraZeneca

4242 '03 JUL -3 A6:19

Date: JUL 01 2003

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

Re: Docket Number 99D-1738, CDER 2002168
Response to FDA Call for Comments
Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

Dear Sir or Madam:

Reference is made to the April 3, 2003 Federal Register notice announcing the request for comments on Docket No. 99D-1738, CDER 2002168. Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Gregory Taylor, Regulatory Project Associate, at (302) 886-1216.

Sincerely,

Barry Sickels, Executive Director
Regulatory Affairs
Telephone: (302) 886-2895
Fax: (302) 886-2822

Enclosure

99D-1738 C21

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Docket No. 99D-1738, CDER 2002168. Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

General Comments

- Comment 1

  To base the entire BE approval of any nasal solution product solely upon in vitro criteria is flawed unless there is sufficient in vivo correlation to establish the predictability and objectivity of the tests. Clinical relevance of the proposed in vitro tests for nasal products has not been established.

- Comment 2

  Method validation is mentioned extensively in this draft guideline. We believe that method validation pertains to the general analytical procedures guideline and should not be included in this guidance. We are especially concerned about the indirect request for accuracy in the validation as there is no current way to assess this currently in Droplet Size Distribution measurements.

- Comment 3

  VIII. PD or Clinical studies for systemic absorption: In this section, a design for assessment of HPA axis function is outlined, with a recommendation to include prednisone as an active control as well as a placebo arm. Suggested treatment time is 6 weeks followed by thorough HPA axis measurements. There are several challenges associated with this design. First, few patients would be willing to be treated for 6 weeks with prednisone if they do not need this treatment. On the other hand, if they do require prednisone treatment, they probably have more severe disease and it would not be ethical to treat them with placebo for 6 weeks. Finally, few if any prednisone manufacturers provide placebo tablets, which complicates blinding of the study. If placebo tablets cannot be sourced, but placebo to the test drug can, a reasonable compromise could be to run the prednisone arm unblinded as a shorter [1 week?] treatment course. Alternatively, an independent party (FDA) could be assigned to evaluate a safer active control (BDP?), that is, a dose and treatment duration that generates an appropriate response, and where the availability of placebo can be guaranteed.

Detailed Comments

Section	Page or Line Number	Comment or proposed replacement text
III A	197-202	The terminology used in this section when referring to the nature of the solid state (morphic, hydrous and solvate form, state of solvation) is ambiguous. We suggest the following terms be defined: solid-state composition (anhydrate, hydrate or solvate?); arrangement of drug molecule in solid state (amorphous, crystalline, polymorphic form?); morphology (drug particle shape and size distribution in suspension?). These parameters should provide sufficient information as to guarantee control of the rate of dissolution, which we assume to be the major concern here. Please note that analysis of the first two parameters could require removal of suspension media, which may alter both composition and crystalline arrangement.
III B	216-224	Nasal spray pumps (i.e. actuator/pump) from different suppliers differ considerably in spray characteristics even if the metering chamber volumes and orifice dimensions are the same. This is due to differences in the design of the pump and actuator. It will be necessary to use the same brand and model of device to show equivalence. The statement that the pump and actuator design shall be as close as possible is not relevant and should be deleted.
V B	395-397 400-402	Blinding is often not feasible and it complicates the test protocols. These types of issues are also taken care of in the validation of the methods and are more a general GMP issue.
V B	397-400	As the automated actuation is recommended in all in vitro tests, the text concerning automated actuation should not be placed as a footnote, but rather it should be included in the 'main text'.
V B 2a	479-480	Delete "in flight". Laser diffraction is not based on a prerequisite that the droplets are in flight.
V B 2a	499	*'the data of a single scan (sweep) only at the maximum obscuration (or minimum percent T)'*. It is a great risk to present the DSD data this way. The obscuration may not always be directly proportional to the droplet size. Results may vary a lot. An average over several sweeps is recommended.
V B 2a V B 5c	518 – 521 748 - 751	For both Droplet Size Distribution and Spray pattern it is recommended to analyze at two different distances from the nasal spray tip. To evaluate at one distance should be enough. The validation of the method should be done at several distances to justify the distance selected.
V B 3a	569 - 601	The percentage of small droplets (potentially respirable) in the spray is estimated in the determination of the Droplet Size Distribution. This value is typically very low for nasal sprays. Additional impactor measurements would appear to be redundant testing. Furthermore, it can be very hard to do relevant CI tests on nasal sprays because of

Section	Page or Line Number	Comment or proposed replacement text
		several factors such as evaporation, airflow through CI, design of induction port, and assay problems because of low dose in CI.
V B 3b	602-629	The use of a one-liter induction port for aerosols has no general scientific support nor has it any clinical similarities to the human nasal cavity. We suggest therefore that the impactor is equipped with an inlet with a similar volume to the nasal cavity.
VII. A.	1081-1083	Sentence unclear and should be changed to "If a sponsor has convincing data based on unsuccessful attempts to conduct the PK study, a PD or clinical study for systemic absorption could be used in lieu of the PK study."
VIII. A.	1164-1189	This paragraph contains several specific design details, which more logically belongs to VIII.C (Clinical BE study designs and subject inclusion criteria). See above for comment on the active control design.
VIII. A.	1191	Section A and C provide specific design recommendations, in spite of the fact that the sentence on row 1191 says it does not.
VIII. C.	1222	Sampling frequency has not been suggested. Is every 4 hours acceptable?
X. B	1362	If a generic company develops different strength products, in vivo studies should be performed – otherwise the recommendation under IIIA, line 265-267 is unfounded, since a generic batch hardly can be identical in terms of micronization parameters and PSD.