Generic ophthalmic drug products, physical characteristics, and bioequivalence

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Generic Ophthalmic Products

- Generic drug regulatory framework

  Therapeutic equivalence to a Reference Listed Drug (RLD) product (i.e., brand)

  - Pharmaceutical equivalence: e.g., same active, excipients, route, and dosage form
  - Bioequivalence: types of BE studies for ophthalmic products

- Physical characteristics
  - Identifying, measuring, and understanding how the physicochemical properties of a product affect its quality and performance

- GDUFA* research and development of product-specific guidances for ophthalmic products
  - *Ensure, through a scientific and regulatory process, that Americans receive safe, effective, and high-quality generic drugs.*

*GDUFA: Generic Drug User Fee Amendments

Regulatory Pathways of Drug Applications

New Drug Application (NDA)	Abbreviated NDA (ANDA)
A drug product that may have a New Molecular Entity (NME), new formulation, and/or new indication and includes information/investigations to demonstrate its safety and effectiveness	Must ***reference a listed drug***, contain information to establish ***therapeutic equivalence***, and may not be submitted if studies are necessary to establish safety or effectiveness
Labeling Pharm/Tox Chemistry Manufacturing Controls Microbiology Inspection Testing	*Labeling** Pharm/Tox Chemistry Manufacturing Controls Microbiology Inspection Testing
Animal Studies Clinical Studies Bio availability	Bioequivalence

*ANDA labeling is the same as the labeling for the listed drug (with limited exceptions)

Topical Ophthalmic Drug Products

Dosage Form (2017 sales)	Number of Reference (RLD) products in USA[1]	% of RLDs that have an approved generic[2]
Solutions ($5.9B)	~105	55%
Suspension ($1.1B)	~21	23%[3]
Emulsion ($4.1B)	3	0
Ointment ($660M)	~13[4]	30%[3]

1. Includes RLD products that are no longer marketed but that can still serve as a reference drug
2. Although approved, a generic may not be currently marketed
3. Most (>75%) were approved pre-Hatch-Waxman (1984)
4. A number of ointment NDAs have been discontinued, but may be re-designated as RLD by industry request

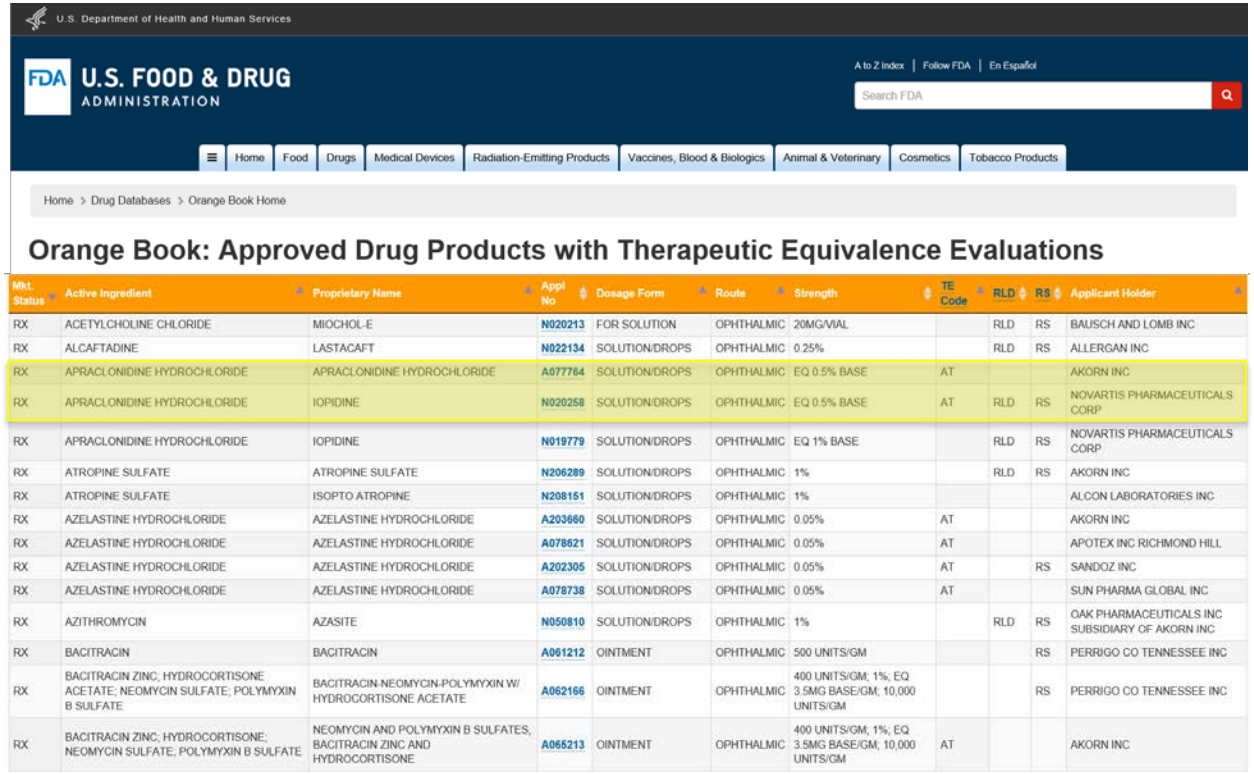
Approval and subsequent availability to a generic version of a branded ophthalmic product has been shown to reduce medication costs and increase patient adherence.

Popovic, Marko, et al. "Comparative cost evaluation of brand name and generic ophthalmology medications in Ontario." *Canadian Journal of Ophthalmology* 53.2 (2018): 173-187.

Stein, Joshua D., et al. "Impact of the introduction of generic latanoprost on glaucoma medication adherence." *Ophthalmology* 122.4 (2015): 738-747.

Schlenker, Matthew B., Graham E. Trope, and Yvonne M. Buys. "Comparison of United States and Canadian glaucoma medication costs and price change from 2006 to 2013." *Journal of ophthalmology* 2015.

Orange Book



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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ACETYLCHOLINE CHLORIDE	MIOCHOL-E	N020213	FOR SOLUTION	OPHTHALMIC	20MG/VIAL		RLD	RS	BAUSCH AND LOMB INC
RX	ALCAFTADINE	LASTACAFT	N022134	SOLUTION/DROPS	OPHTHALMIC	0.25%		RLD	RS	ALLERGAN INC
RX	APRACLONIDINE HYDROCHLORIDE	APRACLONIDINE HYDROCHLORIDE	A077764	SOLUTION/DROPS	OPHTHALMIC	EQ 0.5% BASE	AT			AKORN INC
RX	APRACLONIDINE HYDROCHLORIDE	IOPIDINE	N020258	SOLUTION/DROPS	OPHTHALMIC	EQ 0.5% BASE	AT	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	APRACLONIDINE HYDROCHLORIDE	IOPIDINE	N019779	SOLUTION/DROPS	OPHTHALMIC	EQ 1% BASE		RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	ATROPINE SULFATE	ATROPINE SULFATE	N206289	SOLUTION/DROPS	OPHTHALMIC	1%		RLD	RS	AKORN INC
RX	ATROPINE SULFATE	ISOPTO ATROPINE	N208151	SOLUTION/DROPS	OPHTHALMIC	1%				ALCON LABORATORIES INC
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A203660	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			AKORN INC
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A078621	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			APOTEX INC RICHMOND HILL
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A202305	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT		RS	SANDOZ INC
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A078738	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			SUN PHARMA GLOBAL INC
RX	AZITHROMYCIN	AZASITE	N050810	SOLUTION/DROPS	OPHTHALMIC	1%		RLD	RS	OAK PHARMACEUTICALS INC SUBSIDIARY OF AKORN INC
RX	BACITRACIN	BACITRACIN	A061212	OINTMENT	OPHTHALMIC	500 UNITS/GM			RS	PERRIGO CO TENNESSEE INC
RX	BACITRACIN ZINC; HYDROCORTISONE ACETATE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	BACITRACIN-NEOMYCIN-POLYMYXIN W/ HYDROCORTISONE ACETATE	A062166	OINTMENT	OPHTHALMIC	400 UNITS/GM; 1%; EQ 3.5MG BASE/GM; 10,000 UNITS/GM			RS	PERRIGO CO TENNESSEE INC
RX	BACITRACIN ZINC; HYDROCORTISONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	NEOMYCIN AND POLYMYXIN B SULFATES, BACITRACIN ZINC AND HYDROCORTISONE	A065213	OINTMENT	OPHTHALMIC	400 UNITS/GM; 1%; EQ 3.5MG BASE/GM; 10,000 UNITS/GM	AT			AKORN INC

FDA maintains a list of approved drug products that have not been withdrawn for safety or efficacy reasons

New ‘Brand’ Drug

- New Drug Applications (NDA) designated with an ***N*** before the application number and are often designated as a Reference Listed Drug (RLD)

Generic Drug

- Abbreviated NDAs (ANDA) designated with an ***A*** before the application number and if PE and BE are demonstrated they will be given a TE code designation.
- ANDAs rely on, are TE to, an RLD.

Therapeutic Equivalence

Products classified as TE can be substituted with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product.

A generic product that is TE to the RLD product must be:

- Pharmaceutical Equivalent (PE)
  - Contain identical amount of the identical active ingredient(s)
  - Identical dosage form
  - Identical route of administration
  - **Generic ophthalmic products should contain the same inactive ingredients (Q1) at same concentration (Q2)**, 21 CFR 314.94 (a)(9)(v)
  - Meet compendial or other applicable standards
- Bioequivalent (BE)
  - Commonly understood as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in PEs becomes available at the site of drug action when administered under similar conditions

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).

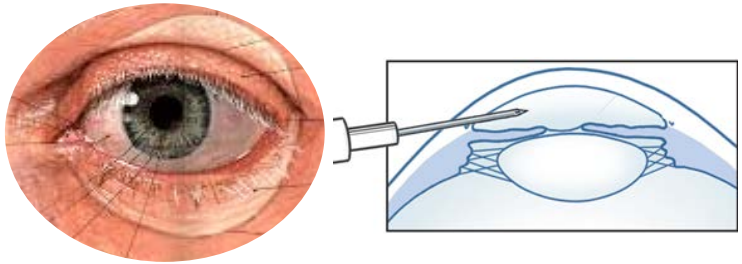
For more complex products where ***manufacturing conditions, processing steps, or excipient choice could*** affect the properties of the final product, the "[b]ioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro 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 BE studies;
  3) clinical endpoint BE 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.***

Demonstrating BE: In Vivo PK

Local PK: Aqueous Humor



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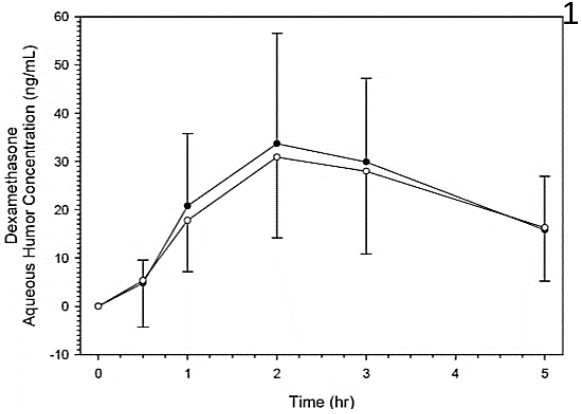

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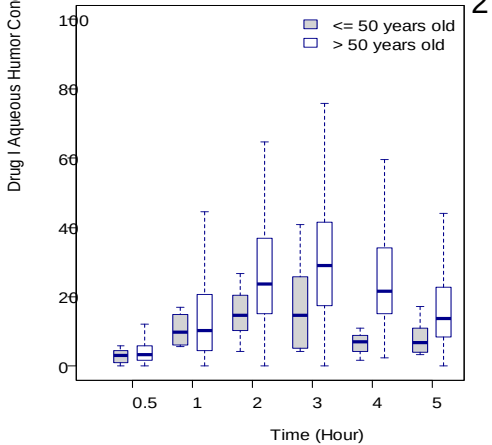


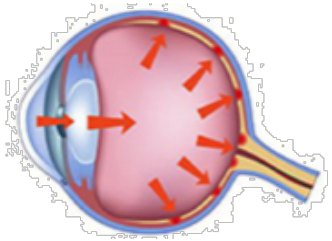
- Compare drug concentration at the local site of action.
- Sparse sampling, single sample per subject, gives rise to the need for large study population and statistical bootstrapping.[3]
- Subject Ethnicity and age affects AH PK of topical ophthalmic corticosteroid suspensions[2]

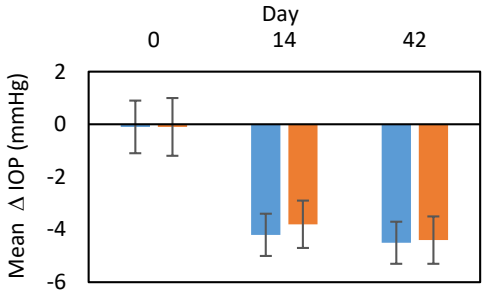
1. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/050818s000clinpharmr.pdf
2. Harigaya, Yoriko, et al. *Pharmaceutical research* 36.1 (2019): 13.
3. See *Draft Guidance on Loteprednol Etabonate* for aqueous humor PK study recommendations

Demonstrating BE: In Vivo BE Clinical Endpoint

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

Comparative clinical endpoint BE study:





- Compare a pivotal clinical outcome (e.g., change in intraocular pressure (IOP) over 42 days)[1]
- 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

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

Demonstrating BE: In Vitro Sameness

- Totality of evidence approach to confirm that the physicochemical properties of two similarly formulated products are comparative, such that bioequivalence may be considered self-evident.*

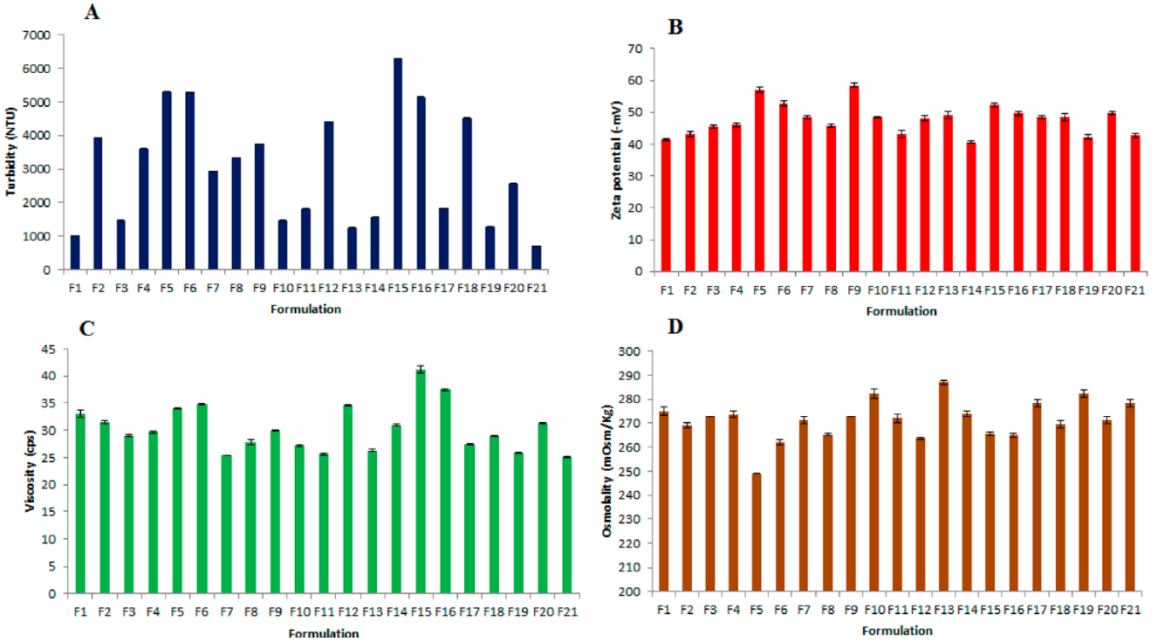
* "A product that meets Q1/Q2 sameness, comparability of physicochemical properties, and an acceptable comparative in vitro release rate should become available at the site of action at a rate and to an extent that is not significantly different from that of the RLD, thus meeting the requirement for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

In Vitro BE: Additional Considerations

- Even if a product is formulated the same (Q1/Q2), there could be differences in the arrangement of matter within the dosage form that 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*.

Product Critical Quality Attributes (CQA)

Identifying the CQAs (i.e. physicochemical properties) of a product, how the manufacturing process may affect these CQAs, and developing sensitive methods to compare these properties is fundamental to ensuring product quality and in vitro BE.



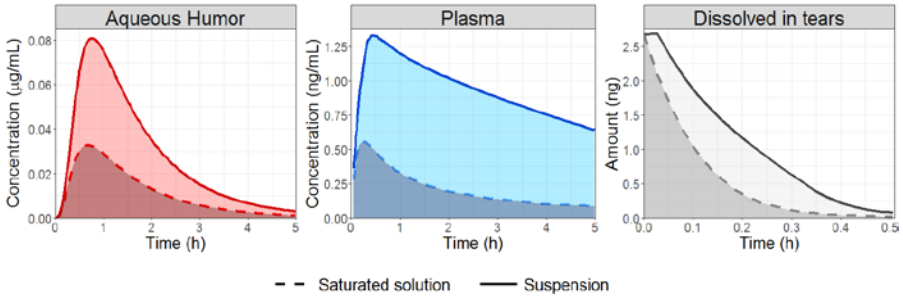
Research on 21 (Q1/Q2) ophthalmic emulsion formulations indicated that: particle size, zeta potential, viscosity, osmolality, and turbidity were CQAs most dependent ($p < 0.05$) on changes in the manufacturing process variables.

Rahman, Z., Xu, X., Katragadda, U., Krishnaiah, Y.S., Yu, L. and Khan, M.A., 2014.. Molecular pharmaceutics, 11(3), pp.787-799.

Critical Properties of Ophthalmic Suspensions:

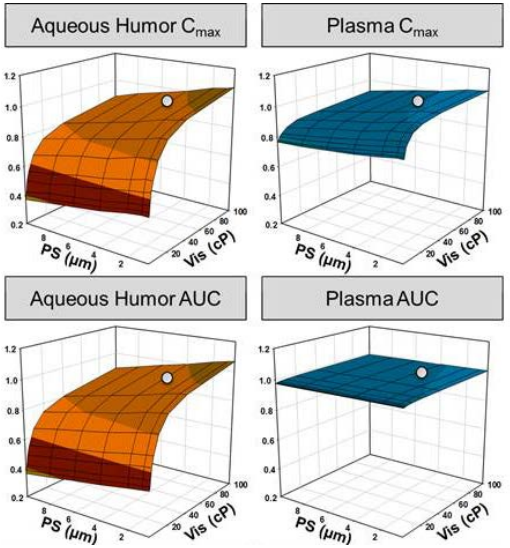
Formulation viscosity and drug particle size (PS) on ocular bioavailability

In vitro and in vivo formulation testing in combination with PBPK modeling



Saturated solution vs. suspension simulations

- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks



Parameter sensitivity analysis in rabbit on PS and viscosity

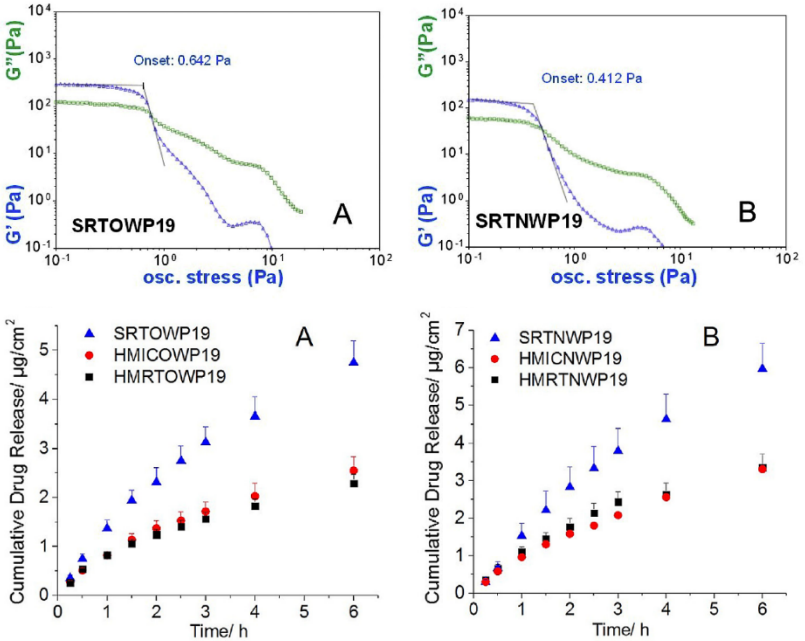
- Viscosity is a critical attribute affecting BE
- Plasma/systemic PK is not reflective of local concentrations

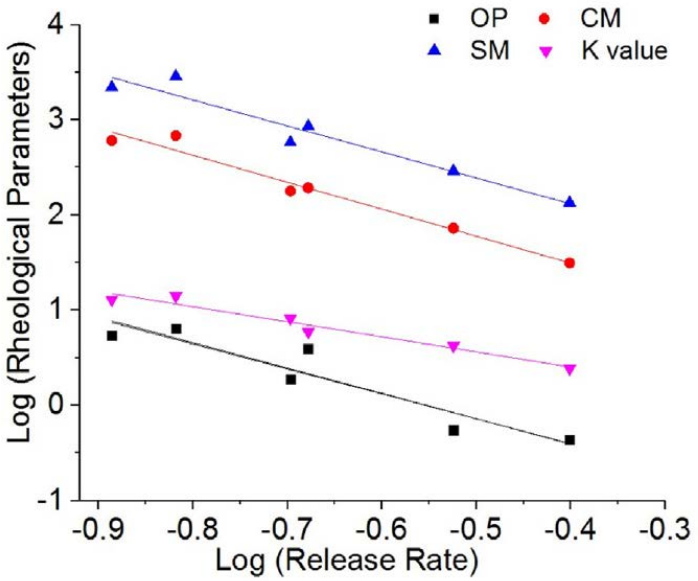
LeMerdy, Maxime, et al. *In submission AAPS Journal* (AAPSJ-D-18-00376)
LeMerdy, Maxime, et al. ASCPT AM 2019 poster.

Source: Dr. Andrew Babiskin, DQMM/ORS/OGD/CDER, 2019 ASCPT meeting

Critical Properties of Ophthalmic Ointments:

Correlation between rheology and in vitro release





Bao, Q., et al. International journal of pharmaceutics 523.1 (2017): 310-319. (FDA-1U01FD005177-01)
Bao, Q., et al. International Journal of Pharmaceutics (2017). (FDA-1U01FD005177-01)

Facilitating High-Quality Generics

GDUFA Research[1]

- 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 modeling and simulation

Product-Specific Guidances[2]

- 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.

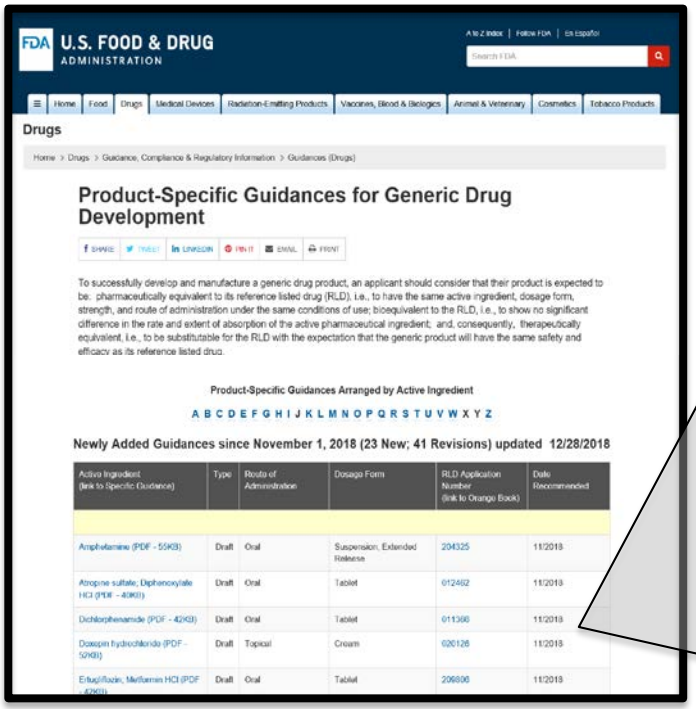
Pre-ANDA meetings[3]

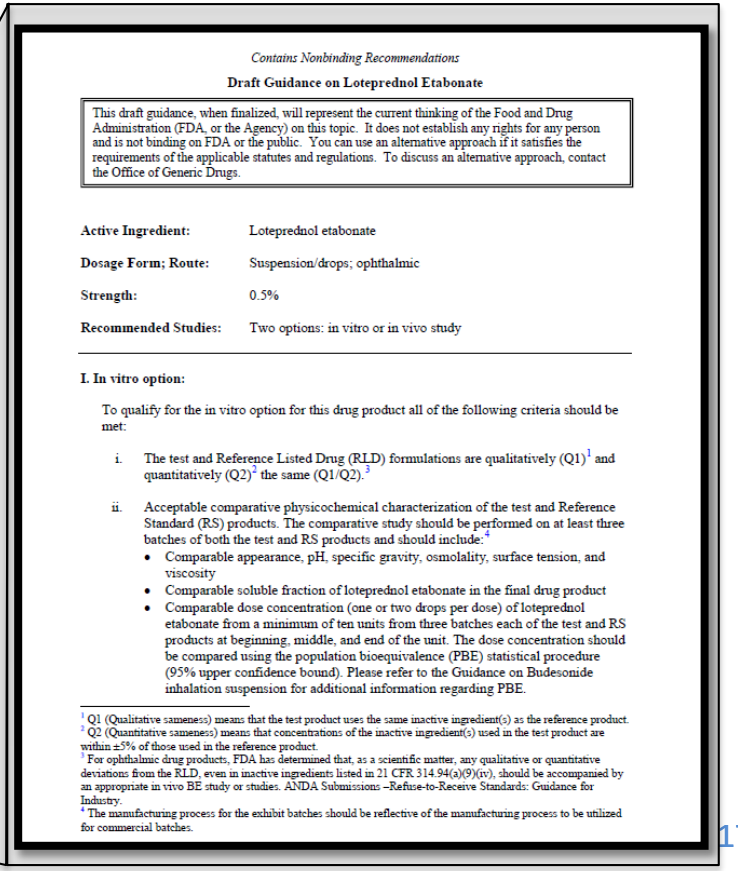
- Industry can request a meeting to gain FDA feedback on proposed product development and BE approach.

1.https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm
2. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
3. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578366.pdf

Product-Specific Guidance

FDA develops and maintains a list of product-specific guidance that outline the Agency's current thinking on generic drug product development





Contains Nonbinding Recommendations

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
- Comparable dose concentration (one or two drops per dose) of loteprednol etabonate from a minimum of ten units from three batches each of the test and RS products at beginning, middle, and end of the unit. The dose concentration should be compared using the population bioequivalence (PBE) statistical procedure (95% upper confidence bound). Please refer to the Guidance on Budesonide inhalation suspension for additional information regarding PBE.

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference 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 reference 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. ANDA Submissions –Refuse-to-Receive Standards: Guidance for Industry.
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

Summary

- A therapeutically equivalent generic product must demonstrate that it is pharmaceutically equivalent and bioequivalent to the RLD ‘brand’ product
- 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, develops product-specific guidances, and holds pre-ANDA meetings to aid industry’s development and ultimate approval of high-quality generic products.

Acknowledgements

OGD

- Rob Lionberger
- Lei Zhang
- Markham Luke
- Jeff Jiang
- Darby Kozak
- Yan Wang
- Bin Qin
- Andrew Babiskin
- Jianghong Fan
- Jenna Hammer

OPQ

- Bing Cai
- Patricia Onyimba
- Vincent Li
- Xiaoming Xu

OGDP & CDRH

- Jiwen Zheng
- Harry Schwirck
- James Myers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