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September 7, 1999

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

via certified mail - return receipt

Dear Sir or Madam:

Comments Regarding the Draft Guidance for Industry — Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
Federal Register Docket No. 99D-1738
Prepared in collaboration with Charles R. Eck, Ph.D., Primedica Corporation, 83 Rogers Street, Cambridge, MA 02142

II. Background

A. Bioavailability and Bioequivalence (BE) Data

The draft Guidance assumes that no methodologies for determining the particle size distribution (PSD) of drug in a carrier suspension, i.e., microcrystalline cellulose, is feasible for suspension products. However, the document does not make clear that, if a method is developed for a suspension ANDA product and the test product shows in vitro BE to the precursor product, then there should be no requirement for in vivo testing.

We strongly feel that, considering the expense as well as the highly variable and relatively insensitive clinical endpoints associated with BE clinical study testing and endpoints (TNSS), a PK study establishing systemic exposure BE to the precursor product, when coupled with acceptable BE in vitro test results, is all the in vivo testing that should be required, with the assumption being that PSD is not feasible.

For a suspension ANDA corticosteroid nasal product in which a PK study is not feasible, as determined by a pilot study, an additional clinical study for systemic absorption is not needed, as long as a literature search discloses no evidence of suppression of the HPA axis with the nasally administered precursor product.

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III. Formulation and Container and Closure System

B. Container and Closure System

There commonly exists differences (test to precursor product) in the complex container and closure systems found in nasal sprays. Therefore, we object to the in vitro statistical comparisons required in the Guidance (Section IX).

We base our objections on our experiences that precursor containers are often unique designs, protected by patents or other agreements with their suppliers. As such, they are unavailable to the ANDA sponsor. Furthermore, components such as pumps are continuously improved by the manufacturer to improve performance, with the changed, enhanced component not necessarily adopted by the precursor (NDA) holder. Thus, the test product may utilize an improved design in one or more components, making it different than the precursor product, and certainly different in terms of one or several test parameters, such as droplet particle size, spray pattern, and plume geometry, that the FDA is asking to be statistically compared.

IV. Documentation of Bioavailability and Bioequivalence

The need to show Q_2 sameness, within ±5%, of formulation excipients of the reference precursor drug product is an unreasonable request given the analytical complexity of most pharmaceutical excipients. A prime example of this is soya lecithin which, depending on the experience of the analytical team, can be demonstrated to contain over 100 analyzable components. The begs the questions — which component must meet the 5% sameness rule, and which component or components are significant to a particular formulation?

One of the excipients that is the focus of our research efforts is microcrystalline cellulose. Given that the key analytical parameter for showing ±5% sameness is the particle size distribution of the excipient, then the criterion of comparison becomes the same as demonstrating the equivalency of the particle size distribution of the drug substance in the formulation, something that the FDA has acknowledged in the Guidance as being a difficult, if not an impossible task.

We believe that the solution to this sameness issue is to require full disclosure, including for example, the particle size and source of the excipients used in the precursor product. If that is not feasible, for whatever reasons, then the Q_2 should be amended to eliminate the ±5% requirement.

V. Bioavailability and Bioequivalence: In Vitro Studies

A. Batches and Drug Product Sample Collection

2. ANDAs

Our work on a suspension nasal spray product has shown that, for both the test and the precursor products, there are significant changes in the viscosity, droplet particle size, and nasal plume geometry of the product as a function of time and storage conditions. Since there is likely something on the order of 12 to 18 months age difference

between the newly made test and the commercially obtained precursor product, and given that the storage/handling of the commercially obtained precursor product are unknown up to the time of purchase, we object to the requirement in the Guidance, as stipulated in Section IX, for statistical analysis of the in vitro work. We believe that it is unreasonable to suppose that statistical comparisons between test and precursor product of different shelf ages and different histories of storage and handling will provide a demonstration of equivalence sufficient to meet the required confidence intervals.

B. Tests and Metrics

We object to the troubling requirement to perform all in vitro tests on blinded samples when the FDA is also asking for mechanical actuations to remove operator/analyst bias.

We agree with the Guidance in so far as we believe that an argument can be made that the physical act of shaking and actuation of the test articles can indeed be biased. One can confirm this by performing droplet size distribution studies by using laser light diffraction where it is possible to obtain a wide range of MMAD values by changing the mode of shaking and actuation. Therefore, we accept that mechanical actuation systems should be applied to certain performance tests that are sensitive to these parameters. However, based on our experience, it is only the electronic data collection routines (specifically, Malvern, API Aerosizer) that appear sensitive to analyst manipulation.

In order to comply with the FDA request to use mechanical actuation for all in vitro tests, a significant outlay of capital is required in order to obtain sufficient numbers of the commercial mechanical actuation stations needed to perform the required workload. More significantly, these items are produced only on demand, usually requiring 8 to 12 weeks for delivery. The waiting period imposes serious compromises to product development timelines. This, coupled with the blanket requirement for mechanical actuations, represents an undo and unjustified burden to the generic industry.

We would also like to point out that the commercially available actuation stations are not manufactured with any performance control features allowing one to document that the station has performed acceptably. An example of this is the requirement of a source of air pressure to drive the actuation piston. There is no output that allows the user to document that the air pressure did not vary from the required settings during use. Loss of air pressure would significantly affect the actuation of the nasal spray station.

Regardless of the method used to acutate the test samples, the additional requirement to extend the blinding procedure to post actuation evaluations is unwarranted and impractical. All subsequent actions (i.e., post actuation) involve analyst steps that are directed by validated test procedures, such as test sample generation, sample recovery, sample analysis, and data recording. Each of these actions are mandated by standard operating procedures, and routinely checked for compliance by the Quality Assurance department.

In addition, as we commented on Section III. B., Containers and Closures, blinding itself represents an enormous challenge when the test product physically differs from the precursor product. In the case in which the test product utilizes a different container material (e.g., amber glass) than the precursor product (e.g., HDPE, changed

from amber glass), effective blinding is unrealistic. Thus, we strongly disagree with the need for sample blinding in these tests.

1. Dose or Spray Content Uniformity Through Container Life

We object to the requirement for a stability indicating chemical assay for this test; the assay should only be quantitative for drug substance in the formulation. Content uniformity testing need only measure drug content per spray. Total contents analysis is performed with a stability indicating assay in order to assess the stability, purity, and level of degradants and impurities in the formulation as a function of time and storage conditions. These data are normally captured as part of drug product stability testing.

2. Droplet and Drug Particle Size Distribution (PSD) by Laser Diffraction

The experimental data required is routinely generated by Malvern's latest spray test version of its Mastersizer instruments (cost, approximately $60,000). To generate this information using the Malvern Mastersizer X series requires a significant and routine alteration in testing parameters, adding significant time (threefold) to the testing.

There are several specifics of the droplet particle size test as now recommended by the Guidance to which we object.

With respect to the use reporting of particle size data based on different delay times, i.e., obscuration, we strongly believe that this information does not provide any more qualification data than a plot of the obscuration profile itself. Obscuration profiles of test and reference products can then be compared directly.

Furthermore, our data from work performed in development of a suspension nasal spray product reveals that data collection at only two distances from the nasal spray cone to the laser light beam, as opposed to the three required in the Guidance, provides ample information since the data sets collected at 2.5 cm and 5.0 cm are identical. Moreover, all of these data are normally generated as part of method development and should be product specific, not a general requirement. Testing at one set distance should be sufficient.

Generation of D_{90} data is simply not warranted for nasal sprays since RSD values of 100% or greater are commonly observed at this value. Although not to the same extent, the same is also true of the D_{10} values. From the control side of the issue, these numbers have no significance to product quality .

The most troubling request in the Guidance with respect to droplet particle size determination is the request for droplet particle size distributions at different obscuration values. Obscuration (light) is a time event post actuation that reflects the density of the aerosol cloud. For example, at some time post actuation the aerosol cloud reaches its maximum density. We are being asked to present droplet particle size data at this maximum obscuration point, and then at points that are 50 % and approximately 0% occurring during the dissipation of that maximum cloud density. The time that it takes to reach maximum obscuration values is typically around 100 milliseconds (msec). If a typical nasal spray has a velocity of 1 meter per second, then at 100 msec the cloud would

have traveled around 10 cm, or 4 inches. The length of the nasal passage of a normal adult male is approximately 5 cm. To travel this distance takes approximately 50 msec. Therefore a typical nasal spray has impacted on the tissue of the nasal passages 50 msec before maximum obscuration is seen on the laser light scattering detector. There is no practical reason to generate droplet size data on a nasal spray in a time frame (300 to 500 msec) that does not approach in vivo (patient) criteria; it simply has no value.

Multistage Cascade Impaction (CI) or Multistage Liquid Impinger (MSLI)

Reference is made to our previous comments regarding no need for mechanical actuation for this test.

3. Spray Pattern

In the case of a nasal spray suspension that we are developing, where the drug substance is measured in micrograms, it is not possible for the visualization technique to be drug specific. From our experience, this is possible only when there exists no formulation excipients, or excipients in very low concentration relative to the active drug substance.

4. Plume Geometry

It is our experience that only the initial plume angle can be statistically reproduced; even so, RSD values are very high. The high speed photographic image does not allow the plume length or plume width to be measured to any degree of meaningful reproducibility; it simply has no value. Again, the argument of the actual in use situation says that only the plume seen in the first 50 msec post actuation has in vivo significance. Therefore, we question the validity of this test other than perhaps the initial plume angle in comparative BE data.

6. Tail Off Profile

During product development it will have been determined what the typical tail off profile looks like for both test and reference products. The total number of sprays in a container system is volume or container controlled. In the likely situation where different containers are used with different fill volumes, the total number of sprays may differ significantly for the test product than for the reference product. As a consequence, tail off profiles will likely be different. The only requirement we need to meet is the total number of doses specified on the product labeling.

We recommend that the tail off profile be based on mass of drug product delivered per spray, until shot weights begin to vary by more than ±15% between two consecutive shots. At that point, concentrations of selected endpoint sprays can be documented until product exhaustion. Again, we believe that it is only necessary to meet the number of full dose sprays present on the product labeling. If it does, comparative tail off information is of no value.

X. Multiple Strengths

The requirement in Item 1 of this Section is confusing — that for high strength test and reference (precursor) products, comparative in vivo data is necessary. First, the type of in vivo test is not clear. Does this Item refer to a clinical endpoint study, such as a TNSS determination, or is it also intended to mean a PK systemic exposure study, and/or a systemic absorption study?

Second, Item 5, that specifies PSD comparisons for high and low dose strengths (test and reference), appears to be inconsistent with the inference prevalent throughout the Guidance that, if PSD in vitro comparisons are confirmed, then no in vivo testing is required. If that is in fact the case, then the next sentence of the Guidance, that absolves the applicant from conducting in vivo testing on only the low strength product (what type of study is again not clearly stated), is confusing and unnecessary.

Please feel free to contact us with any questions or concerns regarding these comments to the draft Guidance.

Sincerely,

Daniel A. Kaminski
Director, Regulatory Affairs

cc: Charles R. Eck, Ph.D. (Primedica)

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