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Questions about generic ophthalmic medications from AGS members, answered by Wiley Chambers, MD, FDA Deputy Director for the Division of Transplant and Ophthalmology Products, March 2011.

Q: Can you explain the FDA policies for generic ophthalmic medications and what kind of clinical testing is performed?

Dr. Chambers: For ophthalmic products, the formulation of a generic product often depends on when the innovator product and generic product were approved. Prior to 1992, the FDA used to permit changes in inactive ingredients for ophthalmic generic products without testing. In 1992, that policy was changed. Currently, generic ophthalmic solutions, such as latanoprost are expected to have the same active and inactive ingredients in the same concentrations (both active and inactive). If they are not the same, then a study comparing the clinical bioequivalence has to be performed. If the product is anything other than a solution, where manufacturing issues could potentially make a difference, the generic has to have a study demonstrating equivalence, even if the actives and inactives are the same. It is therefore important to distinguish between old ophthalmic generics (before 1992) and newer ophthalmic generics.

Another example is the fixed combination of dorzolamide/timolol, also a solution. The generic product has the same active and inactive ingredients in the same concentrations. As a solution with all of the actives and inactives dissolved, it is difficult to postulate a mechanism that could lead to a difference between the innovator and the generic. Without a plausible reason of how the solutions could be different, the FDA generally does not ask for comparative studies. This is in contrast to suspensions, ointments, or emulsions. In these dosage forms, the distribution of particles can make a difference, the milling of the particles (i.e., particle size) can make a difference and therefore the FDA would ask for comparative studies prior to approval of a generic product.

Q: I have been told that "back-engineering" generic solutions is difficult because although there is a list of inactive ingredients that must be adhered to, the generic manufacturers do not have the "original recipe" or maybe the manufacturing processes that the brand names do, and so the list of inactives may be the same but there may be slight differences in proportions of constituents that may or may not be important, or may or may not be clinically significant.

Dr. Chambers: Back engineering is not difficult when you have a complete list of the ingredients. In the case of topical ophthalmics, by regulation, all of the ingredients, active and inactive are required to be listed in the package insert. Most of the time, a potential new manufacturer can figure out exactly how to make a copy. Additional incentives to make an exact copy come from the desire to have the generic be considered interchangeable with the innovator. The most common reason for a proposed generic to differ from the innovator is usually due to patent protection of the formulation. It is very rare for a company to deviate from the original, unless they are blocked by a patent.

Q: I'm also concerned about manufacturing tolerance. The dose response effects of PG analogs has been shown to be clinically observable with very small changes in concentration. Anyone going to be monitoring this?

Dr. Chambers: The concentration of the active is always measured in the stability studies. Typical time points cover the entire proposed shelf life period and often include baseline, months 3, 6, 9, 12, 18 and 24. The acceptable tolerance is +/- 10% for both innovators and generics. For latanoprost, this would mean that the concentration could vary from 0.00450% to 0.00550%. Since degradation is usually temperature dependent, the accelerated stability studies (i.e., studies at higher temperatures than permitted on the labeling) will typically show a problem well before that recommended temperature conditions. The FDA also looks for trends, so if the projected degradation line will fall outside the acceptable parameters before the intended shelf life, the shelf life is shortened to make sure this would not happen.

While there is often concern that the active ingredient of a product will degrade or be absorbed into the plastic bottle during shelf life, there are often opposing factors which may serve to balance the concentration. An example of this is the water loss that can occur through some plastic bottles. The effect of water loss is to increase the relative concentration of the active ingredient by decreasing the total volume. The best way to monitor the quality of a product throughout shelf life is to actually monitor representative samples of the product throughout the shelf life period. This is done with both innovator products and generics on a regular basis.

Q: What about stability studies and their completion?

Dr. Chambers: Stability studies are required of generics. Stability studies are designed to monitor a representative portion of different lots of the drug product throughout the full shelf life, although at the time of approval, only the first part of these studies may have been completed. When full shelf life data is not available, stability studies under accelerated conditions (studies at higher temperatures) are expected. Stability studies under accelerated conditions will generally predict the stability of a drug product at later time points under normal storage conditions. This is also true of the innovators, which rarely have completed stability studies at the time of approval.

Q: I've been told the issue with the PG analogs is not as much degradation as adsorption of the drug to the bottle material. If the generic companies use a standard bottle and standard concentration (0.005%) then would that affect the product concentration and stability?

Dr. Chambers: As it happens there are not that many makers of bottles, so it is not uncommon for both the innovator and a generic to use the same source of bottles. Regardless, we set specifications for both the innovators and the generics to catch migrating materials from the bottles into the solutions and vice versa. Most innovator products have several known impurities that come either from the bottles, degradation of one of the components in the product, inks on the box, glue on the box, or an interaction between these. Besides the known impurities from the bottles, we set specifications to detect potential unknown impurities at a level of 0.1% of the active ingredient. At least one batch per year is expected to be placed in an ongoing stability program and if it falls out of its specifications at any time, the failure can subject the entire lot to be recalled.

Q: Since almost half of experienced patients touch the bottle tip to their eye or adenexae, do the generic formulations inhibit contamination as well?

Dr. Chambers: Multidose ophthalmic products are required to have an antimicrobial preservative. They have to meet the USP preservative effectiveness test which consists of purposely contaminating the solution with particular bacteria and fungus and observing the kill rate. There are several bacteria specified in this test including Pseudomonas. Some of the ophthalmic antimicrobials are self preserving, but the rest of the ophthalmic drug products have an antimicrobial preservative specifically added to the formulation for this purpose. If they do not have an antimicrobial preservative, they generally have to be packaged as a maximum volume of 0.5 mL and labeled for single time use. We have a provision to potentially label an ophthalmic drug product for a single day's use if it can be demonstrated that the product will not support the growth of bacteria for at least 48 hours, however, so far no product that has been able to meet this standard has asked for it.

Q: I have noticed that some generics have only white caps and white bottles, and are not following the color codes we have come to expect in brand name medications.

Dr. Chambers: If you notice a generic (or innovator) not following the color code, please let me know. There was a period of time when it was missed on some applications, the review is supposed to catch them now.

For further questions, Dr. Chambers can be contacted at Wiley.Chambers@fda.hhs.gov

Approvals

Compiled by Cynthia Mattox, MD, Chair, AGS Patient Care Committee. Reviewed by Dr. Chambers, September 2011; Reaffirmed May 2015.

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