

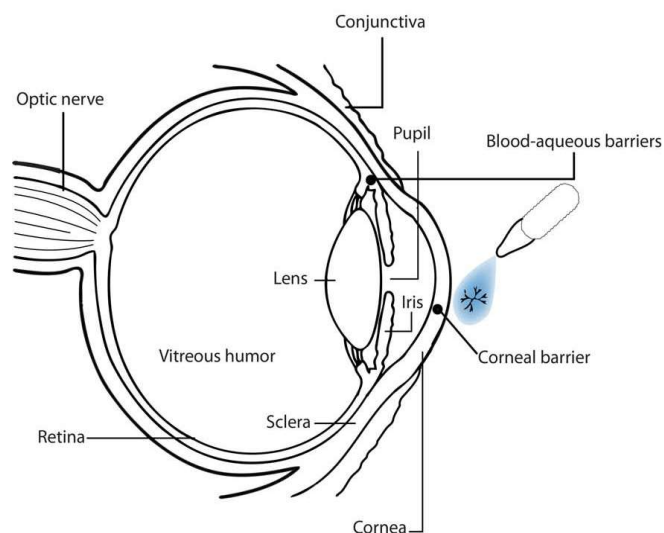


The Complex Biology of Vision

Equivalence Strategies for Complex Ophthalmic Products

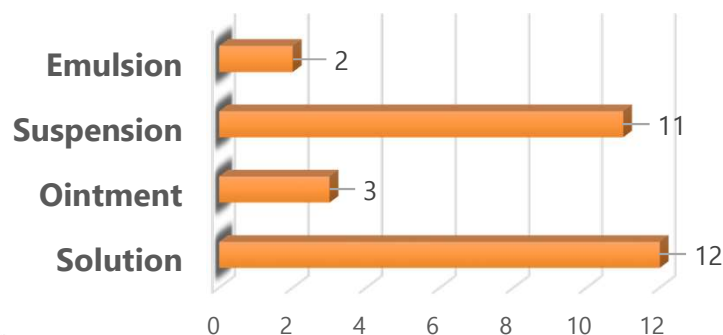
Vatsala Naageshwaran
Vice President Corporate Development

Barriers for Generic Product Development



- Blood is downstream of site of action
- Drug concentration at site of action challenging/impossible to measure
- Drug in plasma is not detectable

28 product specific guidances



CDP Breakdown (16)



Aqueous Humor PK Studies

- *Inclusion/exclusion criteria*
- *Other ocular co-morbidities*
- *Limited sample size*

Clinical endpoint BE studies

- *T must be superior to P ($p < 0.05$)*
- *R must be superior to P ($p < 0.05$)*
- *T must be equivalent to R*

Q3 Characterization

- *Matching physicochemical characteristics to ensure equivalence in (in vivo) performance*

Addressing Chemical and Biological Complexity

Chemical Complexity: Release, Viscosity, pH, Surface tension, Particle size distribution, Globule size distribution, Soluble fraction, Crystalline habit, Zeta potential



Biological Complexity: Pre-corneal dynamics, Permeation, Accumulation, PK and Distribution, PD Effect

Characterize the Brand

- Review of scientific, patent and regulatory information
- Measurements for reference product performance
- Evaluation of multiple lots of reference
- Range and variability of RLD performance

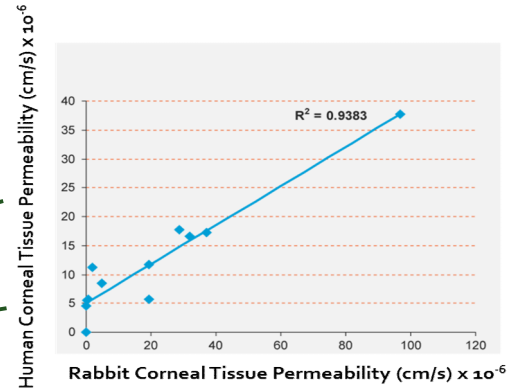
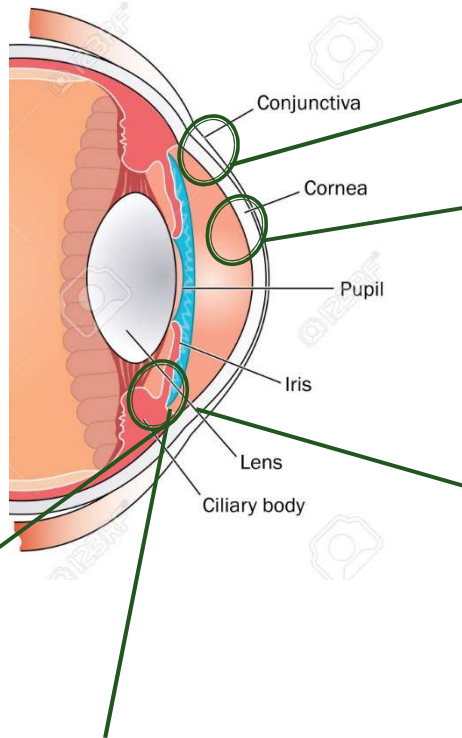
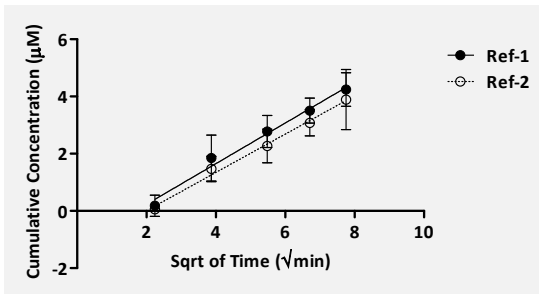


Define Criteria for the Test

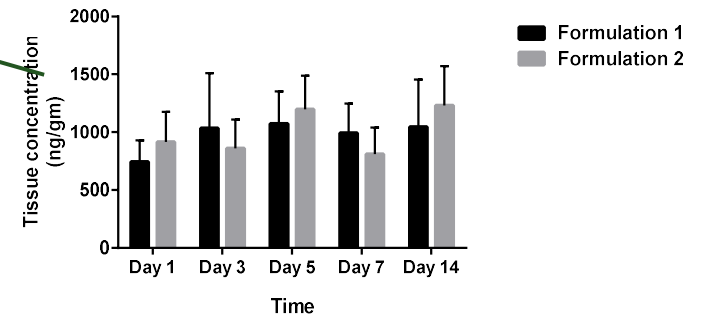
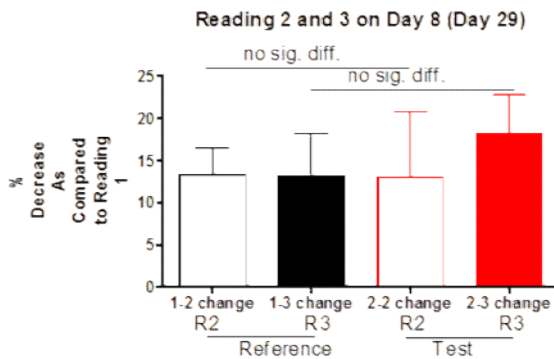
- Q1 and Q2 Sameness
- Q3 characterization
- Comparative Studies to Assure BE
 - Permeation
 - Accumulation
 - Pharmacokinetics and Distribution
 - In Vivo Effect (Efficacy)

Address residual uncertainty through biocharacterization

Science of Comparison – Orthogonal Measurements



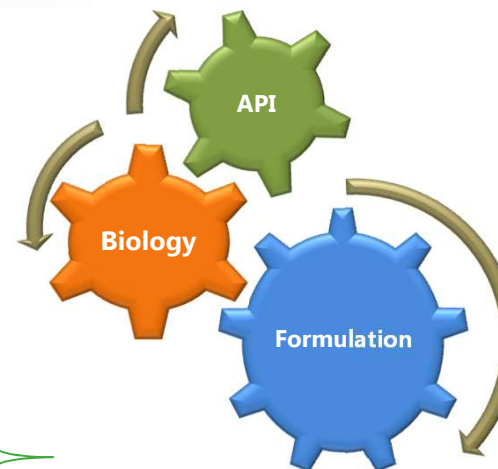
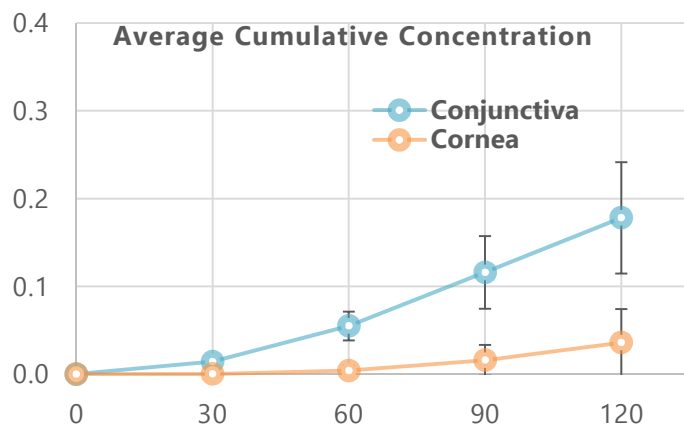
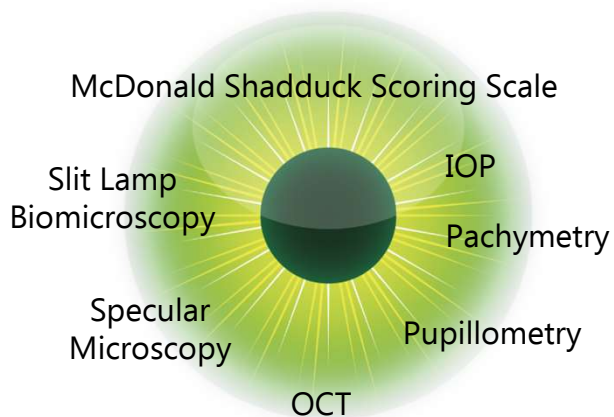
Compound Topical CAI, Tissue: Iris/ Ciliary body



Reference Compound	Mechanism of Action	Human			Rabbit		
		Used Clinically	Concentration	Response	Used Experimentally	Concentration	Response
Topical CAI	↓ aqueous formation	Yes	2%	-5 mmHg	Yes	2%	-4 to -6 mmHg

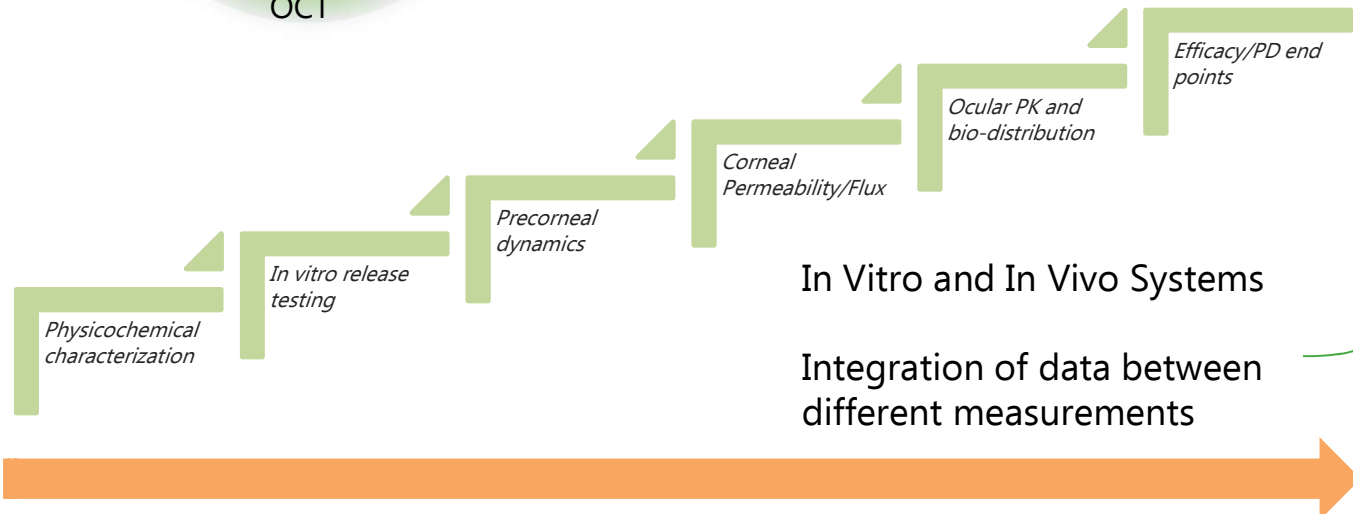
Totality of Evidence – Using Complex Biology

Building a Performance Matrix



- Validation Details
- Category specific tools
- Site of action
- Translatable efficacy
- Discriminatory models

Therapeutic Equivalence



Increasing Complexity