Contains Nonbinding Recommendations

Draft Guidance on Timolol Maleate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Timolol maleate
Dosage Form; Route:	Solution, gel forming/drops; ophthalmic
Strength:	0.25% and 0.5% (Eq Base)
Recommended Study:	One option: in vitro study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

i. The Test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).[3]

ii. Acceptable comparative physicochemical characterization of the Test and Reference Standard (RS) products including pH, specific gravity, buffer capacity, osmolality, and viscosity. Comparative studies should be performed on at least three batches of both the Test product and RS product.[4]

iii. Acceptable comparative rheological properties of the Test and RS gels formed using physiologically relevant media and dilution.[5] This can include measuring the gel strength and/or the stress-strain profile including yield point. Testing should be performed on at least three batches of both the Test and RS products.

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[1] Q1 (Qualitative sameness) means that the Test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the Test product are within ±5% of those used in the RLD product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. Guidance for industry *ANDA Submissions –Refuse-to-Receive Standards.*
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[5] Gels should be formed using simulated tear fluids. See, e.g., Carlfors, J., et al., Rheological evaluation of Gelrite® In Situ Gels for Ophthalmic Use, Eur. J. of Pharm. Sci., 6, 113-119, (1998), and Paulsson, M., et al., Rheological Studies of the Gelation of Deacetylated Gellan Gum (Gelrite®) in Physiological Conditions, Eur. J. of Pharm. Sci, 9, 99-105, (1999)