August 27, 2015

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: 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, Response to FDA call for comments concerning Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules**.

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 86% 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.

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 due to cost related issues.[2] Some of the concepts posed in the guidance (such as size, shape and coating limits) are often methods used by brand manufacturers, in the form of intellectual property protection of the listed reference drug (RLD), to offset generic competition.

Generic manufacturers are committed to supporting issues that impact patient adherence and safety but continue to have concerns related to the ***final Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*** which imposes arbitrary requirements even in the absence of known safety issues.

[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

The Drug Price Competition and Patent Term Restoration Act of 1984 (better known as the Hatch Waxman Amendment), have been enormously successful in providing access to lower cost, high quality generic drugs. In designing the pathway for generic drugs, Congress took special 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 RLD. Where Congress permitted generic drugs to vary from the RLD, e.g., in manufacturing methods and in formulation, Congress provided for FDA to ensure that the generic drugs are safe and efficacious. Hatch Waxman specifically states that FDA may not require more than what is required to satisfy those statutory requirements. Hence there is no provision in Hatch Waxman allowing FDA to deny the approval of an ANDA based on differences in physical attributes between a generic product and the RLD. ***The premise of the guidance, that generic drugs must mimic the reference listed drug in size and shape, has no basis in law.*** Additionally, the guidance does not address the quality attributes of generic drugs. As stated by FDA, there is **one quality standard** and **one quality voice** for all drug products approved by FDA. This single quality standard assures that all human drugs will consistently meet quality standards that safeguard clinical performance.[3] It is our belief that an FDA action related to the physical characteristics of generic drugs, unless it represents a scientifically supported safety and or efficacy concern, exceeds the FDA's statutory mandate.

As FDA is aware, generic manufacturers may propose to manufacture a tablet or capsule that in some cases is larger than the RLD. This may not be a matter of choice. Due to patent protection for the formulation or modified release technology of the RLD, a generic manufacturer may be required to develop a dosage unit that differs in dimensions, which will not be protected by patent, in order to make available lower cost generic products to the consumers. A generic version of a product that differs from the size and/or shape recommendations set forth in the guidance does not automatically raise safety issues. To date, FDA has been unilaterally rejecting proposed differences when not in compliance with the Draft Guidance (now Final Guidance) regardless of the product type, indication(s) or patient population approved in the product labeling. Thus, based on industry experience the Draft Guidance has been a de facto regulatory requirement. Member firms report that Controlled Correspondence inquiries have not been subject to any scientific evaluation, rather are rejected regardless of the level of deviation from the guidance. When the generic product dimensions differ from the RLD, the proposed size and/or shape should be evaluated on a case by case basis to assess actual risks.

With the above illustrative examples, NDA sponsors will have even greater incentives to prevent generic competition, and design patent strategies to achieve this objective. The guidance creates a new life cycle management tool for NDA sponsors to stifle and delay access to lower cost generic medicines based on inflexible criteria that are not necessarily applicable to a proposed

[3] Office of Pharmaceutical Qualtiy, "FDA Pharmaceutical Quality Oversight: One Quality Voice." http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf

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deviation in size and/or shape. NDA sponsors could seek and obtain patent protection for their drugs to cover the ranges of sizes, shapes and other physical characteristics/attributes permitted in this guidance. As a result, generic manufacturers would be unable to comply with the guidance without infringing upon the NDA patents

Further the size requirements established in the guidance are particularly problematic in that they do not provide generic manufacturers sufficient flexibility in generic product design for tablets. The requirements that, when referencing a drug less than 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-patent infringing products even when the proposed dimensions do not raise safety concern for the intended patient population. 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 even when applicants can point to examples of marketed products that exceed these dimensions.

With regards to the recommendation for capsules of size 2 or larger capsule size is similarly restrictive. For these sized capsules, an increase of one capsule size should only be considered when *"adequate justification can be provided for the size increase*." FDA offers no clarity and or definition as to what information or research would qualify as *"adequate justification"* for a size increase. By requiring generic manufacturers to justify such an increase, FDA injects additional uncertainty and risk in the process that will delay product development. And since "adequate justification" is required for any capsule larger than size 2, this restriction would have significant application to a large percentage of products. As with the recommendations for tablet size, these limitations are unnecessarily restrictive. By requiring generic products to more closely resemble the drugs they reference, generic manufacturers will unnecessarily encounter intellectual property barriers that they have long sought to avoid.

Also as requested in GPhA's March 10, 2014 docket response to the draft guidance, GPhA would like to reiterate the same request that FDA confirm that applications received and pending prior to the issuance of the final guidance and under review ***will not*** be held to the new "requirements" of this guidance unless there are specific scientifically supported safety concerns. In the event that FDA deems there are safety concerns, FDA should provide greater detail on what the expectations are with regards to (1) the type of safety information needed to adhere to the FDA expectation(s) and (2) create an implementation period as appropriate for any additional requirements noted in the 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 one of the key factors. Further, manufacturers appear to have little opportunity to achieve resolution of questions in a timely manner, and are provided no mechanism for resolution to obtain additional clarification from the FDA other than recycling of multiple controlled correspondences to address Agency questions or concerns.

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GPhA and our member companies formulated several comments and questions for the FDA as well as submitted in GPhA's March 10, 2014 comments to the draft guidance. To date, the Agency has yet to provide responses to the questions and concerns we have expressed. Therefore, GPhA is resubmitting the same questions and concerns. Our hope is that the questions will create an environment of 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?
- 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.
- Does the Agency have any size and shape criteria for NDAs based on pharmacological class or indications? If so, please provide literature or other support that was used to develop those criteria.
- Are there size and/or shape criteria that innovator firms must adhere to when developing products? If so, please provide those criteria.
- The Final Guidance adopts a pass/fail bright line. If innovator products are not subject to specific size or shape criteria, the Agency should develop objective considerations that could be used to assess risk.

Line-specific Comments/Questions:

- Line 81 – 86: Concern regarding tablets larger than 8 mm - 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.
- Line 123 – 127: Other physical attribute similarities - Is there an expectation when 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?
- Line 140-171 - 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

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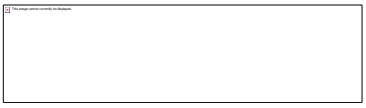
the RLD. How are the limits established, and is there safety data to adequately support their recommendations?

- Line 145 – 156: Actual size limitations/requirements - 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.
- Line 162 – 166: Restrictions on capsule size conventions - 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.
- Line175-194: FDA recommends "similar" shapes as the RLD but often generics can have "better" shapes. 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,



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