



# Bioequivalence Requirements for Ophthalmic Products: CMC and Clinical/Pharmacokinetic Considerations

**Stephanie H. Choi, Ph.D.**

Division of Therapeutic Performance/Office of Research and Standards

Office of Generic Drugs

US Food and Drug Administration

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*This presentation reflects the views of the author and should not be construed to represent FDA's views or policies*

# Outline

- Abbreviated New Drug Application (ANDA) or 505 (j) regulatory pathway
- Bioequivalence considerations of generic ophthalmic products:
  - Changes in Inactive Ingredients
  - Solutions vs. Non-solutions
  - Types of BE studies:
    - Clinical endpoint study
    - PK study
    - In vitro study

# Abbreviated New Drug Applications (ANDA)

- **Drug products that are the same as the Reference Listed Drug:**
  - Same active ingredient(s)
  - Same dosage form
  - Same route of administration
  - Identical in strength or concentration
  - Same labeling, including conditions of use
  - Are bioequivalent

## Bioequivalence

- Refers to the absence of a significant difference in the rate and extent to which the active ingredient in a pharmaceutically equivalent drug product becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions

## Some Key Components of Review Process: New Drug Applications (NDAs) vs. ANDAs

### Brand-name drugs

- Chemistry
- Manufacturing
- Controls
- Pharmaceutical Development
- Labeling
- Animal studies
- Clinical studies
- Bioavailability

### Generic drugs

- Chemistry
- Manufacturing
- Controls
- Pharmaceutical Development
- Labeling
- Bioequivalence




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## Drugs

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# Product-Specific Recommendations for Generic Drug Development

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 1362]

[A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [Q](#) [R](#) [S](#) [T](#) [U](#) [V](#) [W](#) [X](#) [Y](#) [Z](#)

Newly Added Recommendations since June 30, 2015 (40 New; 18 Revisions) updated 9/18/2015

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended
<a href="#">Acidinium bromide (PDF - 97KB)</a>	Draft	inhalation	powder, metered	<a href="#">202450</a>	9/2015
<a href="#">Acyclovir (PDF - 47KB)</a>	Draft	Oral	Tablet, buccal	<a href="#">203791</a>	9/2015
<a href="#">Aminocaproic acid (PDF - 39KB)</a>	Draft	Oral	Tablet	<a href="#">015197</a>	9/2015
<a href="#">Apremilast (PDF - 23KB)</a>	Draft	Oral	Tablet	<a href="#">205437</a>	9/2015
<a href="#">Benazepril HCl; Hydrochlorothiazide</a>	Draft	Oral	Tablet	<a href="#">20033</a>	9/2015

*Contains Nonbinding Recommendations*

## **Draft Guidance on Dexamethasone; Tobramycin**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Dexamethasone; Tobramycin

**Form/Route:** Suspension/Ophthalmic

**Recommended study:** 2 studies

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints  
 Design: Single-dose, parallel design, in vivo in aqueous humor  
 Strength: 0.05% / 0.3%  
 Subjects: Patients undergoing indicated cataract surgery  
 Additional Comments: Specific recommendations are provided below.

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2. Type of study: In vitro bioequivalence study  
 Design: In vitro microbial kill rate study  
 Strength: 0.05% / 0.3%  
 Subjects: Not applicable  
 Additional Comments: Specific recommendations are provided below

# Product-Specific Recommendations for Generic Drug Development

- Ophthalmic guidances (27) as of Oct 2015:
  - Solution (13)
  - Ointment (3)
  - Suspension (10)
  - Emulsion (1)



# Changes in Inactive Ingredients

21 CFR 314.94 (a)(9)(iv) – *Inactive ingredient changes permitted in drug products intended for ophthalmic use.*

Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients (qualitatively the same – “Q1”) and in the same concentration (quantitatively the same – “Q2”) as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, substance to adjust tonicity, or thickening agent** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

A formulation which contains an excipient not contained in the RLD and not considered to be an “exception excipient” cannot be submitted as an ANDA.

## Q1/Q2 Equivalent Formulations

- All inactive ingredients – **including preservative, buffer, substance to adjust tonicity and thickening agent** – are the same as that in the RLD and in the same concentration
- The Test does not contain an inactive ingredient not contained in the RLD
- The difference in amounts of inactive ingredients between Test and RLD are less than 5%

# Q1/Q2 Equivalent Formulations

- Solutions – Bioequivalence is self-evident (waiver of in vivo study under 21 CFR 320.22 (b)(1))
- Non-solutions – Bioequivalence should be demonstrated by one or more of the following studies:
  - Clinical endpoint study
  - PK study in aqueous humor
  - Microbial kill rate study
  - In vitro studies (Q3 characterization)

# Clinical Endpoint Studies

- Posted draft guidances:
  - Brimonidine tartrate; Brinzolamide suspension
  - Brinzolamide ophthalmic suspension
- Double-masked, parallel, two-arm study in patients with chronic open angle glaucoma or ocular hypertension in both eyes
- Drug is applied as one drop in each eye 3 times/day for 6 weeks
- Primary endpoint: mean difference in IOP of both eyes between the two treatment groups at 4 time points (pre-dose, 2h, 2w, 6 w)

# Clinical Endpoint Studies

- Posted draft guidances:
  - Nepafenac ophthalmic suspension, 0.1% and 0.3%
- Double-masked, parallel, placebo controlled study in patients undergoing cataract extraction
- One drop administered to the operative eye daily for 14 days
- Primary endpoint: proportion of subjects with cure at Post-op Day 14 defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain

## PK Study in Aqueous Humor

- Posted draft guidances:
  - Dexamethasone; Tobramycin ophthalmic ointment
  - Loteprednol Etabonate ophthalmic suspension
  - Prednisolone Acetate ophthalmic suspension
- Single-dose, parallel study in patients undergoing cataract surgery
  - Option to conduct a cross-over design but washout should not exceed 35 days

## PK Study in Aqueous Humor

- One sample of aqueous humor collected from one patient
  - Number of subjects to be enrolled should be determined from a pilot study
  - Bootstrapping technique can be used to evaluate bioequivalence for the Test to RLD ratio of AUC and C<sub>max</sub> (90% confidence interval must be between 80-125%)
- \*For combination products which include an antimicrobial agent, the Microbial Kill Rate Study should also be performed

## Microbial Kill Rate Study

- Posted draft guidances:
  - Dexamethasone; Tobramycin ophthalmic suspension
  - Loteprednol Etabonate; Tobramycin ophthalmic suspension
- In Vitro study to evaluate the antibiotic component (tobramycin) of the combination product



## Microbial Kill Rate Study

- Antimicrobial activity of Test and RLD should be compared against all organisms listed in the USP Preservative Effectiveness Test and all organisms listed in the “Indications” section of the RLD label.
- At least 12 replicates should be used for each kill rate study of each organism.
- Population for each test organism/product at designated time intervals is determined by counting surviving colonies after incubation.
- Equivalence should be evaluated by using the two one-sided test procedure to determine the 90% confidence interval for the T/R ratios of average kill rate for each sampling time point.

# In Vitro Studies (Q3 Characterization)

- Posted draft guidance:
  - Cyclosporine ophthalmic emulsion
- Two options: In Vitro or In Vivo (clinical endpoint) Study
- Acceptable comparative physicochemical characterization of the Test and RLD
- Acceptable comparative in vitro drug release rate from Test and RLD

# In Vitro Studies

## (Q3 Characterization)

- 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 (structural similarity – “Q3”) arise from differences in manufacturing
- Differences in Q3 can be evaluated by comparative physicochemical data
- Sameness in physicochemical characteristics will ensure equivalence in in vivo performance

# In Vitro Studies (Q3 Characterization)

- In vitro methods can detect formulation and manufacturing changes
  - **Quality by Design Approach for Understanding the Critical Quality Attributes of Cyclosporine Ophthalmic Emulsion.** *Mol. Pharmaceutics*, **2014**, *11* (3), pp 787–799
  - Q1/Q2 test products (21) were formulated by changing formulation and process variables
  - Results indicated that a significant change in the physicochemical properties was predictive of changes in the manufacturing process

# In Vitro Studies (Q3 Characterization)

- Recommended characterization data:
    - Globule size distribution (with PBE analysis)
    - Viscosity
    - pH
    - Zeta potential
    - Osmolality
    - Surface tension
- \*These characterization studies are specific to this product, and do not apply to other products.

# In Vitro Studies (Q3 Characterization)

- Globule size distribution
  - Drug release/clearance
  - Product stability
- Viscosity
  - Ocular retention time (bioavailability)
  - Drug release
- pH
  - Irritation (drug absorption)
  - Stability, solubility, permeability

# In Vitro Studies (Q3 Characterization)

- Zeta potential
  - Adhesion to cell membranes
  - Product stability
- Osmolality
  - Irritation, tissue damage
  - Permeability
- Surface tension
  - Corneal permeation
  - Irritation

## Non-Q1/Q2 Formulations

- Changes in any of the inactive ingredients can change the safety and efficacy of an ophthalmic drug product.
- If a Test product contains **a different inactive ingredient**, a clinical endpoint study is requested
- If there is **a difference of more than 5% in any inactive ingredient** in the Test product compared to that of the RLD, a clinical endpoint study is requested
- This is applicable to both solutions and non-solution dosage forms
- A protocol should be submitted to OGD for review and concurrence prior to conducting the clinical endpoint study



# “AT” Coded Products in FDA’s Orange Book

- Products for which there are no known or suspected bioequivalence problems
- In vivo BE studies not required provided the conditions specified in 21 CFR 314.94 (a)(9)(iv) are met
- Posted guidances:
  - Bacitracin ointment
  - Erythromycin ointment

# Summary

- A variety of studies can be performed to demonstrate bioequivalence for an ophthalmic product submitted in an ANDA
- The type of study that can be used to demonstrate bioequivalence depends on information such as the drug product's API, dosage form, indication, site of action, mechanism of action, and scientific understanding of drug release/drug availability and drug product characteristics
- Product-specific bioequivalence recommendations are posted publicly on FDA's website and give information on the type of bioequivalence study that should be conducted

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