Ocular PBPK/PD Modeling to Explore In Vitro Bioequivalence Approach for Brinzolamide Ophthalmic Suspensions

2025 FDA-CRCG Workshop: Visionary Standards: Advancing Science and Regulatory in Generic Ophthalmic Products

Day 1, Session 2: Regulatory Science Applied to Ophthalmic Dispersion Products

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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 models for rabbit and human
- Brinzolamide suspension PBPK/PD models for ANDAs
- VBE analysis and sensitivity analysis
- Summary

Ophthalmic Suspensions for IOP Reduction

- An in vitro 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 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Draft Guidance on Brinzolamide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In vitro Option for Brinzolamide Suspensions?

- Comparative clinical endpoint 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)

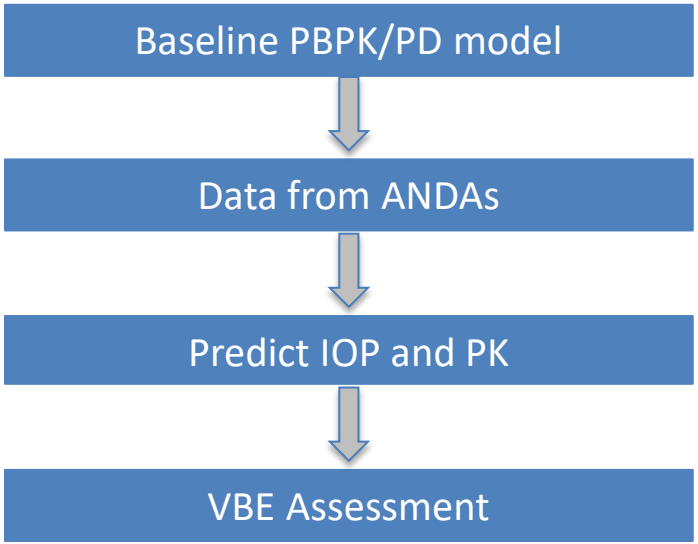
- Formulation CQAs
  - Multiple publications and FDA funded research
- Rabbit PK and IOP data available from literature and FDA funded research
- Human IOP data available from literature
- FDA internal data: Human IOP and formulation CQA data available from submissions

CQA: critical quality attribute; IOP: intraocular pressure

PBPK/PD Modeling

Purpose: Correlate formulation CQAs with the ocular PKs/PDs in a mechanistic model using data from ANDAs.

PBPK modeling approach:



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

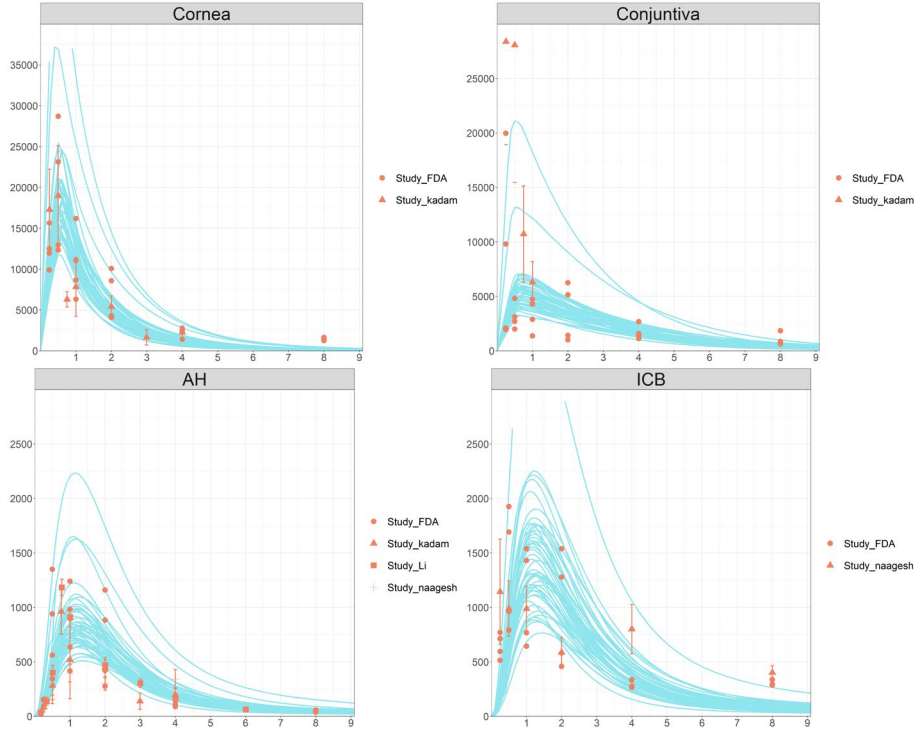
VBE analysis was conducted to assess BE in ocular tissue

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

Brinzolamide PBPK Models for Rabbit

Brinzolamide suspension

Rabbit PBPK model development and validation



AH: aqueous humor; ICB: iris ciliary body

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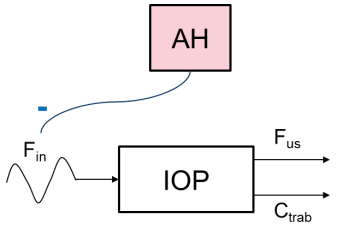
Brinzolamide PBPK/PD Models for Rabbit



Brinzolamide suspension

Rabbit PBPK/PD model development and validation

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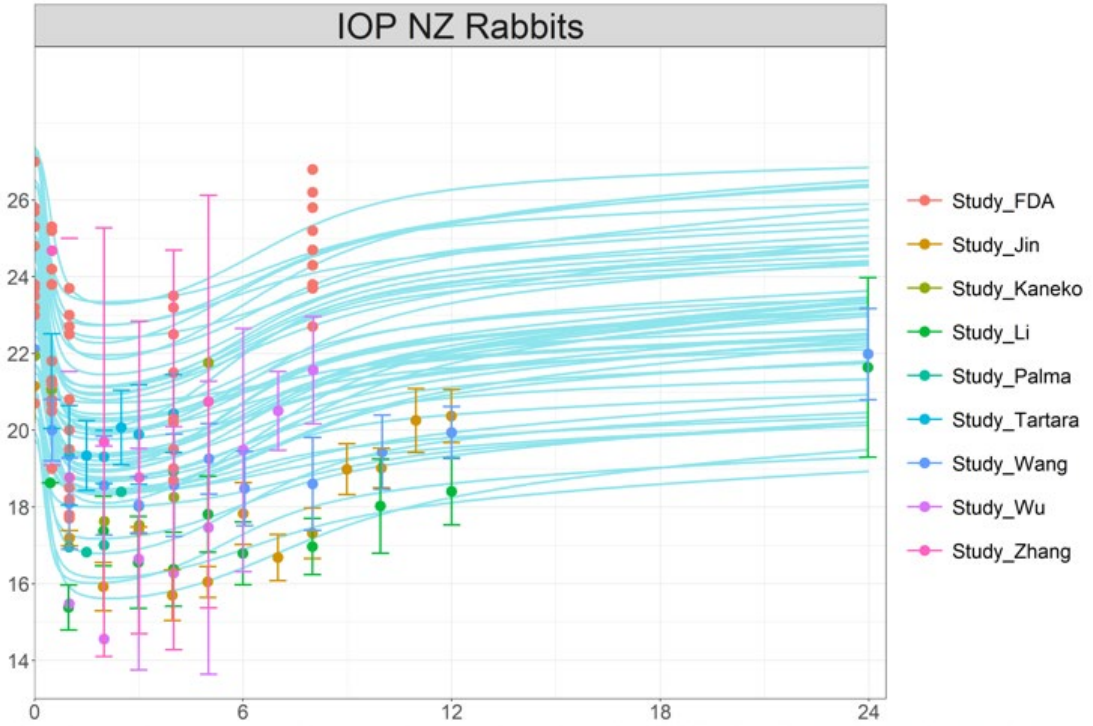

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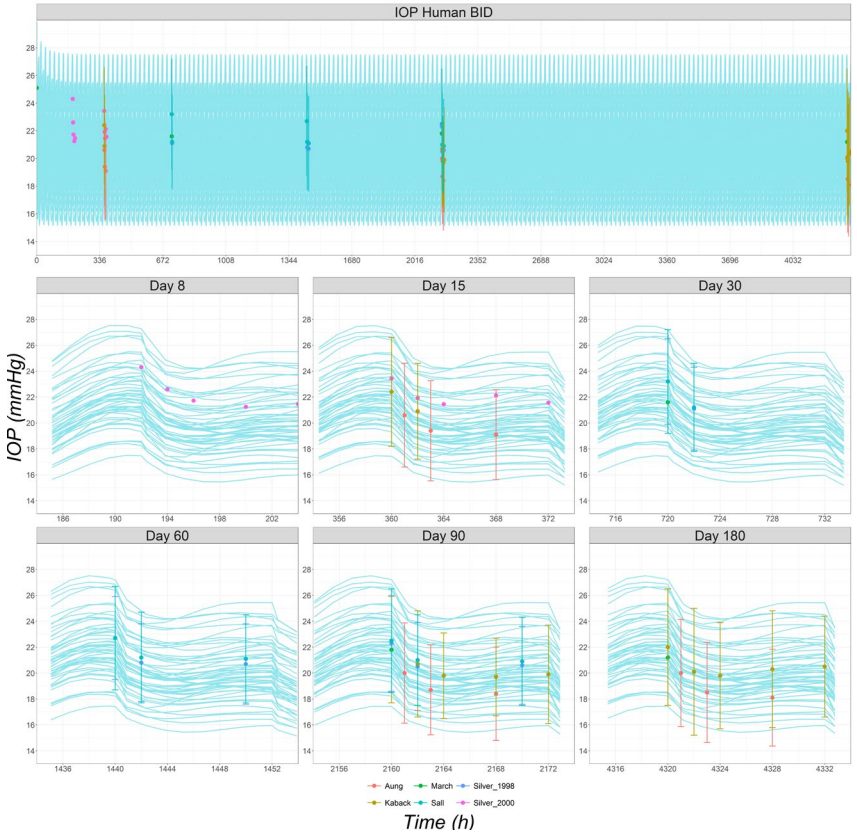
Brinzolamide PBPK/PD Models for Human

- Validated rabbit model was extrapolated to human
- Interspecies differences in anatomy and physiology were accounted for
- Human model extrapolation was validated against literature IOP data

Twice daily (BID) study



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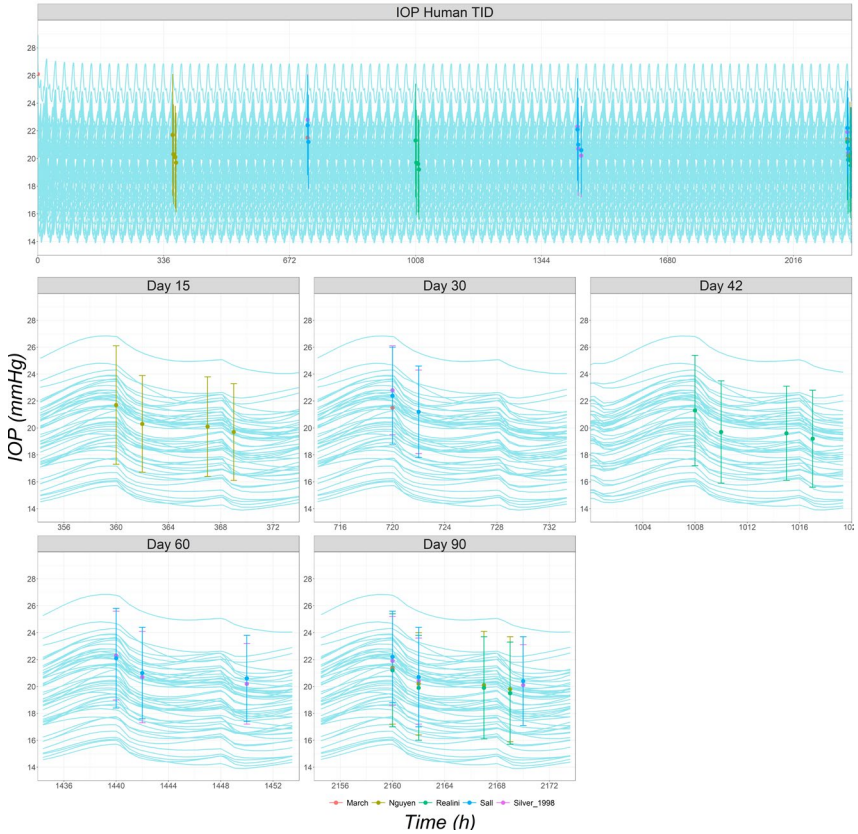
Brinzolamide PBPK/PD Models for Human

- Validated rabbit model was extrapolated to human
- Interspecies difference in anatomy and physiology was accounted for
- Human model extrapolation was validated against literature IOP data

Three times daily (TID) study



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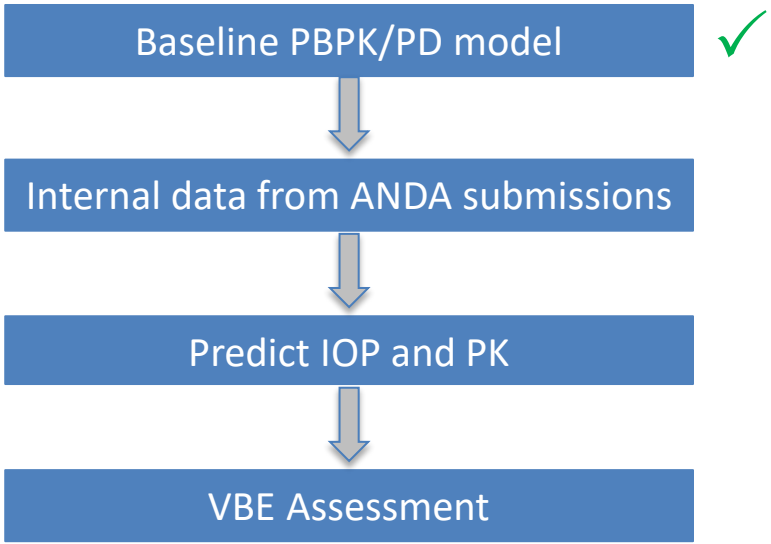
PBPK/PD Modeling for ANDAs

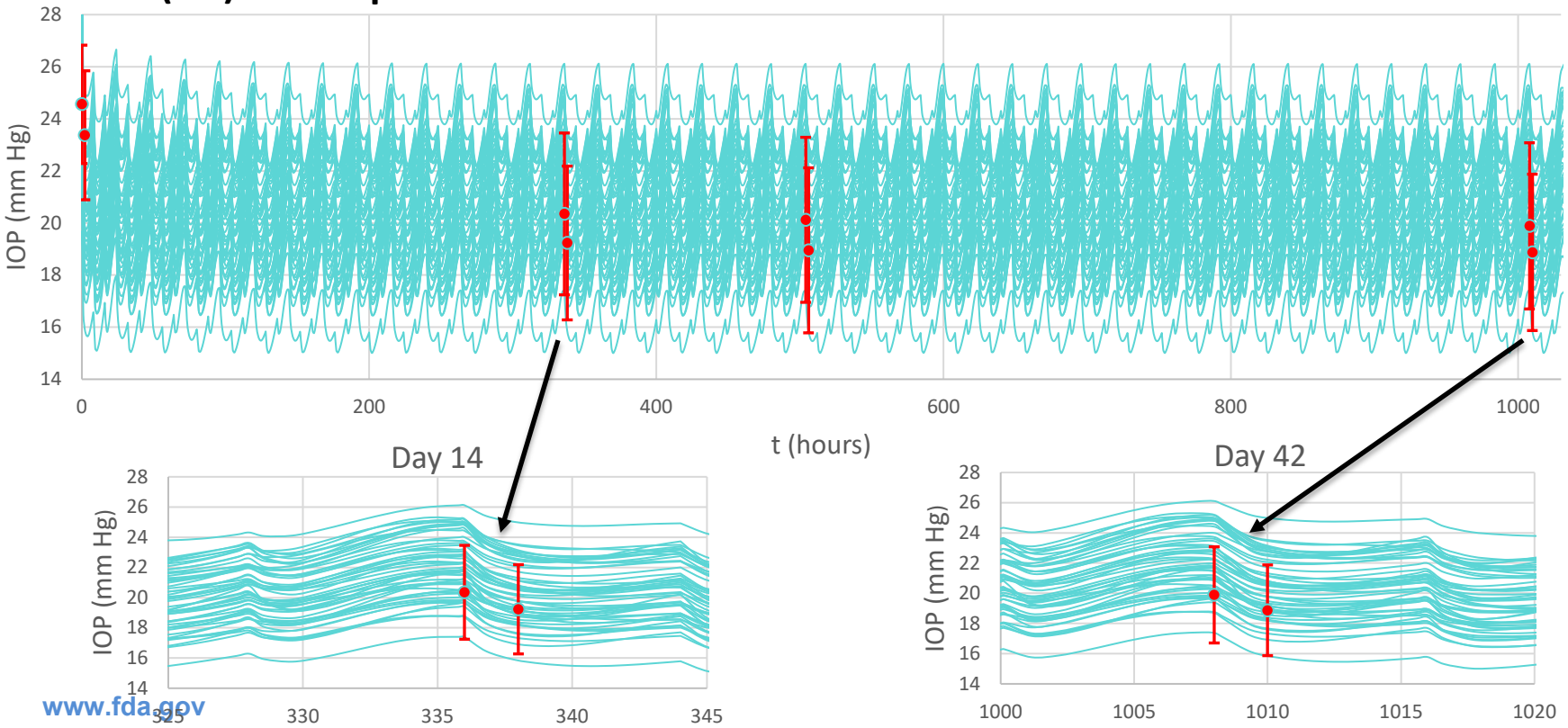
PBPK modeling plan for ANDAs:



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

IOP Predictions in Human

IOP (PD) model prediction:



VBE Assessment in Ocular Tissue

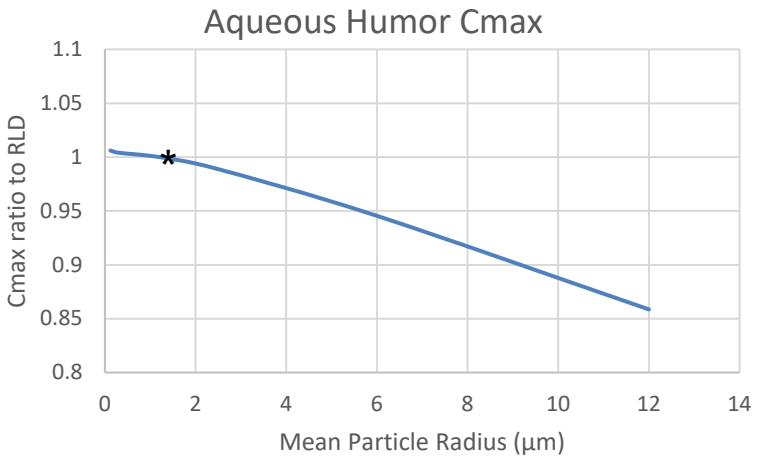
Virtual BE assessment results between RLD and T in ANDAs based on predicted aqueous humor drug concentrations (N=50)

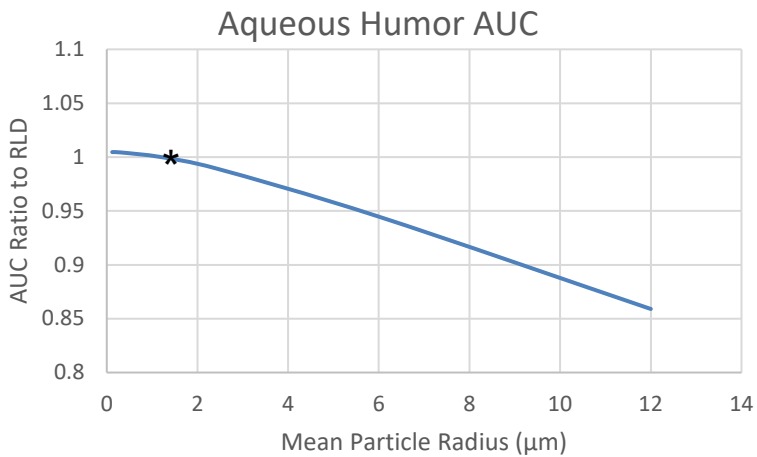
		T/R ratio	90% CI lower	90% CI upper	BE outcome
ANDA A	Cmax	90.56	82.44	99.48	PASS
	AUC	92.98	84.44	102.39	PASS
ANDA B	Cmax	98.20	95.97	100.47	PASS
	AUC	98.22	95.75	100.75	PASS
ANDA C	Cmax	98.81	96.77	100.90	PASS
	AUC	96.96	96.46	101.06	PASS

Ocular PK BE in aqueous humor: pass for all ANDAs

Sensitivity Analysis

Particle size distribution



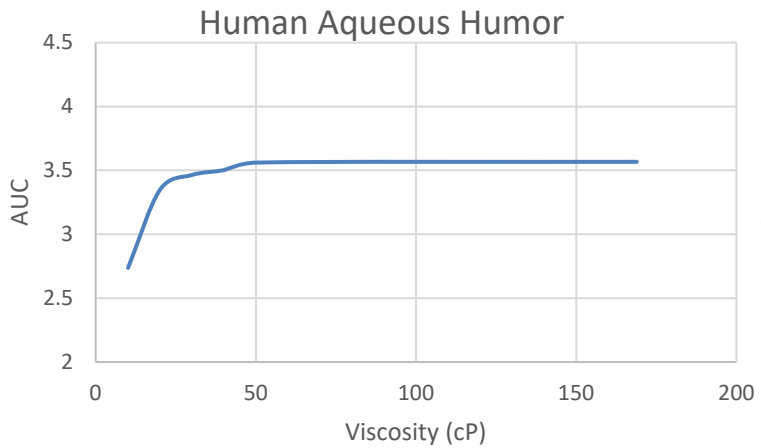


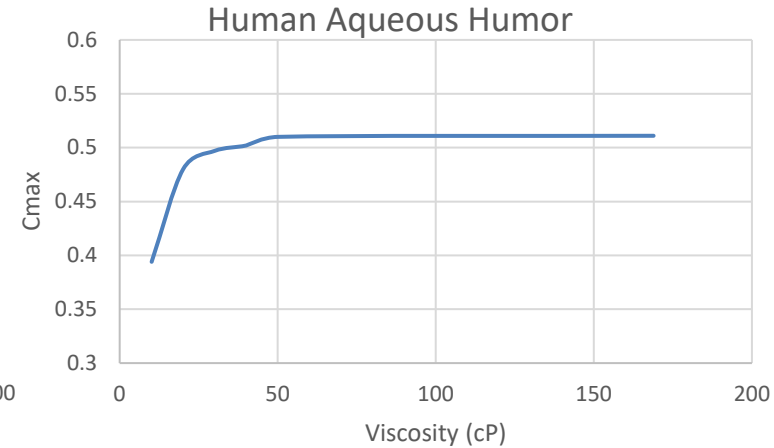
*Mean particle radius of 1.42 µm measured for RLD: Naageshwaran V et al, Int J of Pharma. 2023, 642:123183

Drug exposure in ocular tissues decreases as particle size increases

Sensitivity Analysis

Viscosity





Drug exposure in ocular tissues reaches a plateau when viscosity reaches ~50 cps

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 CCE BE studies
- Sensitivity analysis suggests that the ocular tissue exposure is sensitive to PSD, while less sensitive to viscosity in the case of brinzolamide suspensions

References cited in the plots

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FDA study: data obtained from contract 75F40119D10024 with Pharmaron

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Questions

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