In vitro bioequivalence testing for topical ophthalmic suspension products

Complex Generic Drug Product Development Workshop

Session 4: Complex Route of Delivery: Ophthalmic

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In Vitro BE for Generic Topical Ophthalmic Products: When, How and Why

- Regulatory background and when in vitro testing may be considered / recommended for demonstrating bioequivalence.
- Current thinking on the information to support an in vitro approach.
- GDUFA* research and development of product-specific guidances for ophthalmic products.

*GDUFA: Generic Drug User Fee Amendments

Demonstrating Bioequivalence

For simple formulations, such as solutions, where ***manufacturing conditions or processing steps do not*** affect the properties of the final product "the in vivo bioavailability or bioequivalence of the drug product may be self-evident" 21 CFR 320.22(b).

For more complex products where ***manufacturing conditions, processing steps, or excipient choice could*** affect the properties of the final product, the "[b]ioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products." CFR 320.24(a)

Demonstrating Bioequivalence

- Comparative study options to demonstrate BE:
  1) in vivo PK studies;
  2) in vivo pharmacodynamic (PD) effect studies;
  3) clinical endpoint studies; and
  4) in vitro studies.
- Each BE option has inherent benefits, risks, and limitations. Not all options may be appropriate for a proposed generic.
- *Ultimately, a BE approach must provide an accurate, sensitive, and reproducible measure to ensure bioavailability and BE*.

Formulation Q1/Q2 Sameness

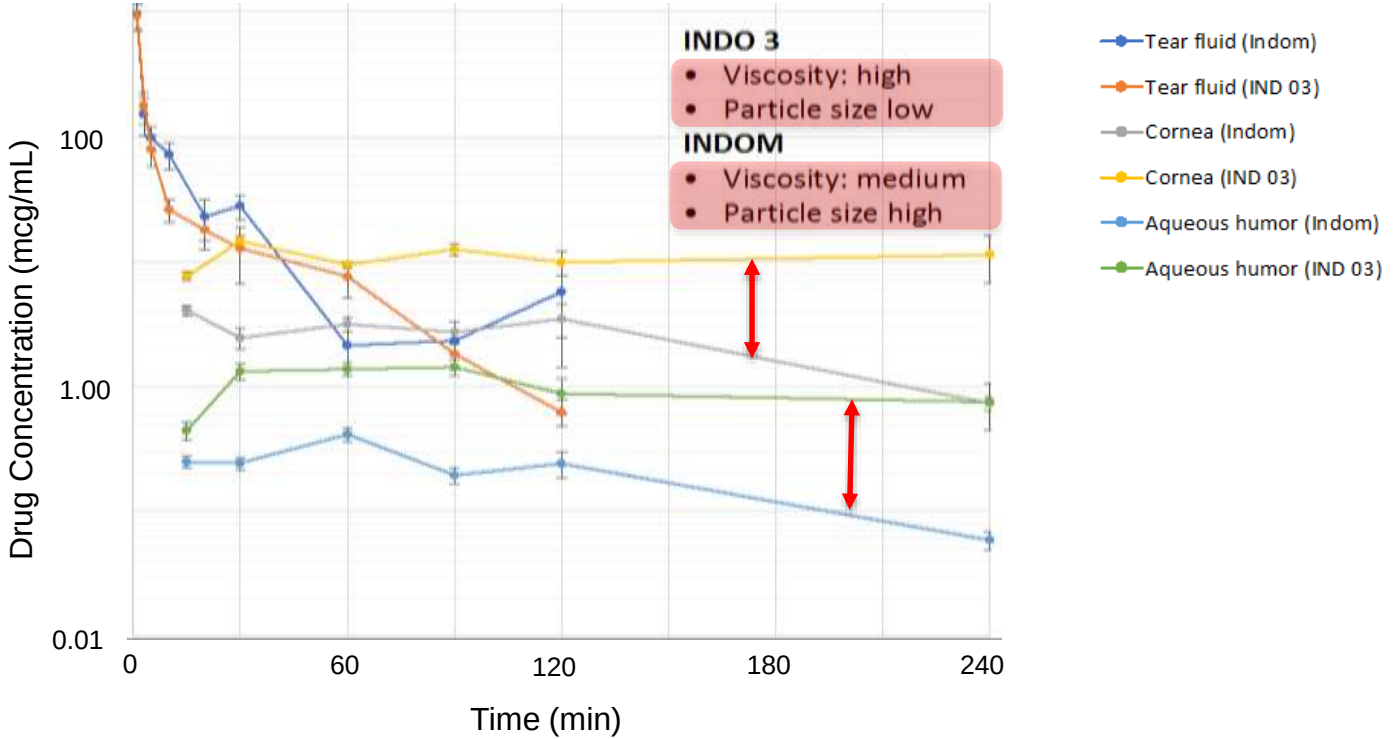
Generic ophthalmic topical drug products should be formulated qualitative (Q1) and quantitative (Q2) similar (i.e. ± 5%) to the reference listed drug (RLD).

- Ophthalmic may differ in preservative, buffer, tonicity, or thickening agent (CFR 314.94(a)(9)(iv)), but such differences cannot change product safety or efficacy.

- Changes in formulation may affect ocular bioavailability by altering drug retention time and/or permeability of ocular tissues.

Formulation Q1/Q2 Sameness

- Increasing viscosity and reducing particle size can increase ocular drug absorption



1. From GDUFA grant: 1U01FD005180 (Arto Urtti: Univ EastFinland)

Formulation Q1/Q2 Sameness

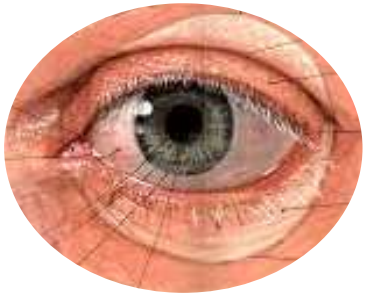
- So, despite a similar allowance (to parenteral products) provided for ophthalmic drug products in 21 CFR 314.94(a)(9)(iv), FDA has determined that, as a scientific matter, any qualitative (Q1) or quantitative (Q2) deviations from the RLD should be accompanied by an appropriate in vivo BE study or studies.[2]

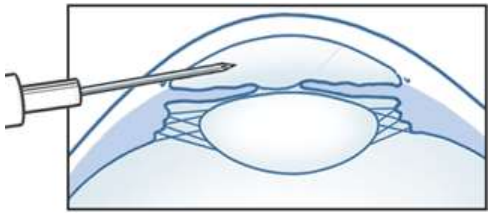
2. Guidance for Industry: *ANDA Submissions – Refuse-to-Receive Standards*

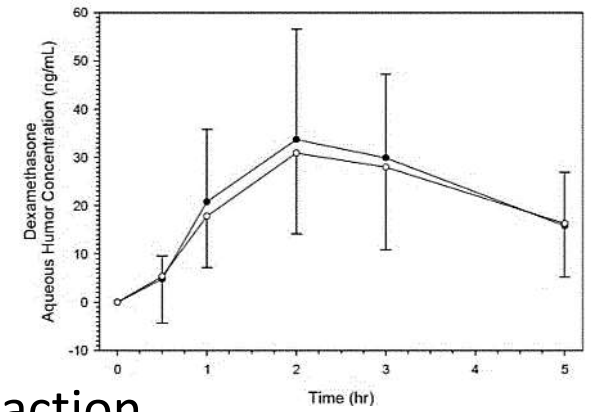
Demonstrating BE of Topical Ophthalmic Products

Comparative measure of bioequivalent in vivo performance of the generic to RLD.

Local PK: Aqueous humor







3

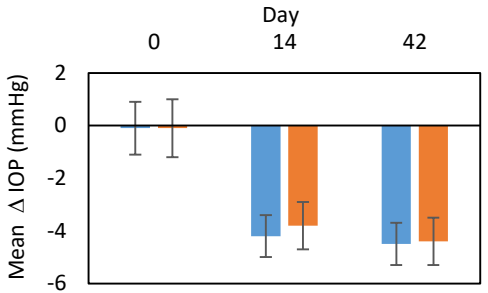
- Compare drug concentration at the local site of action.
- Sparse sampling, single sample per subject, gives rise to the need for large study population and statistical bootstrapping.[4]

3. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/050818s000clinpharmr.pdf
4. See *Draft Guidance on Loteprednol Etabonate* for aqueous humor PK study recommendations

Demonstrating BE of Topical Ophthalmic Products

Comparative measure of bioequivalent in vivo performance of the generic to RLD.

Comparative clinical endpoint:



- Compare a pivotal clinical outcome (e.g., change in intraocular pressure (IOP) over 42 days)[5]
- Endpoint can be semi-qualitative and confounded by patient disease state
- Poor discriminator between similar products and requires large patient population to adequately power the study

5. See *Draft Guidance on Brinzolamide* for IOP comparative clinical study recommendations

In Vitro BE: Current Thinking

- Totality of evidence approach to confirm that the physicochemical properties of two products are comparative, such that they must have comparable in vivo bioavailability, and bioequivalence may be considered self-evident.[6]

6. "A product that meets Q1/Q2 sameness, comparability of physicochemical properties, and an acceptable comparative in vitro release rate should become available at the site of action at a rate and to an extent that is not significantly different from that of the RLD, thus meeting the requirement for demonstrating bioequivalence." FDA-2014-P-2301, FDA-FDA-2016-P-2781, FDA-2016-P-2782

Additional Considerations

- Even if a product is formulated Q1/Q2, there could be differences in the arrangement of matter within the dosage form which may impact product performance
- These differences in arrangement of matter can only arise from differences in manufacturing, processing, or excipient grade/source
- These differences can be evaluated by comparative physicochemical tests
- Sameness in physicochemical characteristics demonstrate overall product sameness, and thus equivalence:
  - *Similar to testing used to support batch-to-batch equivalence of a product*.

Information to Support In Vitro BE

- Establish Q1/Q2 formulation sameness to RLD
- Identify product critical quality attributes (CQAs)
  - Properties affected by manufacturing process, formulation steps, or excipient grade/source
  - Literature and/or internal studies on product CQAs that affect product quality and/or bioavailability
- Comparative testing of Generic and RLD product CQAs
  - Justification for analytical method(s) used
  - Analytical method development
  - Justification for sameness criteria

Facilitating Generics

GDUFA Research[7]

- OGD funds and conducts research to provide new tools to evaluate generic drug equivalence and for industry to efficiently develop new generic products.
- Ocular projects include
  - Assessing product CQAs
  - Developing new in vitro release testing (IVRT) methods
  - Developing new analytical and statistical methods
  - Developing in vitro in vivo correlations (IVIVC)
  - Ocular drug molding and simulation

Product-Specific Guidances[8]

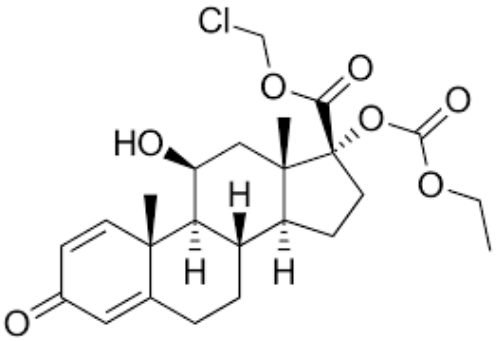
- FDA develops guidance recommendations of current thinking on best methods for demonstrating BE.
- These are recommendations to guide generic drug product development.
- Alternative approaches to the guidance can be used to demonstrate BE.
  - A Pre-ANDA meeting request can be submitted to gain FDA feedback on the proposed approaches.

7. https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm
8. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Example of In Vitro BE Approach

Loteprednol etabonate ophthalmic suspension 0.05%

- Topical administrated corticosteroid for the treatment of steroid responsive inflammatory ocular conditions.



Loteprednol etabonate

Each mL contains:
Loteprednol etabonate, benzalkonium chloride, tyloxapol, edetate disodium, glycerin, povidone, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

Example of in vitro BE approach

Draft Guidance on Loteprednol Etabonate

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:	Loteprednol etabonate
Dosage Form; Route:	Suspension/drops; ophthalmic
Strength:	0.5%
Recommended Studies:	Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of 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. The comparative study should be performed on at least three batches of both the test and RS products and should include:[4]

- Comparable appearance, pH, specific gravity, osmolality, surface tension, and viscosity
- Comparable soluble fraction of loteprednol etabonate in the final drug product

Two options for demonstrating BE

Formulation considerations (i.e., Q1/Q2) to be eligible for the in vitro option

Recommended in vitro tests to demonstrate BE:

- Surface tension and viscosity can measure potential variability in formulation stabilizers.
- Manufacture process can change drug partitioning amount, which can affect rate of drug bioavailability

Example of in vitro BE approach

- Comparable drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

iii. Acceptable comparative in vitro drug release of loteprednol etabonate from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

II. In vivo option:

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, crossover or parallel design, *in vivo* in aqueous humor
   Strength: 0.5%
   Subjects: Patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery.
   Additional Comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Loteprednol etabonate in aqueous humor

Bioequivalence based on (90% CI): Loteprednol etabonate

Recommended tests to demonstrate BE (cont):

- Particle size is dependent on the manufacture method and affects drug bioavailability and clearance.
- In vitro drug release test is a performance test (not intended to simulate in vivo conditions) that can discriminate manufacturing effects

Alternatively, an in vivo aqueous humor PK study can be used to demonstrate BE.

- Formulation can, but does not need to, be Q1/Q2 - 21 CFR 314.94(a)(9)(iv)

Summary

- A BE approach must provide an accurate, sensitive, and reproducible measure to ensure bioavailability and BE
- With a Q1/Q2 formulation an in vitro BE approach demonstrating product sameness may be considered, provided;
  - Information on product CQAs, analytical methods, and how these support BE
  - Data demonstrating analytical sensitivity to detect manufacturing or formulation induced product differences
  - Information on how variability in a CQA can affect in vivo bioavailability
  - Comparative data on Generic and RLD product
- OGD funds research and develops product-specific guidances to aid industry's development and ultimate approval of high quality generic products.

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