CLAY-PARK LABS, INC.

AGIS GROUP

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September 22, 1999

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

Re: DOCKET NUMBER 99D-1738

Dear Sir or Madam:

Enclosed, please find Clay-Park Labs, Inc./ Agis' comments on draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" June 1999, docket # 99D-1738.

Should you have any questions, please call the undersigned as follows:

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Sincerely,

Candis Edwards
Director of Regulatory Affairs

CC: Amit Lahav, VP, CSO

Encl:

99D-1738

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CLAY-PARK LABS, INC./ AGIS COMMENTS
TO

GUIDANCE FOR INDUSTRY

"BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR NASAL AEROSOLS AND NASAL SPRAYS FOR LOCAL ACTION"

JUNE 1999

DOCKET NO. 99D-1738

CLAY-PARK LABS, INC./ AGIS COMMENTS ON THE DRAFT GUIDANCE

Comment # 1

Guidance Reference: Entire Guidance

In general, it seems that the intent of the draft guidance is to fulfill the FDA's needs for information gathering in order to establish a database on the behavior of nasal dosage forms. It seems that it is expected by the agency that the industry should perform all of the experimental work and present it to the agency, not for product approval purposes, but for information gathering purposes. It is strongly recommended that the FDA re-draft this guidance, indicating exactly what they are expecting from industry, and leave it up to industry to develop the appropriate methodologies in order to generate the required information to establish BA and BE.

Comment # 2

Guidance Reference: Pages 3-4, Section II A 1
Background

If PSD of the active drug substance can be determined using scientifically sound, validated methodology, then in vitro comparative bioequivalence testing should be acceptable for suspension nasal spray products.

Comment # 3

Guidance Reference: Page 4, Section II A 1
Background

In vitro studies alone should be sufficient for establishing bioequivalence of both solution and suspension nasal spray products which are Q_1 and Q_2 and meet the requirements of Section III b for container and closure system for the following reasons:

1. In vitro methods are less variable, easier to control and validate, and more likely to detect differences (more selective) between products if they exist.
2. Clinical end points may be highly variable and relatively insensitive in detecting differences between products.
3. The clinical relevance of these tests is not a key factor since this is a comparative study of a product to a clinically approved drug product.

Comment # 4

Guidance Reference: Page 6, Section IV B
Documentation of Bioavailability and Bioequivalence

The requirement of Q_1 and Q_2 for nasal spray suspensions is not warranted, since the guidance recommends that clinical comparisons be conducted on the test and reference products. The clinical comparisons should be the determining factor for bioequivalence, not the formulation constituents.

Comment # 5

Guidance Reference: Pages 6-7, Section IV B 1-3
Documentation of Bioavailability and Bioequivalence

It is not clear what the fate is of an ANDA, for which the in vivo studies fail but the in vitro studies are successful.

Comment # 6

Guidance Reference: Page 7, Section IV B 2-3
Documentation of Bioavailability and Bioequivalence
Section VII
Bioavailability and Bioequivalence: PK Systemic Exposure Studies
Section VIII
Bioavailability and Bioequivalence: Pharmacodynamic or Clinical Studies for Systemic Absorption

With regard to the requirement for evaluation of safety parameters related to systemic absorption, this should be measured within the context of a well designed, controlled clinical BE study and not in separate clinical studies.

Comment # 7

Guidance Reference: Page 9, Section V A 2
Bioavailability and Bioequivalence: In vitro Studies

FDA's recommendation for in-vitro bioequivalence data on three (3) lots of the RLD is excessive. FDA, with one exception, never asked for three lots. Lot to lot variability is controlled by cGMP, and should not be included as a factor in a bioequivalence study.

Comment # 8

Guidance Reference: Page 9, Section V A 2
Bioavailability and Bioequivalence: In vitro Studies

For a solution dosage form, testing of three sublots of single manufactured lot of test product and 3 lots of reference products should not be made a general requirement. A chance of reduced testing should be given to a company that:

1. Manufactures an ANDA solution dosage form for nasal spray.
2. Has a tight control over its device components under the CMC section.
3. Uses population BE criteria to its constant scaled form for the statistical analysis of BE data.

In such a situation, if the company wants to test one lot of test vs. one lot of brand, the company increases its own chances of proving non bioequivalent. However, as the company assumes that the reference product has no variability, it reduces the risk to the consumer, which is the ultimate goal of the agency. Besides reduced risk to consumer, small companies with less investment power will have equal chances to develop an equally effective generic product.

Comment # 9

Guidance Reference: Page 10, Section V B
Bioavailability and Bioequivalence: In vitro Studies

Requirement for blinding of in-vitro samples should not be required. Since most of the actuation is done automatically, there is no chance of bias in the results.

Comment # 10

Guidance Reference: Page 10, Section V B 1
Bioavailability and Bioequivalence: In vitro Studies

A stability indicating method for determination of mass (assay), priming, and tail-off should not be required. An UV test should be sufficient for these purposes, or even sample weight (emitted dose) may be sufficient for solutions.

Comment # 11

Guidance Reference: Page 12, Section V B 2 b
Bioavailability and Bioequivalence: In vitro Studies

The number of measurements required for droplet size determination would be approximately 8100 based on the minimum requirements of the guidance (6 lots [3 RLD, 3 Test] x 10 units per lot x 3 delay times x 3 distances x 3 life stages [beg, mid, end of product life] x 5 replicates per measurement). This is excessive. A more acceptable approach to evaluating the droplet size distribution would be to conduct experiments during method development and validation to determine optimum distance, optimum delay time, and test precision. Additionally, experiments show that most of the variability within a container is at the beginning and end of use life of product, therefore comparison may not be necessary at the middle life stage. Appropriate method optimization would allow for the collection of more meaningful data and would eliminate the collection of unnecessary repetitive data.

Comment # 12

Guidance Reference: Page 13, Section V B 2 b
Bioavailability and Bioequivalence: In vitro Studies

The guidance recommends that laser diffraction measurement for Droplet Size Distribution (DSD) should include statistical comparisons based on D50 and Span [Span = (D90 – D10)/D50]. D90 is the most variable value in the DSD profile, with % RSDs as high as 100 in some cases. Therefore meaningful statistical comparisons based on Span will need a sample size much larger than the sample size required for a meaningful statistical evaluation of D50. Since D50 is a true determinant of DSD, similar to average mean and geometric mean in other statistical comparisons, statistical evaluation of DSD for bioequivalence should be based on evaluation of D50, whereas D10 and D90 data should be provided for information only.

Comment # 13

Guidance Reference: Page 15, Section V B 5
Bioavailability and Bioequivalence: In vitro Studies

Assessment of priming during bioequivalence should be compared to label claim of the RLD. It should not be the responsibility of the sponsor to evaluate the innovator product with respect to their label requirements. Additionally, head to head comparison between test and reference product does not guarantee that the label claim requirements will be met.

Comment # 14

Guidance Reference: Page 16, Section V B 5
Bioavailability and Bioequivalence: In vitro Studies

The amount of work required to measure the emitted dose prior to completion of priming is prohibitive (300 assays for priming and 1500 assays for repriming excluding standards and check standards), and has no relevance to bioequivalence. A more appropriate way to obtain this information would be to collect data during method development and validation.

Comment # 15

Guidance Reference: Page 16, Section V B 6
Bioavailability and Bioequivalence: In vitro Studies

Tail Off Profile: If the product is engineered to deliver 200 doses, then any actuation beyond that is not "Bio" anymore. The argument that the patient has no means of counting is irrelevant to BA or BE.

Just for comparison, such a set of tests (by weight of by chemical assay) of the 205, 210, 215, 220, 225 and 230 actuation should be enough. Any testing beyond that is totally meaningless as part of BE.

Comment # 16

Guidance Reference: Page 17, Section VI D
Bioavailability and Bioequivalence: Clinical Studies for Local Delivery

The clinical BE study should not include a dose response study, since this is not required for other BE studies with clinical endpoints for ANDAs.

Comment # 17

Guidance Reference: Pages 16-19, Section VI
Bioavailability and Bioequivalence: Clinical Studies for Local Delivery

Different studies with a clinical end point that tried to establish BE in corticosteroids nasal suspensions failed to do so.[1, 2, 3, 4, 5] The inadequacy of such studies to establish BE is also implied by the FDA's reluctance to accept a clinical trial as the only measurement of BE.

It therefore seems highly unfair to submit generic products to a test that cannot be passed and that is not required from the ethical companies.

The guidance itself states two contradicting statements, "...Although BE and BA studies with clinical end-point are sometimes incapable of showing a dose response relationship and may not be consistently reproducible..." (Section VI A). On the other hand the guidance asks for "A BE study with a clinical end-point to establish equivalent local delivery of drug from test and reference products to the nose should document sensitivity of the study to discriminate between differing doses (i.e. show a dose response relationship)" (Section VI D).

These two statements contradict each other as far as corticosteroids nasal suspension goes, as it has been established that a dose-response relationship in this type of products cannot be seen in this type of clinical studies recommended by the FDA. Apart from that, it seems that the other tests required by the FDA in order to prove BE (In-vitro and Pharmacokinetics (PK) or Pharmacodynamics (PD) tests) should be enough to establish BE.

Comment # 18

Guidance Reference: Pages 18-19, Section VI D 1-3
Bioavailability and Bioequivalence: Clinical Studies for Local Delivery

The guidance suggests three types of possible BE studies. Two of these studies (i.e. Days (s) in the park and EEU study) are not suitable to test the BE of corticosteroids nasal sprays, since in order to see maximal clinical effect of these products, the SAR patients should be under treatment for at least a week prior to the measurement of the symptoms. The traditional study (Section VI D 1) may be suitable to measure efficacy or safety, but it is not suitable to establish BE.

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[1] Summary basis of approval of Vancenase Nasal Aerosol (NDA 18-521), Vancenase AQ Nasal Spray (NDA 19-589), Vancenase AQ 84 mcg, Nasal Spray (NDA 20-469), Beconase AQ Nasal Spray (NDA 19-389).
[2] Beconase AQ Nasal Spray (NDA 19-389) , Summary Basis of Approval.
[3] Vancenase AQ 84 mcg Nasal Spray (NDA 20-469), Summary Basis of Approval.
[4] Nasacort AQ Nasal Spray (NDA 20-468), Summary Basis of Approval Study # 201.
[5] Nasacort AQ Nasal Spray (NDA 20-468), Summary Basis of Approval Study # 304.

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