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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Comments of the Generic Pharmaceutical Association for Docket No. FDA-2013-N-1434-0001: Draft Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules.

The Generic Pharmaceutical Association (GPhA) acknowledges the efforts of the FDA on **Docket Number FDA-2013-N-1434-0001, Response to FDA call for comments concerning Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules**. We would also like to thank you for giving us the opportunity to share our thoughts on this important public health issue.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than three billion prescriptions every year. Generics represent greater than 84% of all prescriptions dispensed in the U.S., but only 27% of expenditures on prescription drugs. GPhA is the sole association representing America's generic pharmaceutical sector in the U.S., while this response letter represents the views of the association these comments may not reflect all member company positions.

Generic manufacturers are always concerned with patient adherence and safety. GPhA supports the FDA's efforts to increase patient safety and compliance. The health and economic impact of medication non-adherence — which contributes to costly health complications, worsening of disease progression, and preventable utilization - has been estimated to be as much as $290 billion.[1] More than one in 10 seniors in America reported reducing use of their required medications because of cost.[2] Some of the concepts posed in the draft guidance (such as size, shape and coating limits) are often methods used by generic manufacturers to design around the intellectual property of the reference listed drug (RLD).

[1] Health Affairs, Seizing The Opportunity To Improve Medication Adherence, August 28th, 2012, available at http://healthaffairs.org/blog/2012/08/28/seizing-the-opportunity-to-improve-medication-adherence/
[2] Congressional Budget Office. 2003. Prescription Drug Coverage and Medicare's Fiscal Challenges

We request confirmation that current approved products and products currently filed and under review **will not** be impacted by this Draft Guidance unless there are specific safety reasons. Please provide more details on what type of safety information would require a generic manufacturer to modify their size or shape of their currently filed products and create an implementation period as appropriate for any additional requirements noted in the Draft Guidance. It is also critical that FDA formulate a policy and allow for case-by-case discretion with regard to physical attributes, continuing to hold clinical relevance based on approved indications and intended patient population as the most important factors. Current standards allow for comparability to other products in the market to support the size and shape of the product if it differed from the RLD. We suggest that allowance be included in the draft guidance as a possible strategy to justify the size and or shape of a product.

The Hatch Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (also referred to as Hatch Waxman), have been enormously successful in providing access to lower cost, high quality generic drugs. In designing the framework for generic drugs, Congress took care to include in the statute the essential requirements and to preclude non-essential requirements that would provide unnecessary barriers to generic competition. Most of the requirements that Congress chose to include, e.g., sameness of active ingredient, bioequivalence, labeling consistency, were designed to ensure that the generic drug would be the same as the drug referenced in the ANDA. Where Congress permitted generic drugs to vary from the drug referenced in the ANDA, e.g., in manufacturing methods and in formulation, Congress provided for FDA to ensure that the generic drug is safe. Hatch Waxman specifically provides that FDA may not require more than what is required to satisfy those statutory requirements.

There is no provision in Hatch Waxman allowing FDA to deny approval of an ANDA based on differences in physical attributes between a generic product and the listed drug it references. The premise of the Draft Guidance, that generic drugs must mimic the reference listed drug in size and shape, has no basis in law. In our view, an FDA action related to the physical characteristics of generic drugs must be tied to the safety of those drugs to avoid exceeding FDA's statutory mandate.

A significant portion of RLD products do not have a discernible compositional proportionality, in some cases making it problematic for generic developers to achieve similarity in size to the respective strength of the brand while maintaining dose proportionality for their generic product. Manufacturers appear to have little opportunity to achieve resolution of questions in a timely manner, and are provided no mechanism for resolution.

As FDA is aware, when generic drug sizes differ from those of the reference listed drug, the generic is generally larger. This is not a matter of choice. A tablet of a larger size means that more excipient is required to manufacture the drug. When a generic developer designs a tablet or capsule that is larger than the reference listed drug, the change is usually necessitated by patents held/licensed by the sponsor of the reference listed drug. Valsartan is a good example. A patent on the reference listed drug prevents a generic drug from having a similar percentage of API in its tablet than the percentage in the reference listed drug. To avoid infringing this patent,

applicants for generic versions of Valsartan must develop tablets with a larger volume of excipient. A larger size, if it doesn't represent a defined safety concern, should be acceptable.

Sponsors of reference listed drugs have substantial incentives to prevent generic competition, and design patent strategies to accomplish those objectives. The Draft Guidance, if adopted, would create a new life cycle management tool for NDA sponsors to stifle or delay generic competition. Sponsors of reference listed drugs could seek and obtain patent protection for their drugs to cover the ranges of sizes, shapes and other physical characteristics permitted in the Draft Guidance for generic versions of those drugs. As a result, generic manufacturers would be unable to comply with the Draft Guidance without infringing the patents on the reference listed drug. As the Valsartan example illustrates, this strategy is one the sponsors of potential reference listed drugs already pursue. Setting limits of the kind specified in the Draft Guidance would make such strategies easier and infinitely more effective.

The size requirements in the Draft Guidance are particularly problematic in that they do not give generic manufacturers sufficient flexibility in product design. The requirements that, when referencing a drug less than or equal to 17mm, a generic tablet cannot be more than 20 percent larger than the referenced drug in any dimension and cannot be more than 40 percent larger than the referenced drug in volume, significantly limit generic manufacturers' options to design non-infringing products. The requirement that, when referencing a drug that is greater than 17 mm in its largest dimension, a generic tablet may not exceed the size of the referenced drug in any single dimension or in volume is even more unyielding.

The recommendation for capsules of size 2 or larger is similarly restrictive. For these capsules, an increase of one capsule size should only be considered when "adequate justification can be provided for the size increase." Draft Guidance at 5, lines 161-62. FDA offers no explanation as to what information or research would qualify as "adequate justification" for such a size increase, but by requiring generic manufacturers to justify such an increase, FDA injects an additional hurdle in the process that will delay product development. And since "adequate justification" is required for any capsule larger than size 2, this restriction will apply to a large percentage of products. As with the recommendations for tablet size, these limitations seem to be unnecessarily restrictive. By requiring generic products to more closely resemble the drugs they reference, generic manufacturers will run into intellectual property barriers that they have long sought to avoid by developing products that differ from the RLDs in size, shape and overall look.

GPhA and our members formulated several comments and questions for the FDA as well. Our hope is these questions will create an environment and interaction between the agency and the pharmaceutical industry to clarify regulations and expectations while addressing outstanding questions.

General Comments and Questions

- What kinds of studies exist to help justify and/or prove ease of swallowing?
- In the "Other Physical Attributes" section, what are the expected criteria for weight, surface area and swelling? We would also like to request additional guidance on the tolerances for disintegration.
- Regarding the techniques that may be used to determine the volume measurements of a tablet or capsule, what degree of accuracy is OGD expecting for the determination of dosage form volume?
- Are there potential concerns related to intellectual property for innovator unit size or shape that could subject ANDAs to unnecessary patent litigation due to restrictions on generic drugs set forth by this draft guidance? Additional barriers to generic product approvability related to dosage form size and shape will likely result in RLD holders pursuing additional intellectual property related to these types of formulation attributes.
- Has the FDA performed any formal assessment of the frequency of adverse events related to size differences between RLD products and generics? The clinical data presented in the guidance are generally related to dosage form size, and not specifically supportive of the position that generics that are larger in size present safety concerns.

Line-specific Comments/Questions

- Concern about tablets larger than 8 mm (81-86) - Will tablets above 8 mm in size receive additional scrutiny? This appears to be the case, and this cutoff appears to be based on limited scientific evidence. IP and technology are significant limiting factors affecting generics ability to have the same size or shape as the brand.
- Other physical attribute similarities (123-127) - Is there an expectation that a wide range of physical attributes will need to be compared between the generic and RLD product, and that differences in almost any attribute (density, for example) could prevent or delay approval?
- Size (137-168) - FDA provides specific upper limits for size based on the RLD. Further, the recommendations state that generic products should be of "similar" size and shape as the RLD. How are the limits established, and is there safety data to adequately support their recommendations?
- Actual size limitations/requirements (144-153) - For low-dose products, this should not be a major impediment, but for moderate to high-dose products, the requirement to be no larger above 17 mm and no more than a 40% volume increase relative to the RLD may present significant issues. Historically, if a higher strength of the RLD product exceeds the dimensions of a lower strength of the generic product, the acceptability of the generic product (from a safety perspective, at least) is established.
- Restrictions on capsule size conventions (159-164) - When the RLD capsule size is 2 or larger, is an increase from 0 to 00 considered one size increase, or is an increase from 0 to 0E one size? Typically, going from 0 to 00 would be considered a single size increase. GPhA requests further clarification concerning restrictions on capsule size conventions and what is considered an appropriate justification for a capsule size increase.

  - Since the requirement for adequate justification occurs with any capsule larger than size 3, a very large percentage of products would fall under the more restrictive criterion. Thus justifications would become a standard requirement. As with tablet dimensions, these limitations seem to be unnecessarily restrictive.
- Shape (170-194) – FDA recommends "similar" shapes as the RLD but often generics can have "better" shapes. In any case, how similar is "similar enough" when considering patents? What are the Agency's expectations as to justification for a shape that "has been found to be easier to swallow than the RLD?"
  - If a tablet or capsule intended to be swallowed intact differs from the criteria recommended in this guidance document, then the applicant should contact OGD before establishing the QTPP as stated in lines. By what mechanism would this occur, and what would be the process?

GPhA appreciates the FDA's views on the size, shape, and other physical attributes of generic tablets and capsules. We understand the importance of the critical issues raised and the impact these issues can have on patients, and look forward to continuing our conversations on the topic.

Sincerely,

Ralph G. Neas
President and CEO