PBPK/PD Modeling to Support Product-Specific Guidance Development for Ophthalmic Drugs

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Advancing Generic Drug Development (AGDD): Leveraging Model-Integrated Evidence (MIE) in the Development & Approval of Complex Generic Drugs – August 27, 2026

Disclaimer

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

Outline

- Background
- Brinzolamide suspension PBPK/PD baseline models
- Brinzolamide suspension PBPK/PD models for ANDAs
- VBE analysis and sensitivity analysis
- Summary

Ophthalmic Suspensions for IOP Reduction

- An in vitro bioequivalence (BE) option has been recommended for multiple ophthalmic suspension products (API: steroids or NSAID). However, an in vitro only approach has not yet been recommended for ophthalmic suspension products indicated for intraocular pressure (IOP) reduction.

- IOP reduction products, such as brinzolamide ophthalmic suspensions, are associated with high risk due to their long term (chronic) use as well as high risk to the patient caused from uncontrolled IOP by a non-therapeutically equivalent product.

- An in vitro approach may be recommended for IOP suspension products **when a better understanding of how their in vitro characteristics affect in vivo performance, e.g., studies/data demonstrating an in vitro-in vivo relationship**.

PSG for Brinzolamide Suspensions

Contains Nonbinding Recommendations

Draft Guidance on Brinzolamide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Brinzolamide

Dosage Form; Route: Suspension/drops; ophthalmic

Strength: 1%

Recommended Studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized (1:1), double-masked, parallel, two-arm, in vivo
Strength: 1%
Subjects: Males and females with chronic open angle glaucoma or ocular hypertension in both eyes
Additional comments: Specific recommendations are provided below

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Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (95% CI): Clinical endpoint

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of open angle glaucoma and ocular hypertension comparing the test product to the reference listed drug (RLD), each applied as one drop in both eyes three times daily at approximately 8:00 a.m., 4:00 p.m., and 10:00 p.m. for 42 days (6 weeks).

2. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or nonpregnant females aged at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes

   b. Subject requires treatment of both eyes and is able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period.
   c. Adequate wash-out period prior to baseline of any ocular hypotensive medication (see Table 1). In order to minimize potential risk to patients due to intraocular pressure (IOP) elevations during the washout period, the investigator may choose

Recommended Apr 2014; Revised Dec 2014, Mar 2015, May 2019

Current PSG recommends comparative clinical endpoint BE study to demonstrate BE between Test and RLD

In vitro Option for Brinzolamide Suspensions?

- Comparative clinical endpoint (CCEP) BE study: challenges
  - Confounded by patient disease severity
  - Variability in measuring drug response
  - Lack of meaningful discrimination to formulation characteristics

- In vitro option for BE?
  - In vitro characterization of ophthalmic suspensions
  - The impact of formulation in vitro characteristics on in vivo performance
  - Could PBPK modeling approaches be used to understand and demonstrate the in vitro-in vivo relationship?

Data Available for Brinzolamide Suspensions

Brinzolamide Suspensions (RLD and Test formulations)

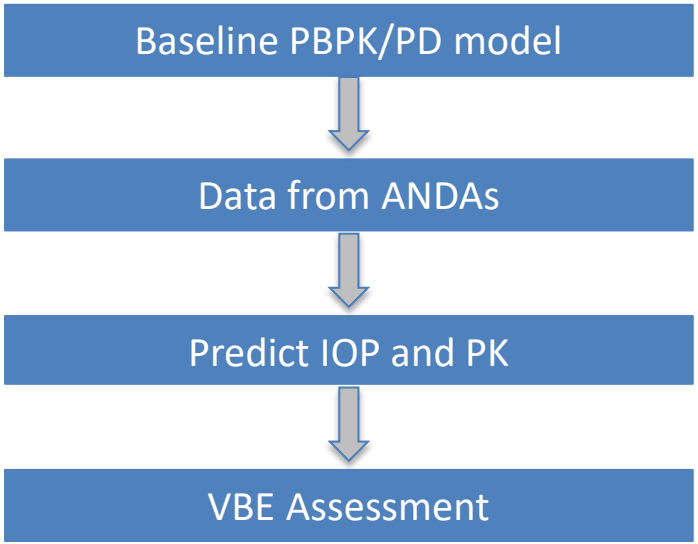
- Formulation CQAs
  - Multiple publications and FDA funded research
- Rabbit PK and IOP data available from literature and FDA funded research
- Human IOP data available from literature
- FDA internal data: Human IOP and formulation CQA data available from submissions

CQA: critical quality attribute; IOP: intraocular pressure

PBPK/PD Modeling

Purpose: Correlate formulation CQAs with the ocular pharmacokinetics (PK)/pharmacodynamics (PD) in a mechanistic model using data from ANDAs.

PBPK modeling approach:



ANDA: Abbreviated New Drug Application

Extrapolated from validated rabbit model, validated the human model using literature human IOP data

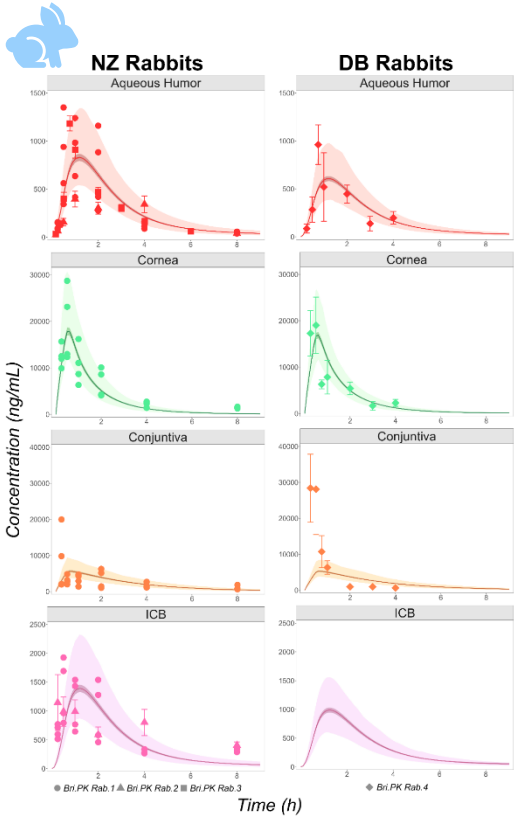
Data from ANDAs, including formulation particle size and viscosity, were incorporated into models

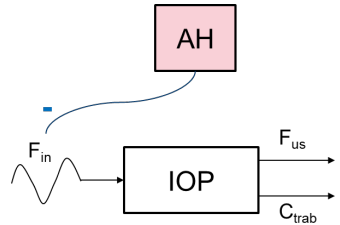
Predicted IOP was compared with the submitted measurement in ANDAs for model validation purposes

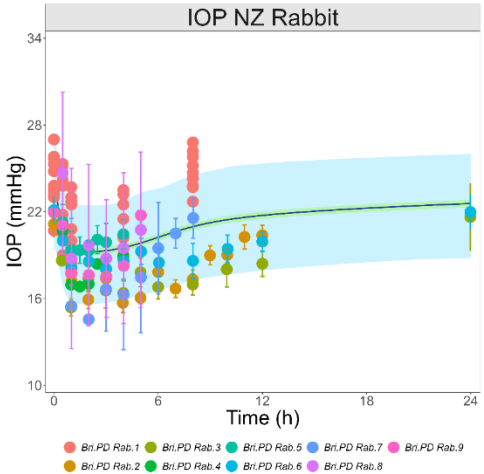
Virtual BE (VBE) analysis was conducted to assess BE in ocular tissue

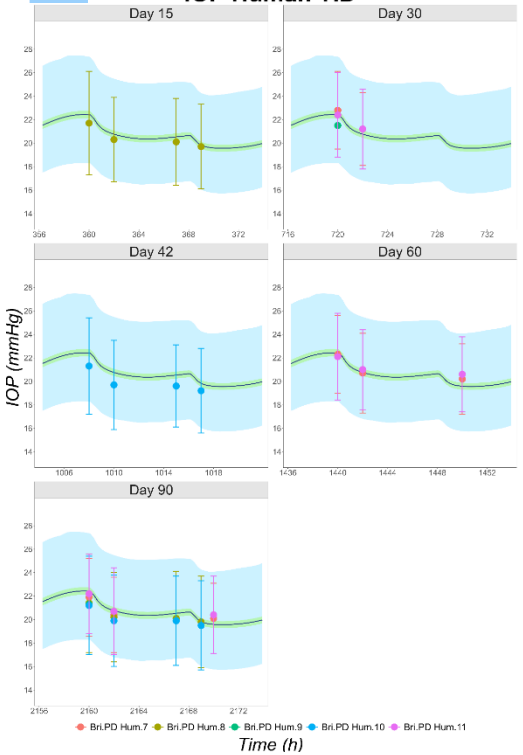
Question: Are the RLD and test products bioequivalent in ocular tissue?

Baseline PBPK/PD Models









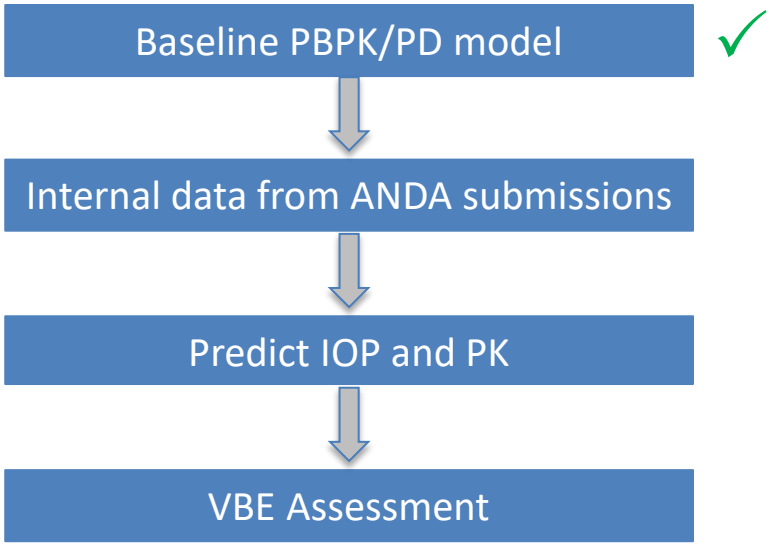
NZ: New Zealand; DB: Dutch Belted; AH: Aqueous Humor

Le Merdy, Mullin, Tan, Tsakalozou, Lukacova. Extrapolation of Clinical Intra-Ocular Pressure Reduction Mediated by Brinzolamide Using a PBPK-Pharmacodynamic Model. *Submitted*

Grant 1U01FD006927: Simulations Plus, Inc.

PBPK/PD Modeling for ANDAs

PBPK modeling plan for ANDAs:



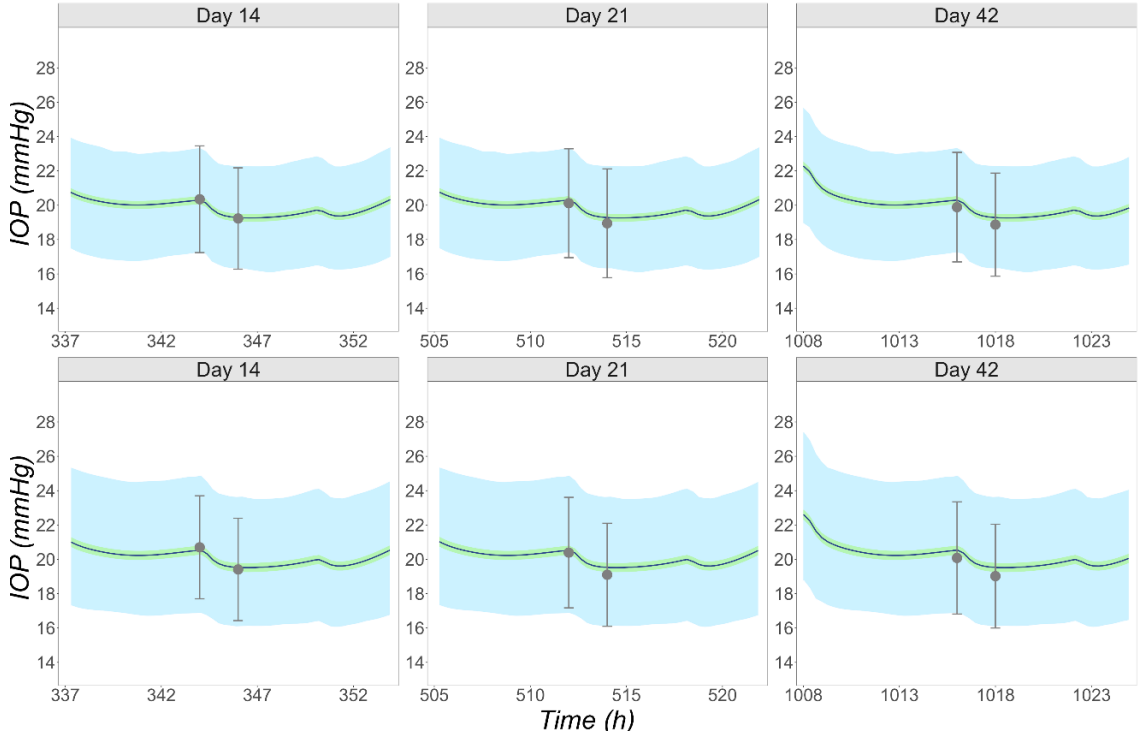
- PBPK/PD models for ANDAs utilizing
  - In vitro formulation characterization data including particle size distributions and viscosity
  - IOP data from submitted comparative clinical endpoint BE studies to further validate the models
- VBE assessments between RLD and test products in local eye tissue
- Sensitivity analysis or safe space exploration

IOP Predictions in Human

Intraocular pressure (IOP) model prediction for ANDA A (N=200)

RLD

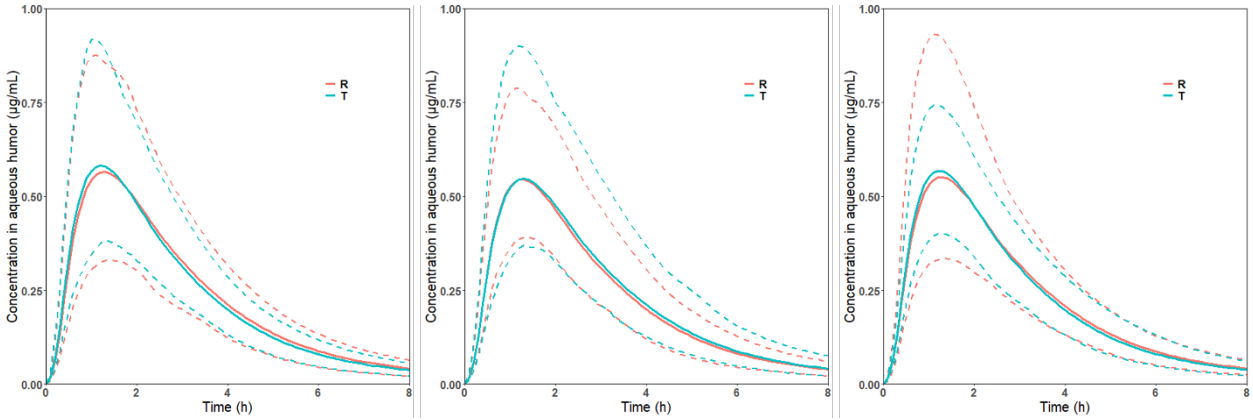
ANDA



The model well captured the IOP measurements

Brinzolamide Exposure in Aqueous Humor

Population predictions of brinzolamide exposure following single dose administrations of RLD and test brinzolamide 1% suspensions (N=60)



ANDA A ANDA B ANDA C

VBE Assessment in Aqueous Humor

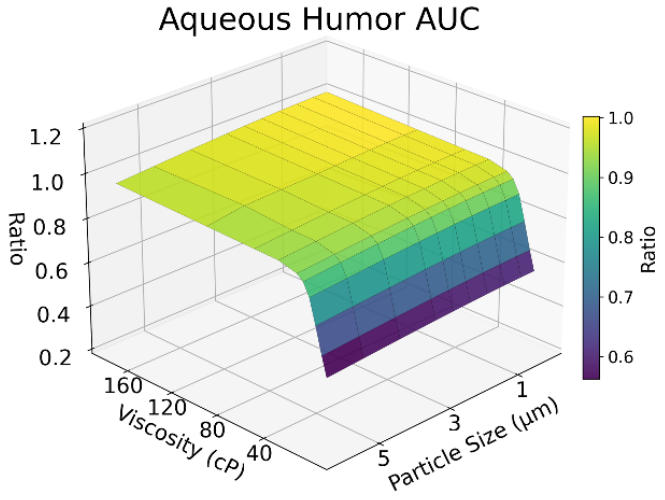
VBE assessment results between RLD and T in ANDAs based on predicted aqueous humor drug concentrations (N=60)

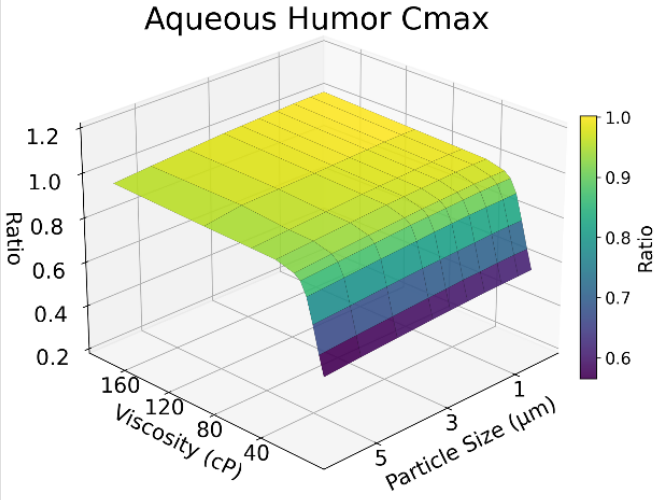
Product	PK parameters	T/R ratio	90% CI lower	90% CI upper	BE outcome
ANDA A	Cmax	96.24	85.60	108.20	PASS
	AUC	95.09	84.96	106.42	PASS
ANDA B	Cmax	99.90	92.15	108.32	PASS
	AUC	102.08	94.12	110.72	PASS
ANDA C	Cmax	104.98	97.04	113.58	PASS
	AUC	100.13	93.14	107.65	PASS

CI: Confidence Interval

Ocular PK BE in aqueous humor: pass for all ANDAs

Sensitivity Analysis





Drug exposure in ocular tissues reaches a plateau when viscosity reaches ~40 cps

Drug exposure in ocular tissues slightly decreases as particle size increases

Summary

- Brinzolamide PBPK/PD model predictions were in agreement with the human IOP data from ANDA submissions through CCEP studies.

- VBE assessment demonstrated that RLD and test products are bioequivalent in aqueous humor tissue for ANDAs that were shown to be bioequivalent through CCEP BE studies.

- Sensitivity analysis suggests that formulation variations within typical manufacturing ranges in the case of viscosity and particle size distribution have limited impact on brinzolamide aqueous humor exposure.

- Research supports the feasibility of adopting an in vitro BE studies option with supportive characterization studies for Q1/Q2 sameness and Q3 similarity formulations.

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Questions

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