

August 3, 2013

To the FDA Center for Drug Evaluation and Research:

Regarding: Docket No. FDA-2007-D-0369

The American Academy of Ophthalmology (AAO) is the largest national membership association of Eye M.D.s. Eye M.D.s are ophthalmologists—medical and osteopathic doctors who provide comprehensive eye care, including medical, surgical, and optical care. More than 90 percent of practicing ophthalmologists in the United States are Academy members.

The American Glaucoma Society (AGS) promotes excellence in the care of patients with glaucoma by supporting glaucoma specialists and scientists through the advancement of education and research. Since the establishment of the Society, the number of members has increased to over 1000 today, including fellowship trained glaucoma specialists, as well as scientists active in glaucoma research.

The AGS and AAO recently became aware of proposed revisions to current standards and procedures for ensuring bioequivalence of ophthalmic emulsions, suspensions and ointments. [Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability (Federal Register/ Vol. 78, No. 119 / Thursday, June 20, 2013)]. Our societies have concerns regarding the safety and rationale of the proposed changes outlined in the Federal Register Notice and the risks that might be encountered by patients under our care if these procedures were to be enacted.

The FDA's Center for Drug Evaluation and Research proposed specific bioequivalence recommendations for studies that support abbreviated new drug applications (ANDAs). As documented in the public notice the "FDA guidelines may enable companies to base applications for generic drugs on laboratory studies and not in vivo clinical trials with living human subjects." While bioequivalence was the standard for generic ophthalmic solutions to date, the new proposal will expand the same requirements to generic emulsions, suspensions and ointments that previously required clinical testing prior to approval. This appears contrary to previous agency actions for ophthalmic products. We would like to address each of the proposed criteria for bioequivalence as noted in the Federal Register Notice:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2) using the following measurement parameters: Globule size distribution, viscosity, pH, zeta potential, osmolality, surface tension.

The AGS and AAO believe the measurement parameters noted above are of great importance and the information provided is too vague to allow for a true assessment of suitability. Each of the parameters above should be explained in detail with specific testing procedures documented so that we can fully comment on the proposed guidelines. When stating that formulations should be "qualitatively and quantitatively the same" are there ranges that define what "same" might be or are they to be identical? Are these the same testing parameters used that subsequently allowed for approval of the RLD? How can clinical efficacy and safety be determined based on results of the above testing?

2. Bioequivalence based on (95% CI): Population bioequivalence based on D_{50} and SPAN ($D_{90}-D_{10}$)/ D_{50} or polydispersity index for the globule size distribution only (the other parameters do not require population bioequivalence analysis). The population bioequivalence analysis should be performed separately for each peak detected in the globule size distribution of the RLD. The separation of the peaks should be determined by the minimum value located between the peaks of the RLD.

How were these parameters selected and how do they compare to the testing undergone by the RLD? How will the results relate to in vivo safety and efficacy?

3. Acceptable comparative in vitro drug release rate tests of cyclosporine from the test and RLD formulations.

It is unclear to the AGS and AAO how release rates will be measured, which specific in vitro assays will be utilized and if cell cultures will be employed in testing or alternatively, will the use of tear simulated fluids and/ or balanced salt solution suffice? What are the specific conditions of the testing? How will these tests predict clinical safety and efficacy in the target treatment group?

4. An in vivo bioequivalence study with clinical endpoints is requested for any generic cyclosporine ophthalmic emulsion, 0.05% that has a different inactive ingredient, a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or unacceptable data from in vitro comparative studies.

These requirements for in vivo studies do not define endpoints and are vague and open to suggestion and interpretation. If a generic substitute is indeed being indicated and delivered to the same population treated by the RLD, then a similar population should be studied in the generic version seeking approval. It would be appropriate to use the same endpoints (safety and efficacy) as required for the RLD. Our organizations ask for more clarity on this point and advocates for the establishment of reliable and relevant metrics to study how generics perform compared to the RLD.

In addition to the concerns raised above, the AGS and AAO continue to have concerns regarding how generic medications are approved and marketed in the United States. Other specific concerns that require attention by the FDA include:

1. Generic formulations have been approved with no apparent regard to patient confusion with respect to bottle top colors, bottle design, or label design. Patients, many suffering from poor vision, frequently use several medications and rely on the bottle top color to select the appropriate drug. Lack of uniformity in bottle top color causes confusion and medication errors. This is an increasingly common occurrence and has become a real safety concern for both physicians and patients. The use of different bottle types and shapes has resulted in poor instillation of medication due to physical limitations. For example, there are recently approved generic products that have spike-top bottle caps that require the patient to pierce the bottle tip before the product can

be used, unlike any other type of ophthalmic medication. Some bottles are more difficult to squeeze and appear to deliver variable drop sizes that may lead to over or under dosing. In addition to problems related to supra-therapeutic medication exposure, over dosing will cause patients to run out of the medication prior to the designated refill time, leading to under dosing as well. These issues are unique to topical ophthalmic medications when compared to oral medications and new standards should be created in recognition of these differences.

2. Recently, the Consumer Product Safety Commission issued a regulation requiring the manufacturers of products containing imidazolines to place products in Child-Resistant Packaging. This could potentially affect topical ophthalmic medications such as brimonidine and apraclonidine. While ensuring child safety is of great importance, a blanket regulatory requirement for packaging will ultimately affect glaucoma patients who frequently have physical limitations hindering their ability to use these commonly used ophthalmic medications. Non-oral medications have a unique set of obstacles for administration, and decisions about packaging should include input from practicing ophthalmologists and end user patients.

In conclusion, it is the opinion of the American Glaucoma Society and the American Academy of Ophthalmology that claims of bioequivalence between a generic product and a RLD should be supported by solid scientific evidence congruent with the requirements for RLD approval. In the absence of stringent requirements, attempts to claim bioequivalence based on potentially flawed in vitro methodology, or ambiguous in vivo endpoints, may result in public health and patient safety concerns. We ask the FDA to review their proposed guideline changes. We also ask for a more general review of guidelines for approval of generic ophthalmic medications, such as bottle cap color and type requirements, and to engage the medical community for further input that will increase patient safety in the future.

Sincerely,



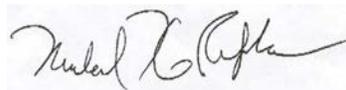
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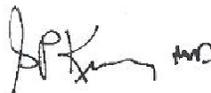
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