GPhA
Generic Pharmaceutical Association

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July 7, 2003

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane
Room 1061 – HFA-305
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Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

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Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) appreciates the opportunity to comment on the above referenced Draft Guidance for this important class of drug products. GPhA represents 98% of generic drug manufacturers whose drugs are dispensed for almost half of all prescriptions filled in the United States, but representing less than 10% of all drug expenditures. GPhA is the united voice of the generic drug industry and is committed to patient health and safety, and strongly supports any measures that will improve our health care system. The following comments are in accordance with the Commissioner's stated goal of advancing scientific policy decision making within the agency and maintaining the high standards of the generic drug review process.

GENERAL COMMENTS

1. Reconsider Necessity of Clinical Endpoint Studies

   The Draft Guidance describes several requirements for nasal aerosols and nasal sprays for local action. Generic versions of solution and suspension nasal products must be the same as the reference listed in drugs for the following parameters: the formulation must be quantitatively and qualitatively essentially the same, the container closure system utilized for the generic product must be essentially the same, and the generic product must demonstrate equivalence for seven (7) specific *in vitro* tests. These *in vitro* tests have stringent statistical criteria for comparing test to reference formulations and are referred to by the Draft Guidance as "*in vitro* BE tests." Additionally, suspensions must also demonstrate bioequivalence based on acceptable results from a pharmacokinetic (PK) study as well as a clinical endpoint study.

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The Orally Inhaled and Nasal Drug Products Subcommittee (OINDP) of FDA discussed the previous June 1999 version of this guidance at the FDA Advisory Committee for Pharmaceutical Sciences on July 19, 2001. In this presentation, the Agency noted that a clinical study is needed in the comparison of suspension nasal products. However, the FDA also stated that "the subcommittee was not in consensus on this issue, but the majority agreed with the above." Therefore, FDA's Advisory Committee for Pharmaceutical Sciences was split on the merit of clinical studies.

In addition to the lack of consensus among Advisory Committee for Pharmaceutical Sciences members, it is acknowledged that clinical studies are inherently more variable than in vitro bioequivalence studies and systemic plasma drug concentration studies. Evidence was presented at the July 19, 2001 meeting that it is difficult to demonstrate a dose response curve for several nasal spray suspensions. Thus, the clinical study lacks the sensitivity of the in vitro bioequivalence study.

GPhA requests that the agency reconsider the requirement for a clinical study for nasal suspensions for local action. The Draft Guidance outlines very restrictive comparability requirements for the formulation and container closure system, along with the extensive in vitro testing and pharmacokinetic testing. Because clinical endpoint studies are more variable than in vitro testing or plasma drug concentration studies, it appears that a clinical study will provide information that is less precise or reliable than the more rigorous in vitro or plasma tests. Reliance on the aforementioned in vitro and pharmacokinetic studies, along with comparability in formulation and the container closure system, provides scientifically rigorous criteria for assuring bioequivalence.

2. Comments Related to Proposed Requirements for Nasal Suspensions if Clinical Study Requirements are Maintained

As noted above, based on the requirements related to the formulation, container closure system and physical performance characteristics, GPhA requests that the agency reconsider its position related to clinical endpoint studies for suspension formulations. However, if FDA determines that clinical endpoint studies will continue to be essential for approval of ANDAs for nasal suspensions for local action, the following comments are provided:

In light of the extensive requirements for similarity of the formulation, container and dispensing agent, *in vitro* testing, and pharmacokinetic studies, the proposed clinical endpoint study is considered "confirmatory" and not "pivotal". Therefore, it is requested that clinical endpoint studies be evaluated on a statistical scale appropriate for the inherent variability of the product as opposed to the traditional 90% confidence intervals (80-125%) used for acceptance of pivotal studies. The basis for this position follows.

a. It is difficult to establish a dose-response relationship. Evidence presented at the July 19, 2001 meeting of the FDA Advisory Committee for Pharmaceutical Sciences showed that it is difficult to demonstrate a dose-response curve for several nasal spray suspensions.

b. Clinical endpoint studies are more variable than *in vitro* bioequivalence studies and systemic plasma drug concentration studies, and are the least sensitive method for detecting differences between drug products.

3. Pass/Fail Criteria for Multiple Test Requirements

If the complete series of testing outlined in the Draft Guidance is required, it is unclear which test(s) is the **primary** measure of equivalence. Additionally, it is unclear how the data will be evaluated if some tests pass and others are marginal and/or fail. GPhA requests that the agency clarify its position regarding the pass/fail criteria for approval of ANDAs performing the proposed tests.

4. Formulation Requirements Create Potential Barriers to Generic Market Entry

The stringent requirements for similarities between the formulation/composition or container and dispensing systems could create barriers to entry for generic products when the innovator lists relevant composition and/or methods patents. For example, if the innovator holds a patent on the reference listed drug it may be possible for a generic applicant to develop a non-infringing formulation that is safe and bioequivalent. However, the Draft Guidance appears to preclude any consideration of approval of an ANDA for a nasal aerosol or spray for local action that differs in formulation or design of the container closure system from that of the reference listed drug. GPhA requests that FDA clarify its position in this regard and include provisions for ANDA approval when differences in formulation are necessary due to patent or exclusivity considerations.

SPECIFIC COMMENTS

1. Section III - Formulation and Container/Closure

(Lines 199-200) The Draft Guidance recommends using the same particle size distribution in the test product as in the reference product. However, the agency has indicated that there is no validated technology available to determine the particle size distribution in suspension. It is not clear how it can be verified that the same particle size is used in the reference and in the ANDA test product if no validated technology exists at this time.

2. Section IV – Documentation of BA/BE

(Lines 251-254) It is recommend that the formulations (test and reference) be Q_1 the same and Q_2 essentially the same. In some cases, the most sensitive analytical methods may not be able to quantify certain excipients within 5% of the reference product given the low levels present in the formulation, analytical variation or the complexity of the excipient mixture. Nevertheless, if all *in vitro* and *in vivo* test results are equivalent and the level of the excipent in question does not raise safety concerns, those data should be acceptable for approval of a generic product even if the test product is outside ±5%.

3. Section V - In vitro Studies

   a. (Lines 634-658) Drug Particle Size Distribution By Microscopy – Experience has shown that it is sometimes very hard to distinguish drug particles from excipients under a light microscope, resulting in substantial subjectivity when testing drug particle size for suspensions. The requirement for light microscopy testing, or any other *in vitro* test without a validated method, should be eliminated from this guidance until a validated technique is available.

   b. b. (Lines 698-700 and lines 716-717) The statistical analysis for non-impaction systems (e.g., SprayVIEW) is based on equivalence of area within the perimeter and ovality whereas the statistical analysis for impaction systems (e.g., TLC) is based on equivalence of D_{max} and ovality. The statistical analysis for equivalence in spray pattern should be the same regardless of the system used (non-impaction or impaction), analyzing D_{max} and ovality for both systems.

   c. (Lines 712-713) The manual analysis of spray pattern for impaction systems (e.g., TLC) recommends that the approximate COM be identified and the D_{max} and D_{min} be drawn through this center for each spray pattern. The determination of an estimated COM should be defined in the Draft Guidance for the manual quantitation of a spray pattern, especially if the pattern is star-shaped or horseshoe-shaped.

   d. (Lines 780-784) The applicant must provide documentation that the plume is fully developed at the selected delay time when determining plume angle, plume width and plume height. A correlation between the Time History Plot from the droplet size distribution by laser diffraction and the image intensity profile from the SprayVIEW plume geometry measurements must be identified. If the same automated actuation station is used for plume geometry and droplet size by laser diffraction, the delay time on the image intensity profile for the fully developed phase of the plume can be identified by the obscuration profile on the Time History plot where obscuration reaches its plateau values.

4. Section VI - Clinical Studies

   a. (Lines 906-907) The Draft Guidance specifies a two-week efficacy trial. Is this the minimum or the maximum length of the study?

   b. (Lines 938-941) FDA is requesting that the baseline TNSS be calculated based on the last 3 days of the placebo run-in (AM and PM TNSS) as well as the AM for day 1 of randomization, for a total of 7 values (4 AM and 3 PM). Since AM and PM scores can be quite different, including the extra AM score could skew the average in favor of the AM score.

   c. (Line 974) The Draft Guidance indicates that the endpoint for equivalence and efficacy analyses should be the patient self-rated TNSS. Are other alternatives for the equivalence and efficacy analyses acceptable? The four-point TNSS scale may not be sufficiently sensitive and a wider scoring system may be more appropriate.

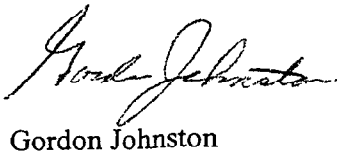
5. Section VII – PK Studies

   a. The FDA is asking for a PK study to show systemic equivalence. However, "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" (lines 1023-1024). What does the agency consider to be "convincing"? Is a pilot study with the lowest available LOQ by standard methods sufficient? It is recommended that FDA clarify the type of data that might be considered 'convincing.'

   b. (Lines 1077-1084) For compounds that demonstrate low systemic but measurable exposure, the full plasma concentration versus time profile is recommended if a specific and sensitive analytical method is available. If a sensitive method is not available, it is recommended that $AUC_{(0-t)}$ be used to assess total exposure instead of $AUC_{(0-\infty)}$.

Thank you for your consideration of these comments.

Respectfully submitted,



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