Integrated Approach For Product Bioequivalence of Complex Ophthalmics

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Complex Ophthalmics: BE Challenges

Prevalence & Need →

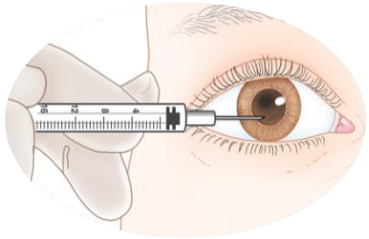
591 product entries under Topical Ophthalmic
106 active pharmaceutical ingredient
1:5 drug to formulation ratio
(FDA Orange Book)

Total Ophthalmic BE Guidances (44)

■ Suspensions, Emulsions, Ointments (21)

■ Solutions (23)

Aqueous Humor PK Studies



Clinical End Point Studies

Grade	Ocular Pain: A positive sensation of the eye, including foreign body sensations, stabbing, throbbing or aching
0	None- absence of positive sensation
1	Patient reports presence of mild sensation of discomfort typical of postoperative ocular surgery, e.g., diffuse or focal foreign body sensation, mild transient burning or stinging.
2	Mild – mild, tolerable aching of the eye
3	Moderate – moderate or more prolonged aching sufficient to require the use of over-the-counter analgesics (e.g., acetaminophen)
4	Moderately Severe – more prolonged aching required the use of any over-the-counter analgesics other than acetaminophen
5	Severe – Patient reports intense ocular, periocular or radiating pain (e.g., constant or nearly constant sharp stabbing [pain, throbbing or aching, etc.) requiring prescription analgesics

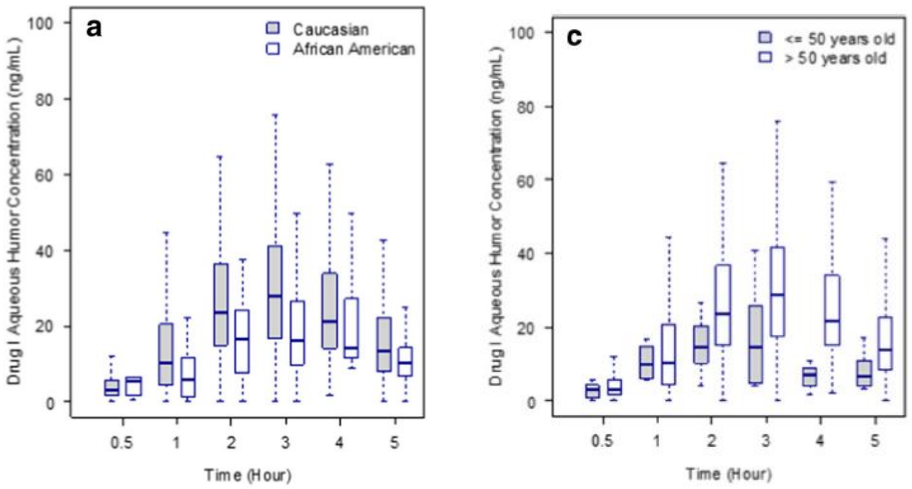
Image adapted from Reichman EF: *Emergency Medicine Procedures, Second Edition: www.accessemergencymedicine.com*

Table adapted from the FDA's "Draft Guidance on Nepafenac"

BE Challenges: Covariate Effects

Summary of AH PK Study Designs for Topical Ophthalmic Corticosteroid Suspensions		
	Parallel	Crossover
Sample	One of two treatments, Test (T) or Reference (R), per subject	A pair of T and R per subject (sequential bilateral surgery)
Sample Size	Large (easier to recruit eligible subjects)	Small
Duration	Short (one period, T or R)	Long (two periods, T-R or R-T, with washout period within 35 days)
Carryover	No	Possible without adequate washout period
Covariate Effect	High (without appropriate randomizations)	Low
T & R Arms	Independent	Related (same subjects are enrolled in each pair of sample time points)
90% CI of T/R ratio	Nonparametric Bootstrap for Parallel Study	Nonparametric Bootstrap for Crossover Study

Division of Bioequivalence II, Office of Bioequivalence, Office of Generic Drug, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, Maryland 20993, USA. November 2018



EGPS vs OHTS study outcomes

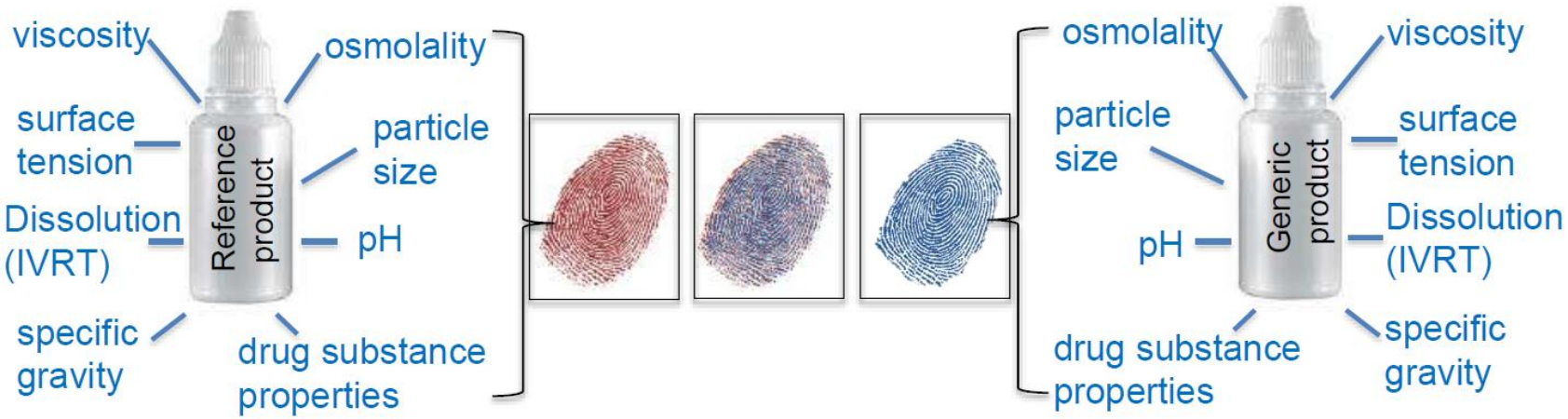
Characteristics of the European Glaucoma Prevention Study that may have impacted the results

Characteristics	Impact
Rigid regimen requiring the use of either tid medication or placebo	Inadequate IOP reduction
Use of a placebo in one arm	Potential confusion of agents between arms or direct effect of placebo on IOP
Inclusion of eyes rather than patients	Crossover effect of drugs used in the non-study fellow eye
Inclusion of younger patients	Inclusion of patients at lower risk
IOP reduction <20% at 6 mo	Inadequate IOP reduction to result in any therapeutic effect
Poor retention of patients	Negative impact on the sample size

IOP = intraocular pressure; tid = three times daily

European Glaucoma Prevention Study. [Ophthalmology. 2005]

FDA Initiatives: *In Vitro* Approach



Draft Guidance on Loteprednol Etabonate

Active Ingredient:	Loteprednol etabonate
Dosage Form; Route:	Suspension/drops; ophthalmic
Strength:	0.5%
Recommended Studies:	Two options: in vitro or in vivo study

Two Options:
In Vitro* or *In Vivo

Image adapted from Darby Kozak, "*In Vitro* Bioequivalence Testing for Topical Ophthalmic Suspension Products"

Characterization Based Equivalence (CBE)

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]

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
- Comparable drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

iii. Acceptable comparative in vitro drug release of loteprednol etabonate from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

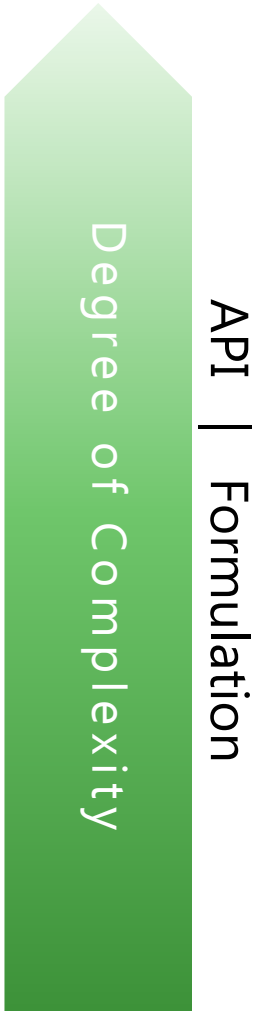
Q1/Q2 Required

Comparable Physicochemical Characteristics

In Vitro Drug Release

CBE Limitations

- Which critical quality attributes to measure?
  - Identifying key factors that impact BA
- How to perform Q3 testing?
  - Outcome can be methodology dependent
- Open-ended process optimization
  - Interpretation of differences observed; do they matter?
- No insights on site of action vs. formulation interaction
  - Complex, multifactorial and layered biology
- IVRT: process variability prediction tool, cannot mitigate any Q3 differences as it lacks correlation to in vivo performance
- Q1/Q2 not possible
  - Unable to use approach; Constraint



CBE Limitations

Viscosity – CQA for a topical ophthalmic

RLD		Average Viscosity (cP) (n=6 or n=3)			
Viscosity @ 25˚C (cP)		6RPM	10RPM	12RPM	20RPM
Lot 1		163.9	127.5	118.3	92.4
Lot 2		117.8	93.9	87.7	70.2
Lot 3		185.2	143.2	132.0	N/A
Lot 4		291.4	224.7	202.8	N/A
Lot 5		230.4	185.4	165.3	N/A
Lot 6		150.3	121.5	114.7	86.5
	Average	189.8	149.4	136.8	83.0
	St Dev	62.3	47.6	41.1	11.5
	%RSD	32.8%	31.9%	30.0%	13.8%

RLD Range and Variability

Considerations

- Selection of spindle
- Shear Rate
- Sample Volume

Particle Size – CQA for a topical ophthalmic

Testing	Result	Conclusion
Particle Size	Different PSD, in their native dispersed state.	Not similar
	PSD of aggregated/ agglomerated shows more similarity.	Comparable

RLD Formulation Characteristics

Considerations

- Temperature
- Sample Preparation
- Native dispersed versus aggregates (product)

Opportunity for Innovation

FDA initiatives and grants to mitigate uncertainties in bioequivalence:

- Development of new release tools that provide bio-relevance to the testing methodology
- Generation of data to support the construction of modeling and simulation tools for ophthalmic formulations

GDUFA Research

- 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* correlation (IVIVC)
  - Ocular drug modeling and simulation

Future Research Directions

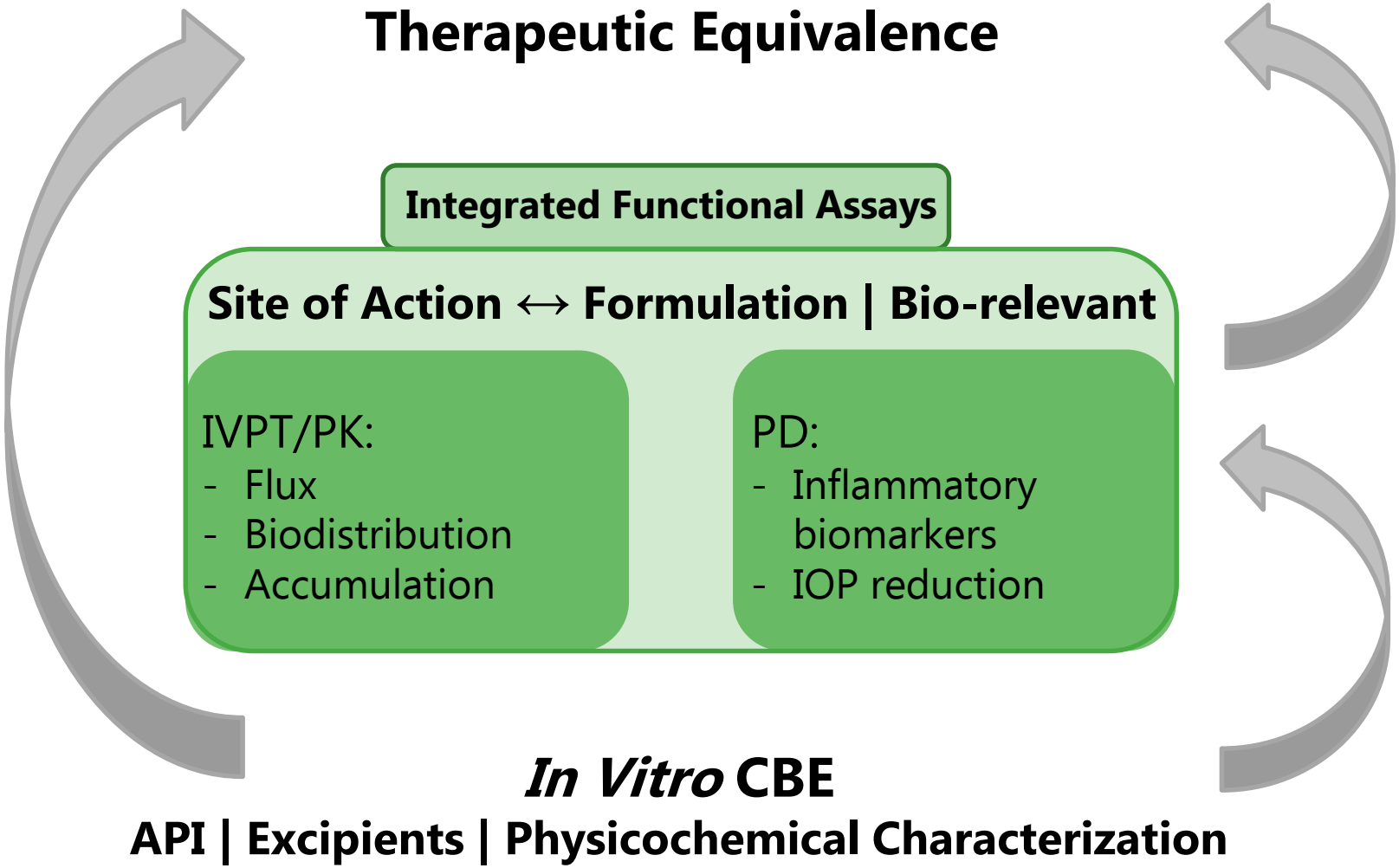
- Goal: increase regulatory applicability of ocular PBPK models

- **Ocular PBPK model improvements:**
  - Enzyme and transporter incorporation
  - Protein content in ocular tissues
  - Tear pH dynamic
  - Impact of blinking rate

- **Planned studies to aid model development work:**
  - Tear film thickness and menisci measurements on rabbit ocular surface with cyclosporine emulsion
  - Tissue distribution, systemic PK, and IOP in rabbits with multiple formulations of brinzolamide suspension
  - *In Vitro* permeability of drug substances through rabbit and human cornea and conjunctiva

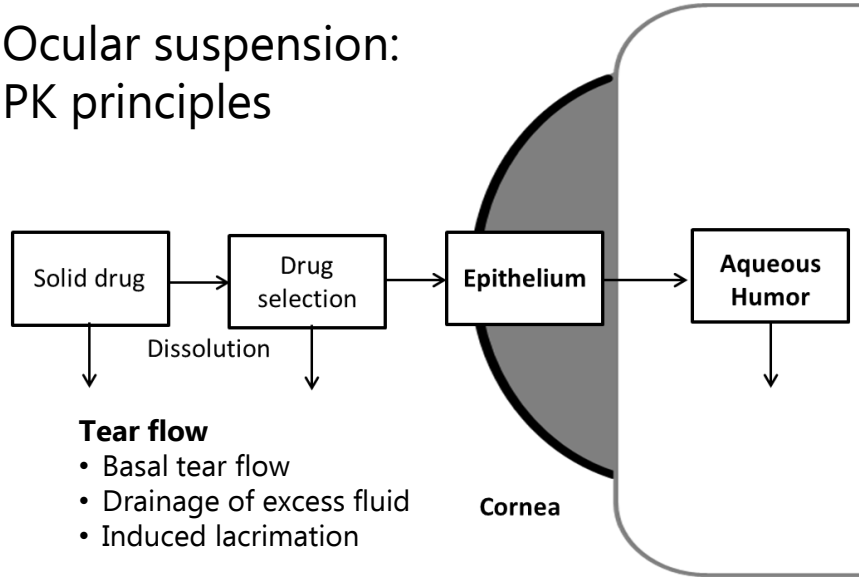
Adapted from Darby Kozak, "*In Vitro* Bioequivalence Testing for Topical Ophthalmic Suspension Products"
Adapted from Andrew Babiskin, "Physiologically-based pharmacokinetic modeling and simulation used in assessing bioequivalence for generic ophthalmic products"

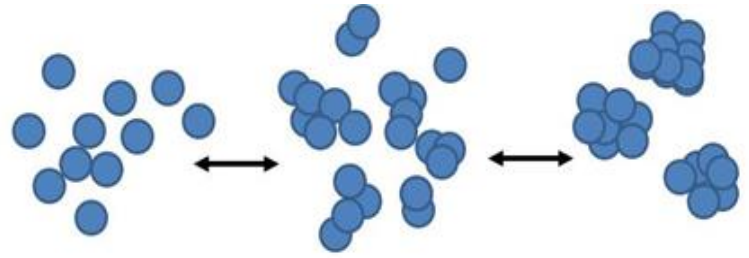
Opportunity for Innovation



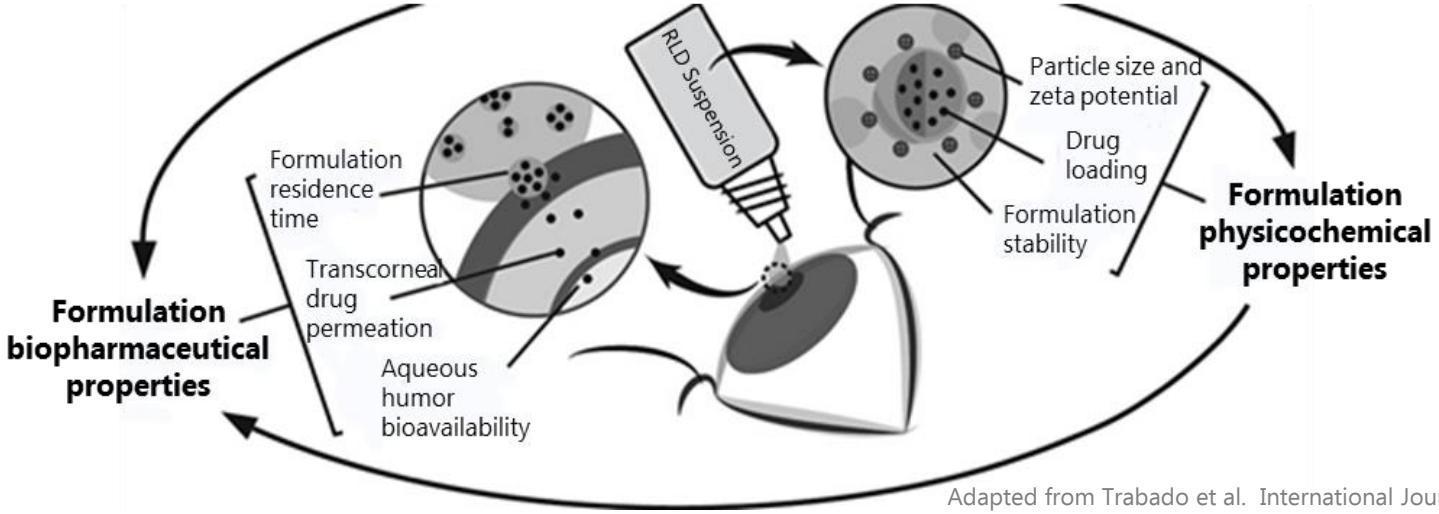
Product Biomorphology – "Secondary Formulation"

Ocular suspension:
PK principles



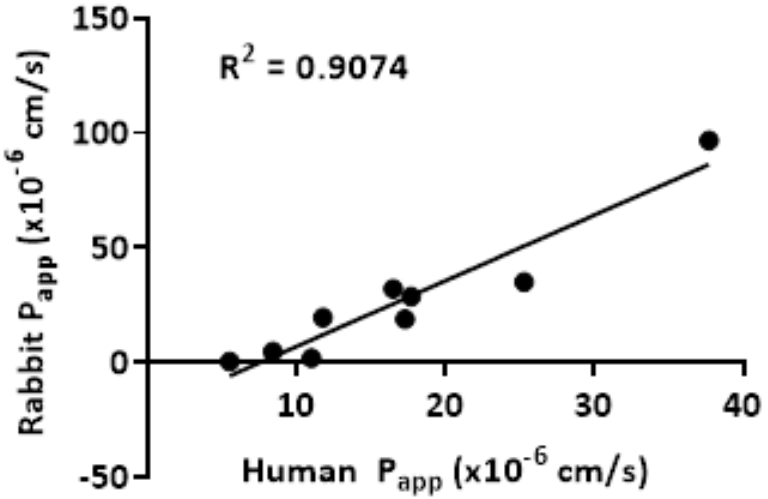


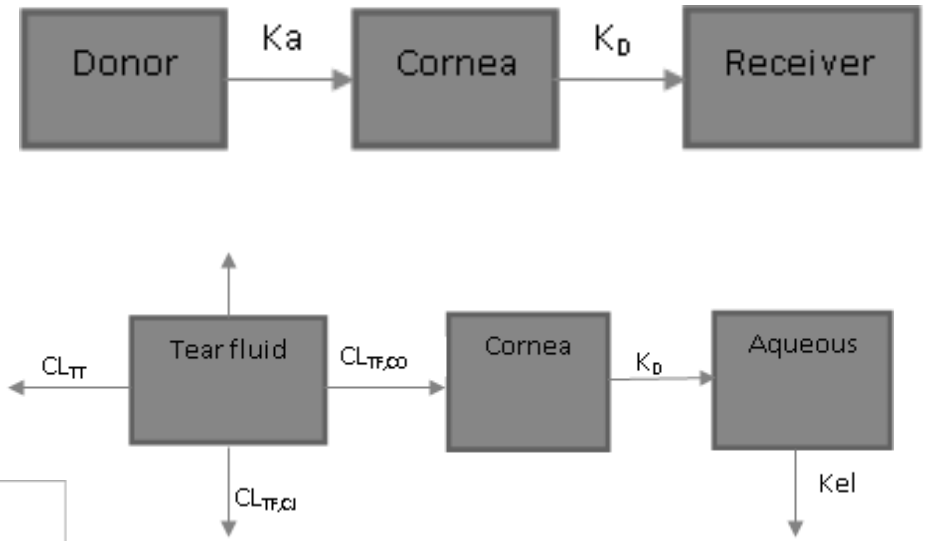
ΔG (dispersed) > ΔG (partially aggregated) > ΔG (aggregated)

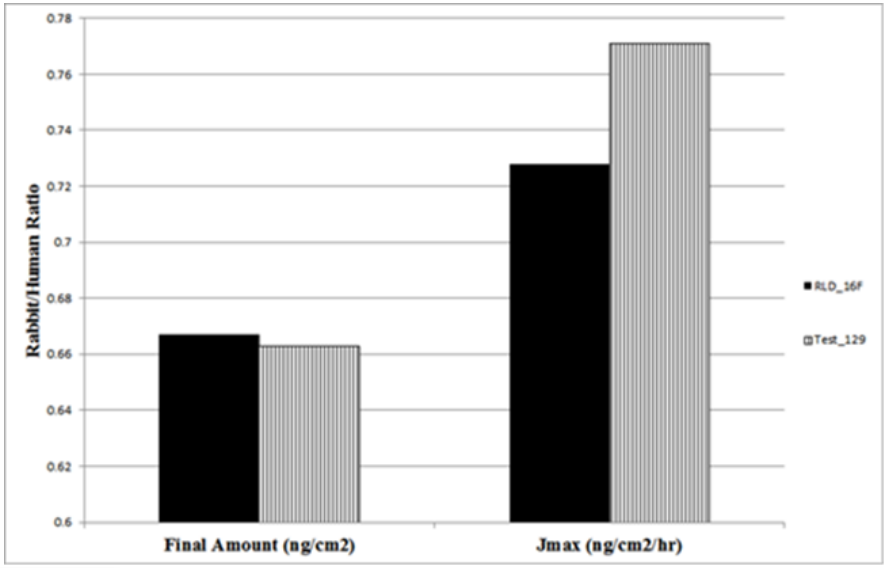


Adapted from Trabado et al. International Journal of Pharmaceutics. October 2017

The Barrier Matters: IVPT

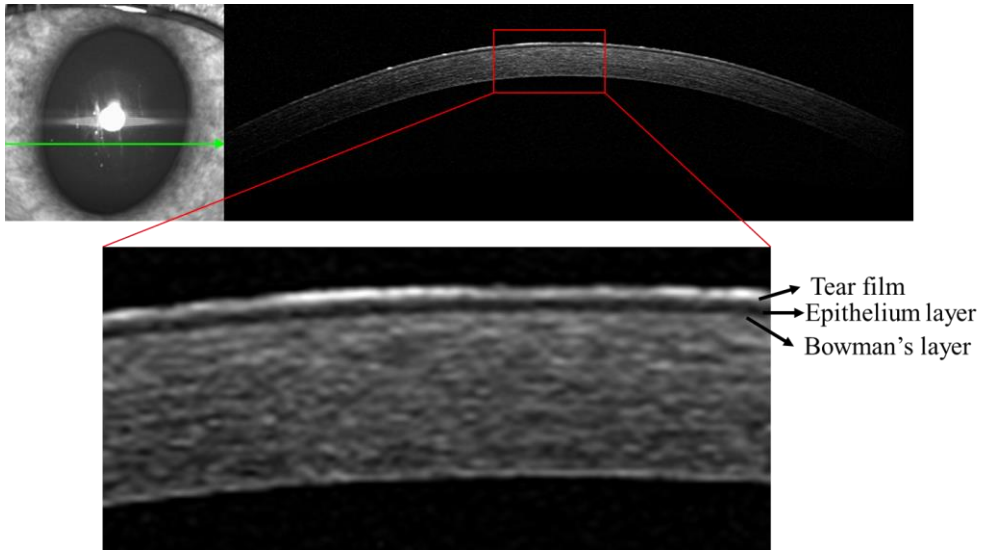




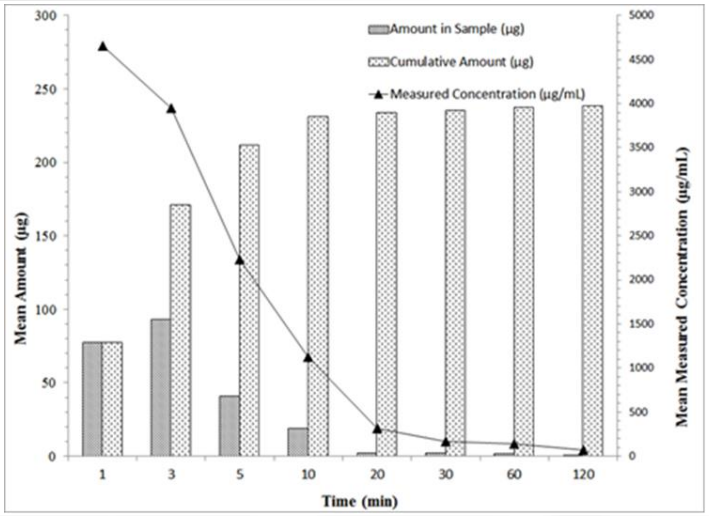


Prediction of Ocular Kinetics – Rabbit and Human

Surface Dynamics: Precorneal Factors



OCT Image of NZW rabbit eye



First order rate constants for the pre-corneal clearance of technetium from solutions of different viscosities (PVP was used as a viscosifier)

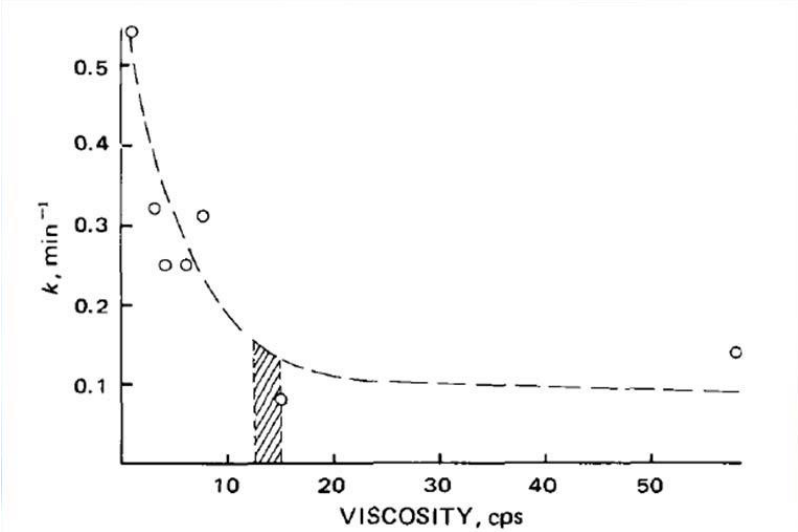
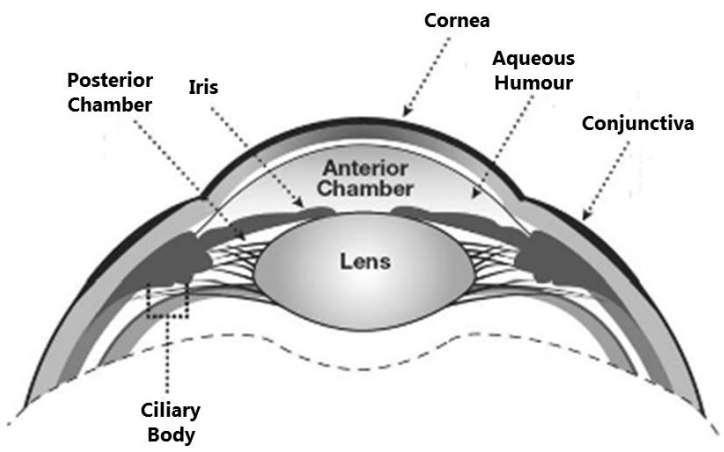
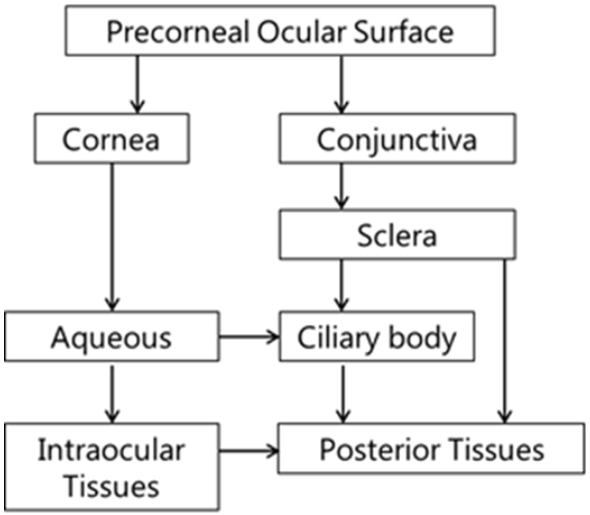


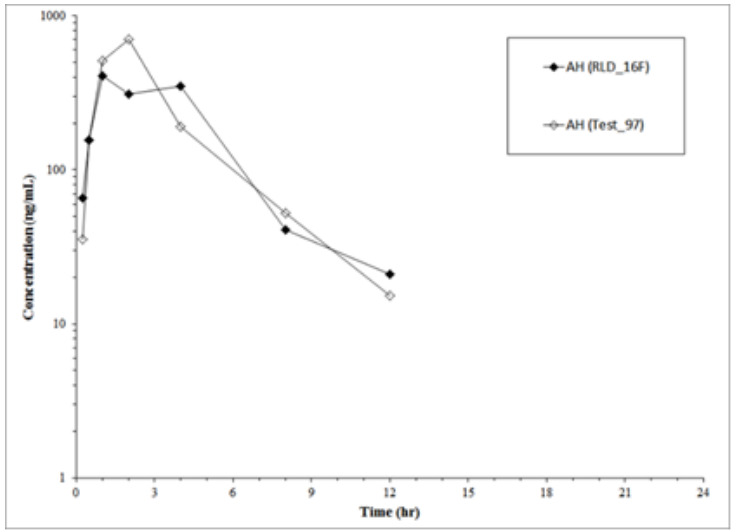
Figure 2—*Drainage rate of various polyvinyl alcohol solutions as a function of solution viscosity.*

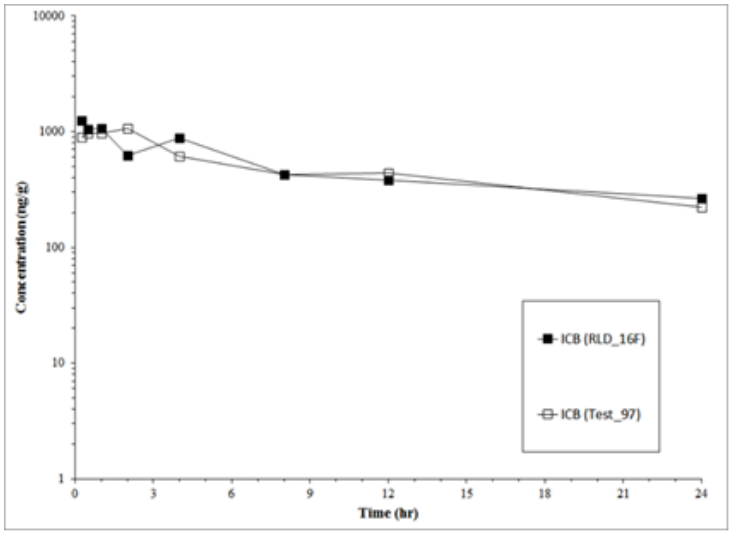
Patton TF, Robinson JR. Ocular evaluation of polyvinyl alcohol vehicle in rabbits. J Pharm Sci. 1975;64(8):1312–6.

Multiple Pathways of Absorption - Bioactivity



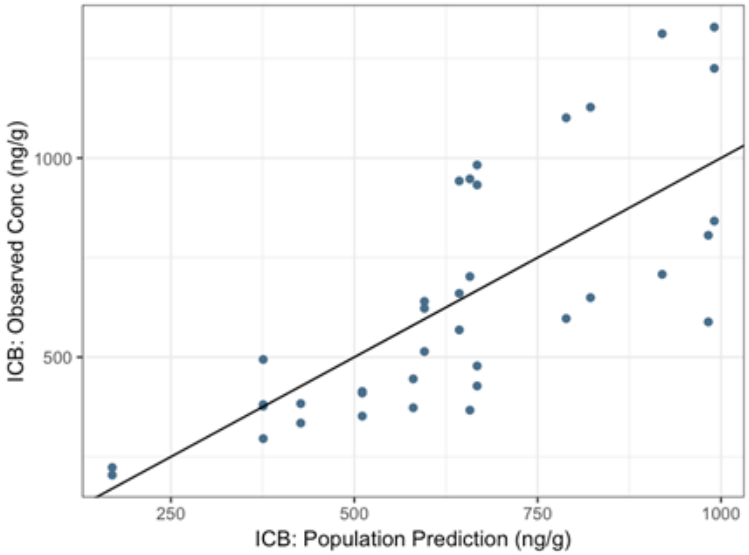


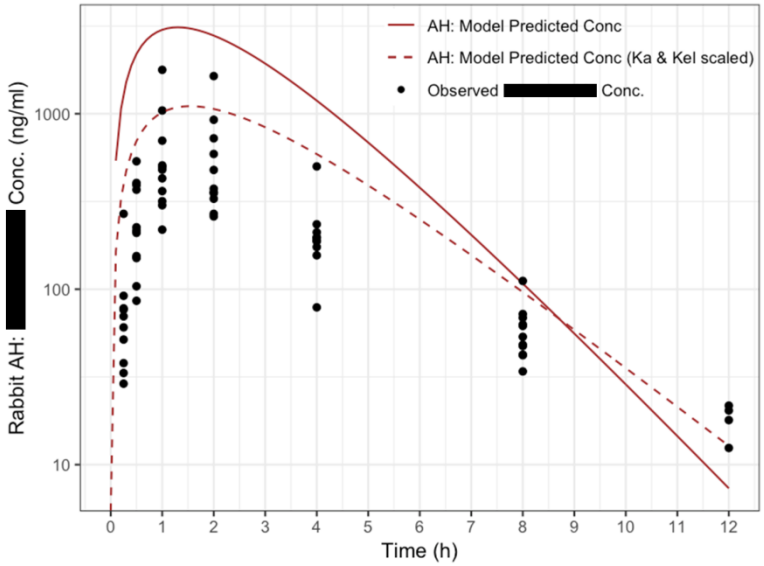




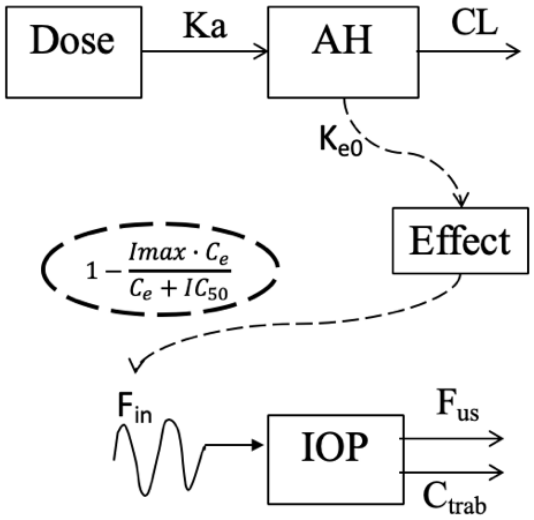
Jie Shen, Guang Wei Lu, Patrick Hughes. Targeted Ocular Delivery with Pharmacokinetic/Pharmacodynamic Considerations. Sept 2018

In Silico Supplemental: BE Confirmation





Sensitivity Analysis of Product Critical Parameters

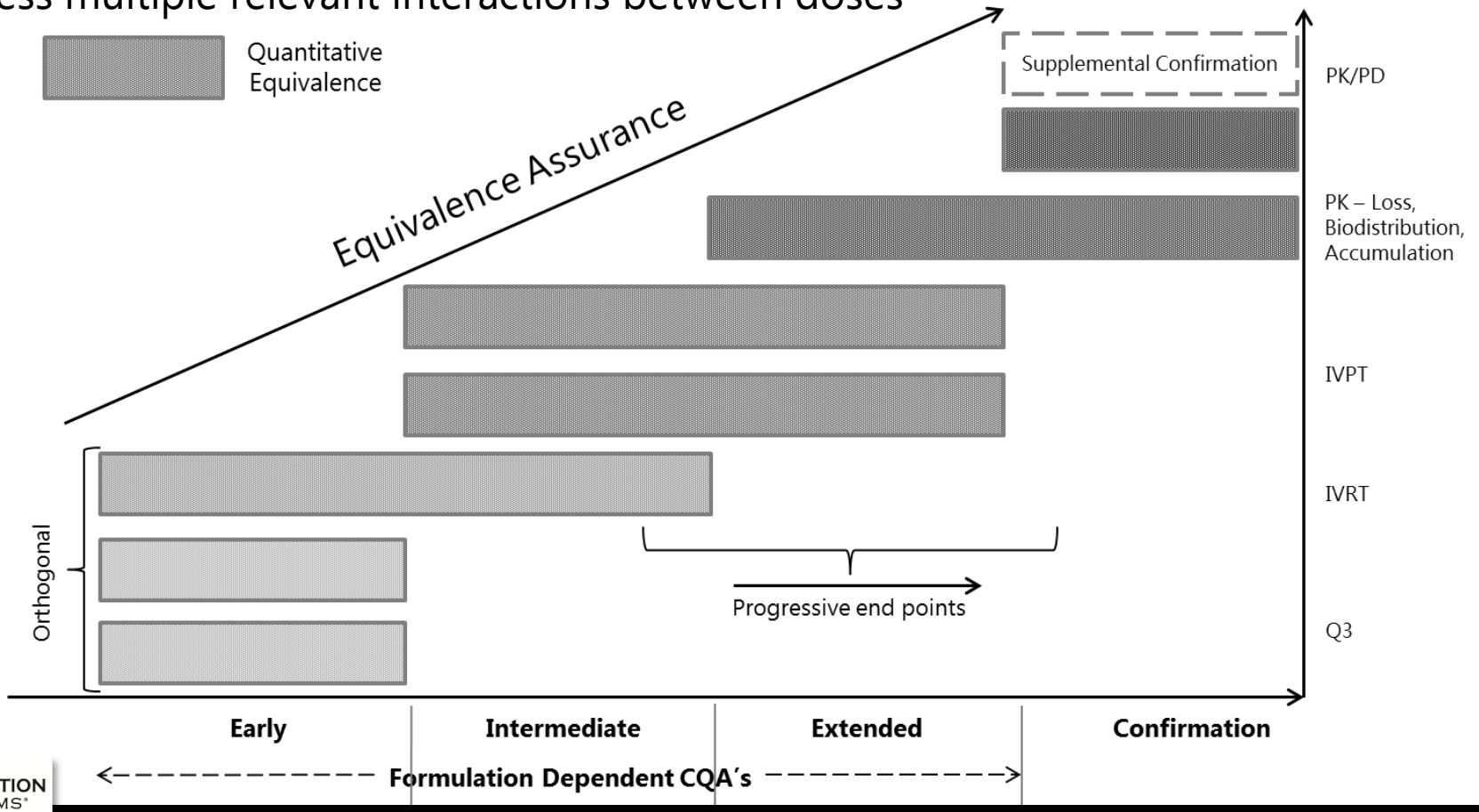


Human PD prediction to supplement equivalence conclusion

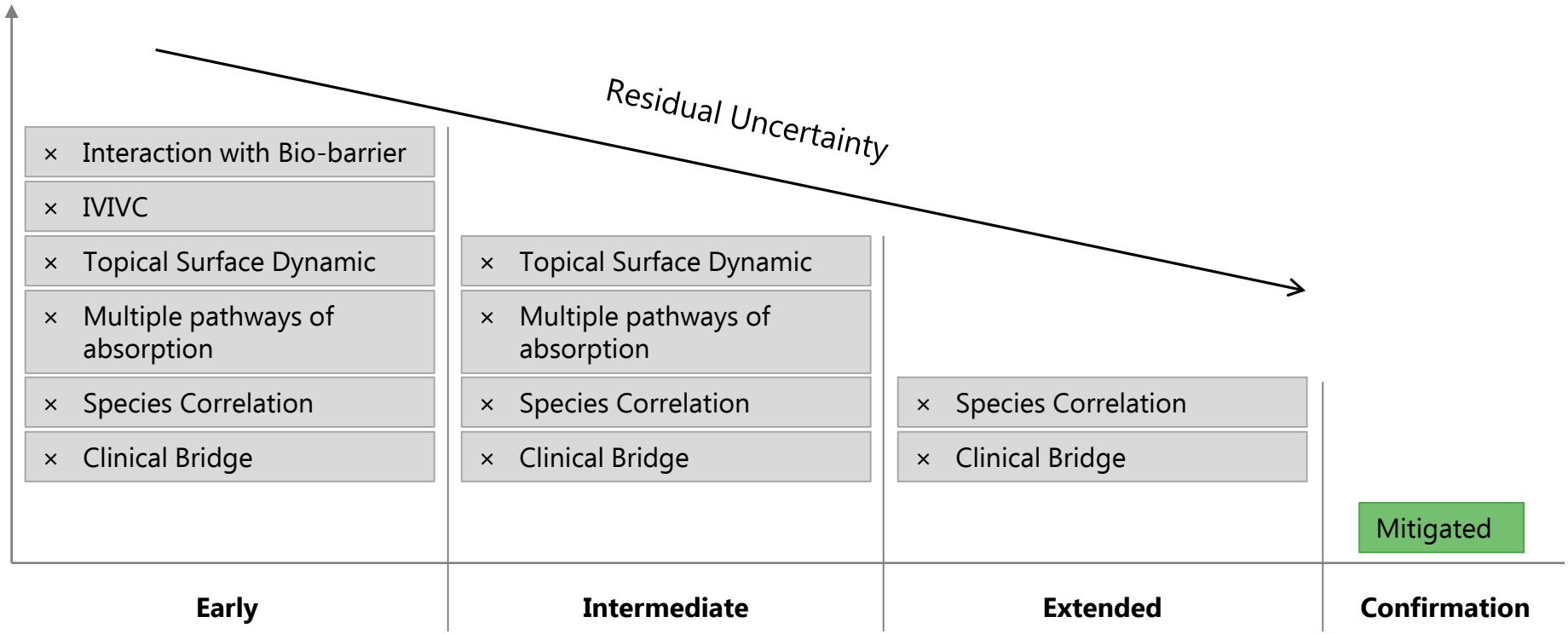
Chandrasekar Durairaj & Jie Shen & Madhu Cherukury. Pharm Res DOI 10.1007/s11095-014-1311-9, January 2014

Bioassays: Elevate Confidence in BE Conclusions

- Quantify a single formulation property
- Evaluate multi-faceted formulation-related effect mechanisms
- Assess multiple relevant interactions between doses

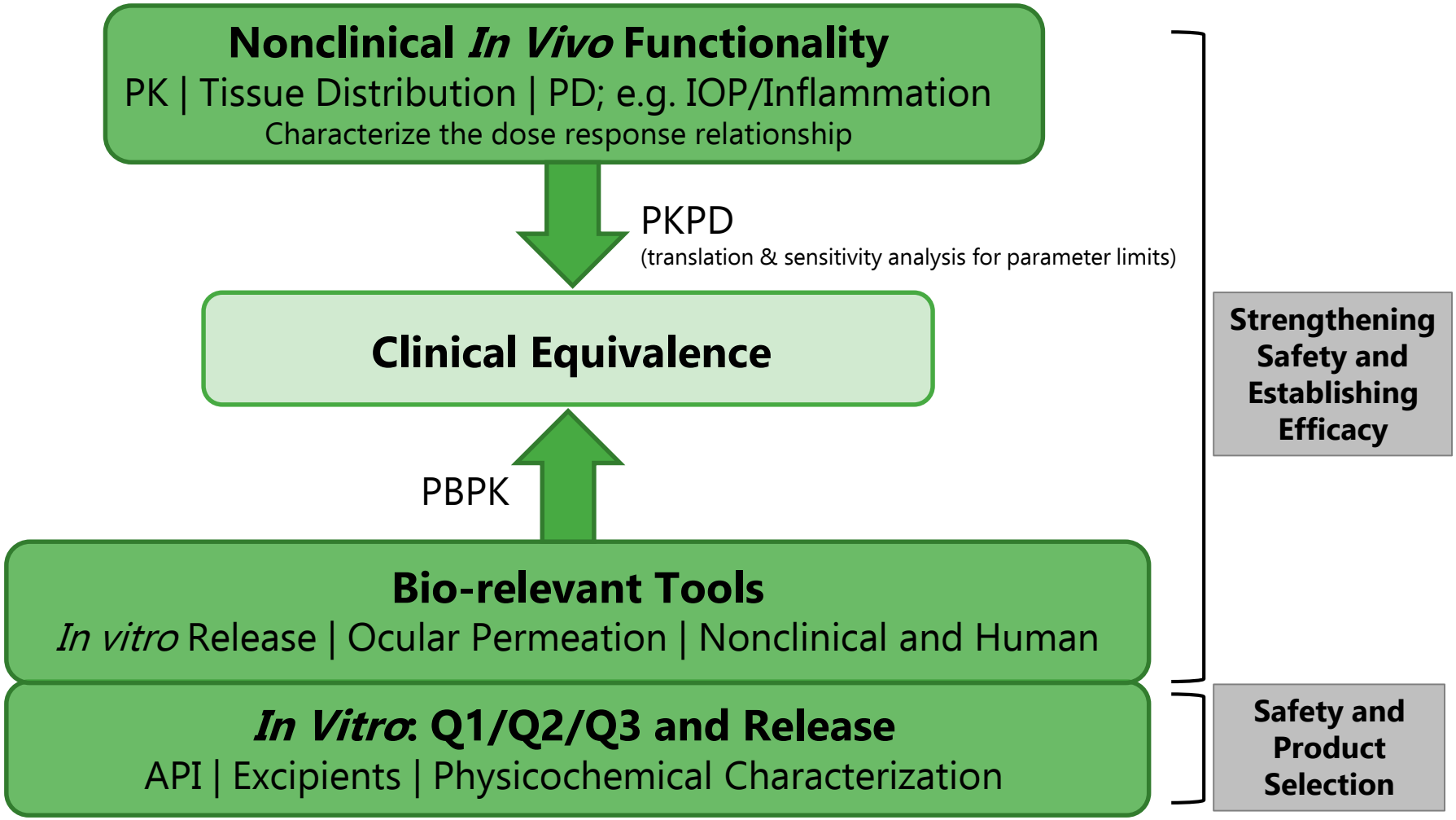


Bioassays: Reduce Residual Uncertainty in BE Conclusions



- API and formulation linked to biological effect
- Scientific evidence that is congruent with requirements for RLD approval
- Supports expected equivalence in human efficacy

Complex Ophthalmics: Opportunity for Innovation



Complex Ophthalmics: Risk Mitigation

Challenges in the current *in vitro* approach

- Uncertainty of Testing Methodologies
- Open-ended process optimization
- No insights on site of action vs. formulation interaction
- IVRT: cannot mitigate any Q3 differences as it lacks *IVIVC*

Using the *in vitro* approach with bio-relevant tools and PK/PD, augments BE

- Less susceptible to the uncertainty of testing methodologies
- Can potentially overcome differences in Q3 that maybe an artifact of the technique
- Provides improved correlation to product *in vivo* performance
- Can be correlated to approaches used in RLD approval for side-by-side comparison of Test vs. RLD
- Using IVRT in conjunction with IVPT and nonclinical PK and PK/PD studies allows use of top-down modeling to solidify BE