Model Informed BE

Expanding the Reach and Utility

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Absorption Systems

Breakout 4: Data Analysis and Model-Based Bioequivalence

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ABSORPTION SYSTEMS®

Expanding the reach and utility

What does this mean?

- Design the QQQ space, i.e., determine the relative space within which the CQAs can vary without impacting in vivo outcomes
- Widen the applicability of modeling supported BE to more product categories
- Strengthen regulatory applicability of PBPK with product category relevant input parameters
- Enhance model informed BE with approaches such as PK/PD

Overview of slides

- Which in vitro data to generate and how?
- Case study 1: How to evaluate and prospectively apply in vitro data?
- Case study 2: Which studies are clinically relevant?
- Research priority recommendations for FY 2021

Which data to generate and how?

Using reliable and relevant in vitro/non-clinical input parameters based on;

- Formulation physicochemical properties

- Properties detailed in the product label
  (did the RLD perform any in vitro assays to characterize its activity/effect?)

- Parameters that are possible to measure with both clinical and in vitro/non-clinical studies (e.g., tear film characteristics, IOP measurements)

- With tools and methodologies that are;
  - Representative of the site of administration and/or action
  - Emulate in vivo processes (In vitro Dissolution Absorption System)
  - Performed under in vivo like conditions or under conditions capable of detecting product differences
  - Validated and reproducible

Case Study 1

Biowaivers for BCS Class 3 Drug Products

How to evaluate and prospectively apply in vitro data to enable BCS based Class 3 biowaivers?

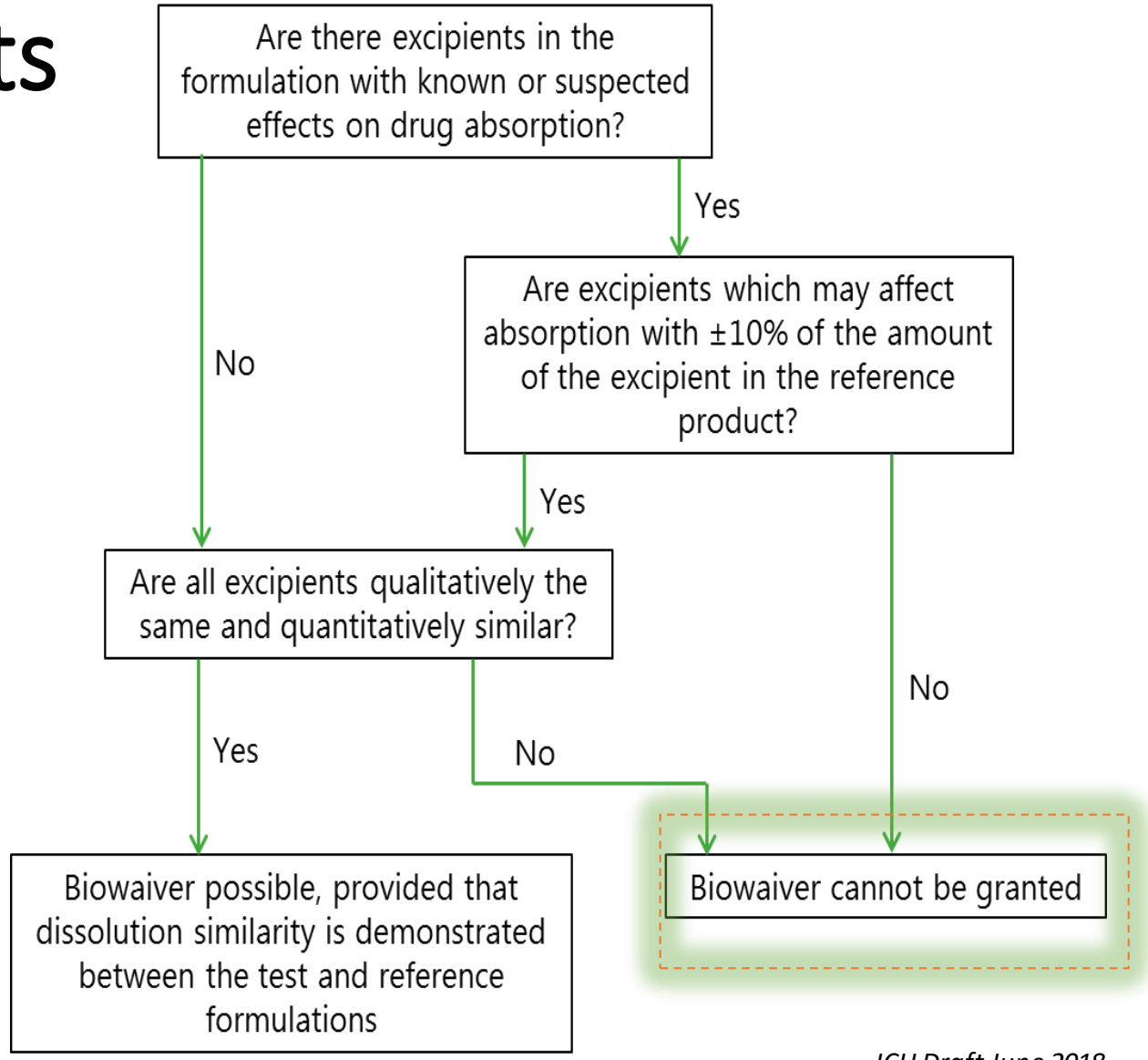
BCS class 3 drug products

(ii) BCS class 3 drug products: Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product. Quantitatively very similar includes the following allowable differences:

- Changes in the technical grade of an excipient
- Changes in excipients, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:
  - Filler (± 10%)
  - Disintegrant, Starch (± 6%)
  - Disintegrant, Other (± 2%)
  - Binder (± 1%)
  - Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  - Lubricant, Other (± 2%)
  - Glidant, Talc (± 2%)
  - Glidant, Other (± 0.2%)
  - Film Coat (± 2%)

The total additive effect of all excipient changes should not be more than 10 percent.

FDA Final Guidance December 2017



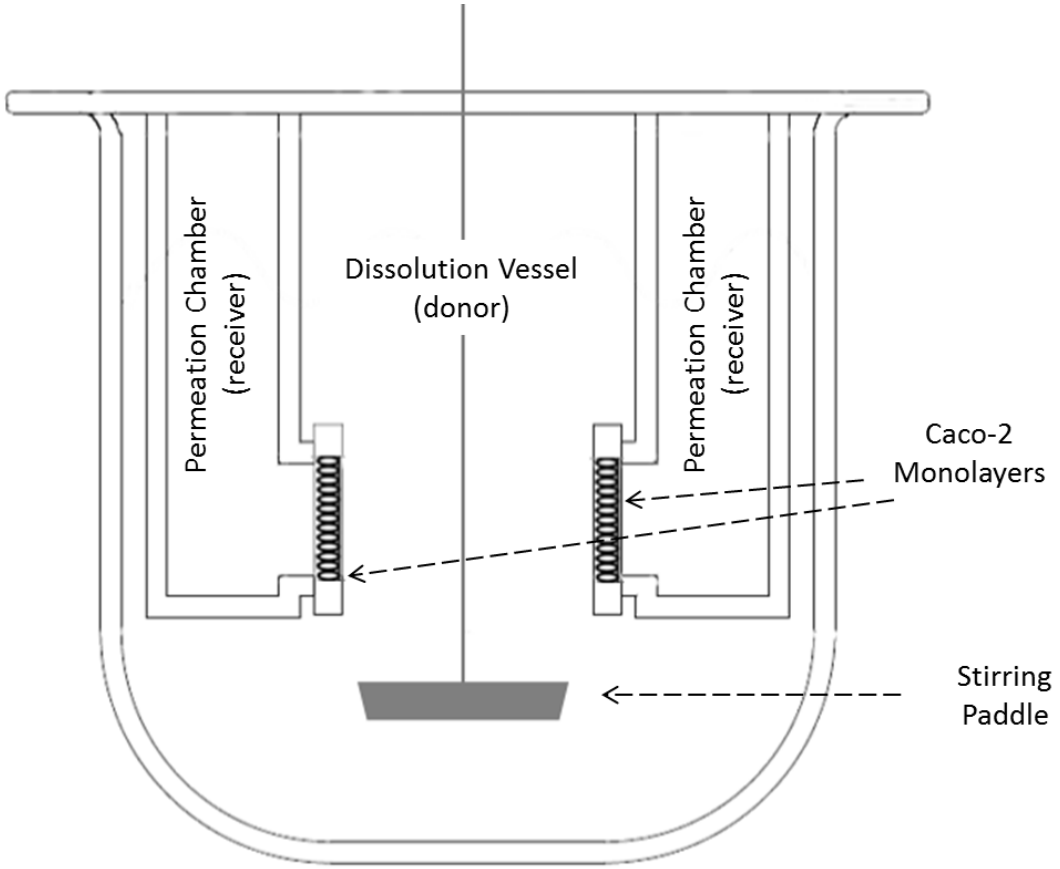
ICH Draft June 2018

Challenges with qualitatively the same and quantitatively very similar

- Legal - Potential Patents
- Will we receive feedback*?
  - "Consistent with the Agency's past and current practices, FDA does not intend to review proposed formulations that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD"
- Logistics - Cycle time for Q1/Q2 response
- Deformulation techniques - Multiple cycles may be required
- Can we create excipient exception categories?
  - Insoluble excipients
  - Excipients that are food constituents

**Controlled Correspondence Related to Generic Drug Development Guidance for Industry, Draft Guidance, November 2017*

In vitro data from a combined system



***In Vitro* Dissolution Absorption System (IDAS)** combines traditional dissolution testing with a means to **determine and quantify** interactions with a bio-relevant membrane.
FDA BAA-19-00123 (2019-2021)

Expanded excipient tolerance range

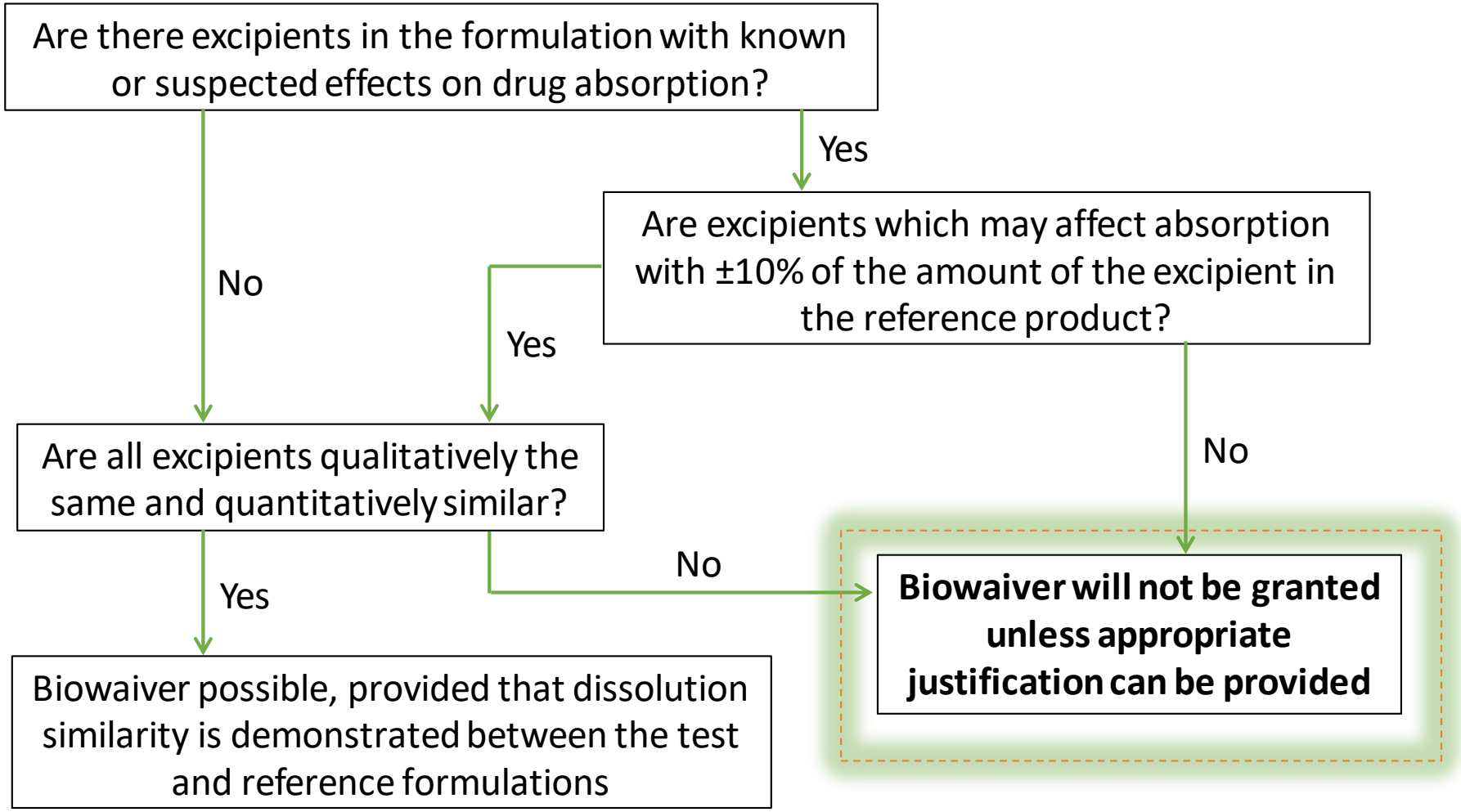
Year 1: System Sensitivity

- Analytical method qualification
- Permeation model optimization
- Effects of individual excipients on permeation: cassette of five model drugs (four Class 3, one Class 1) +/- individual excipients (**total of 15 excipients** × 3 concentrations of each)

Year 2: IVIVC

- Individual Class 3 drug products with published clinical data using different formulations, tested in IDAS with the same formulations dosed clinically.
- Retrospective analysis to establish IVIVC with available clinical BE data and generated in vitro data

BCS class 3 drug substances



ICH M9 on biopharmaceutics classification system-based biowaivers
EMA/CHMP/ICH/493213/2018
Date for coming into effect – 30 July 2020

Continue working towards – Exception categories, alternative pathways for evaluation, expanded tolerance ranges

Potential outcomes and challenges

- **With the current FDA BAA:** Better understanding of the impact of Q2 differences on formulation performance; e.g., If the difference in binder is more than XX%, whether a waiver still can be granted?

- *Investigate an in vitro in vivo correlation using PBPK to set clinically relevant safe space in terms of Q2 differences?**

- *Modeling of the generated in vitro data to expand its utility?**

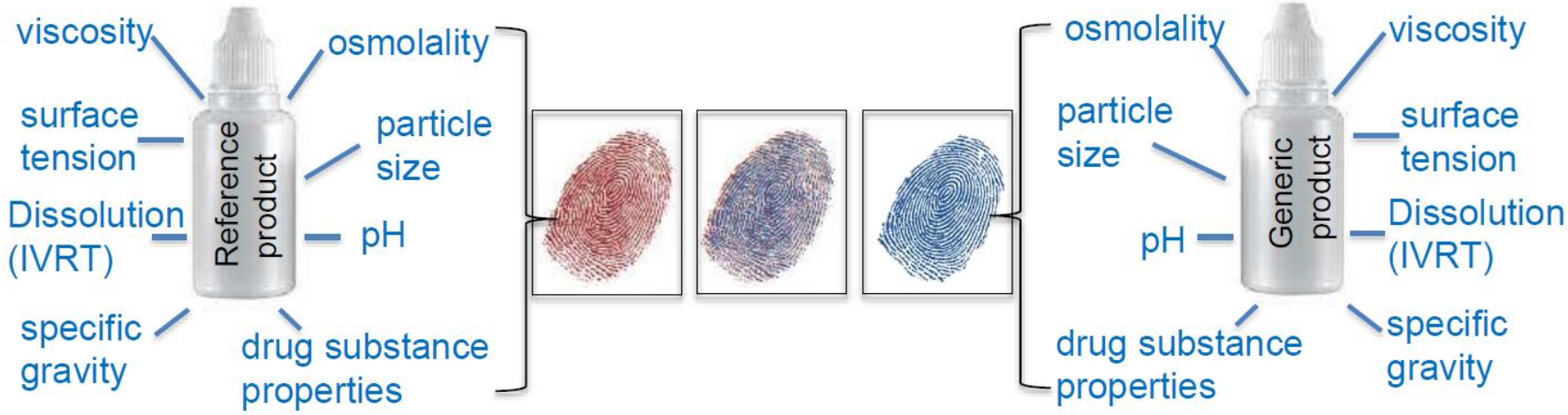
Potential areas for FY 2021 research priorities

Case Study 2

Chronic Complex Ophthalmic Products

Which studies are clinically relevant for an in vitro, model informed BE approach?

FDA initiatives: in vitro approach, Characterization Based Equivalence



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

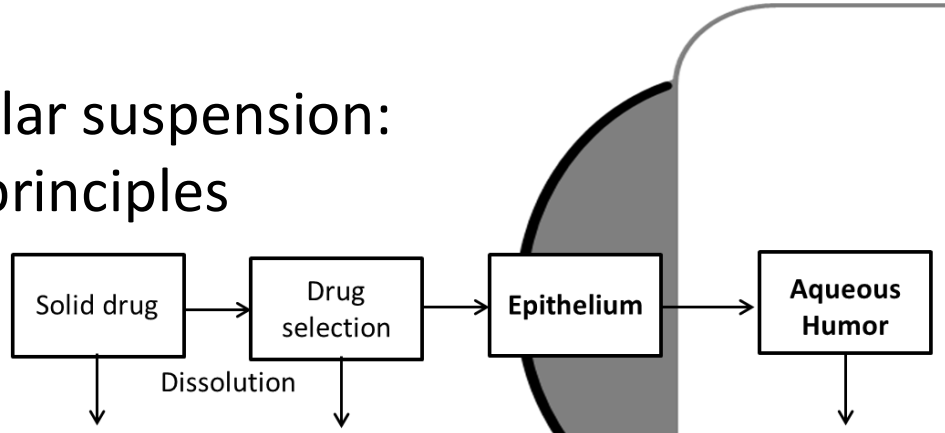
Acute vs. chronic complex ophthalmic products

Recommendations based on complexity of the formulation, its indication, and potential risk of therapeutic failure

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

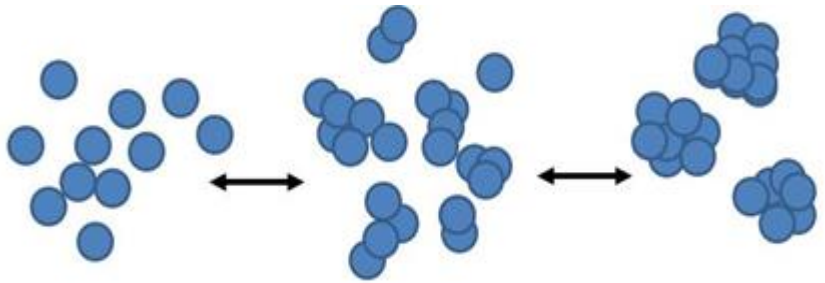
Product “Bio-morphology”?

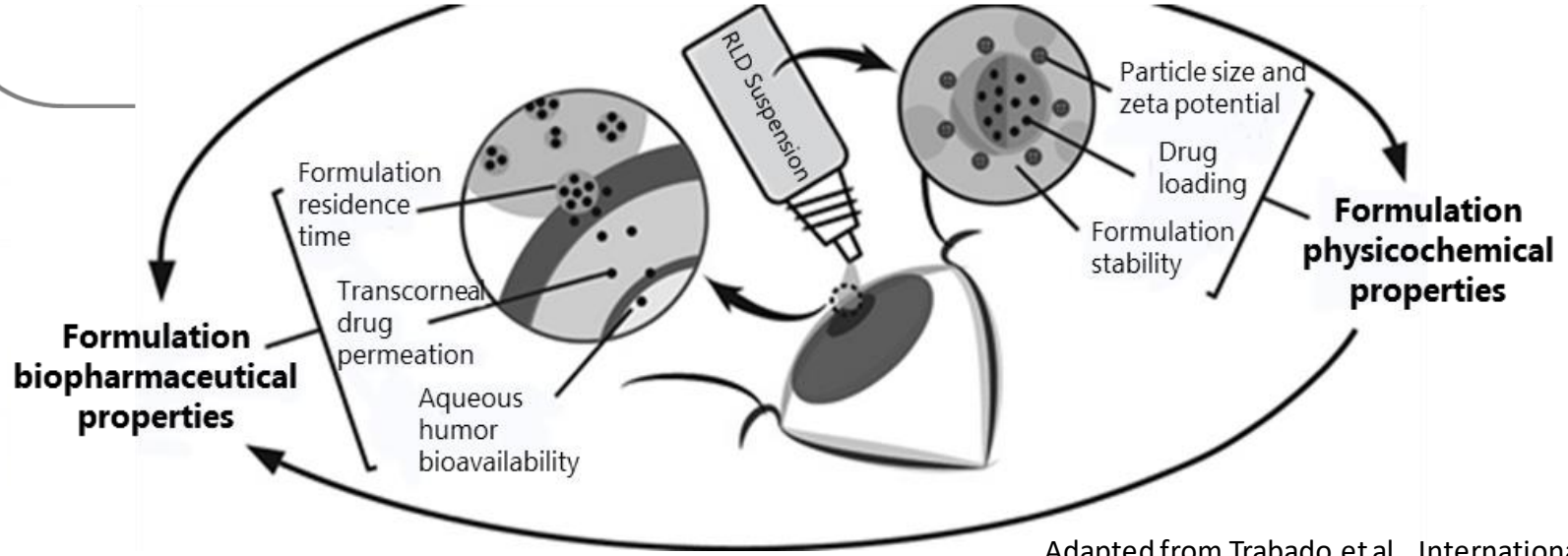
Ocular suspension:
PK principles



Tear flow

- Basal tear flow
- Drainage of excess fluid
- Induced lacrimation

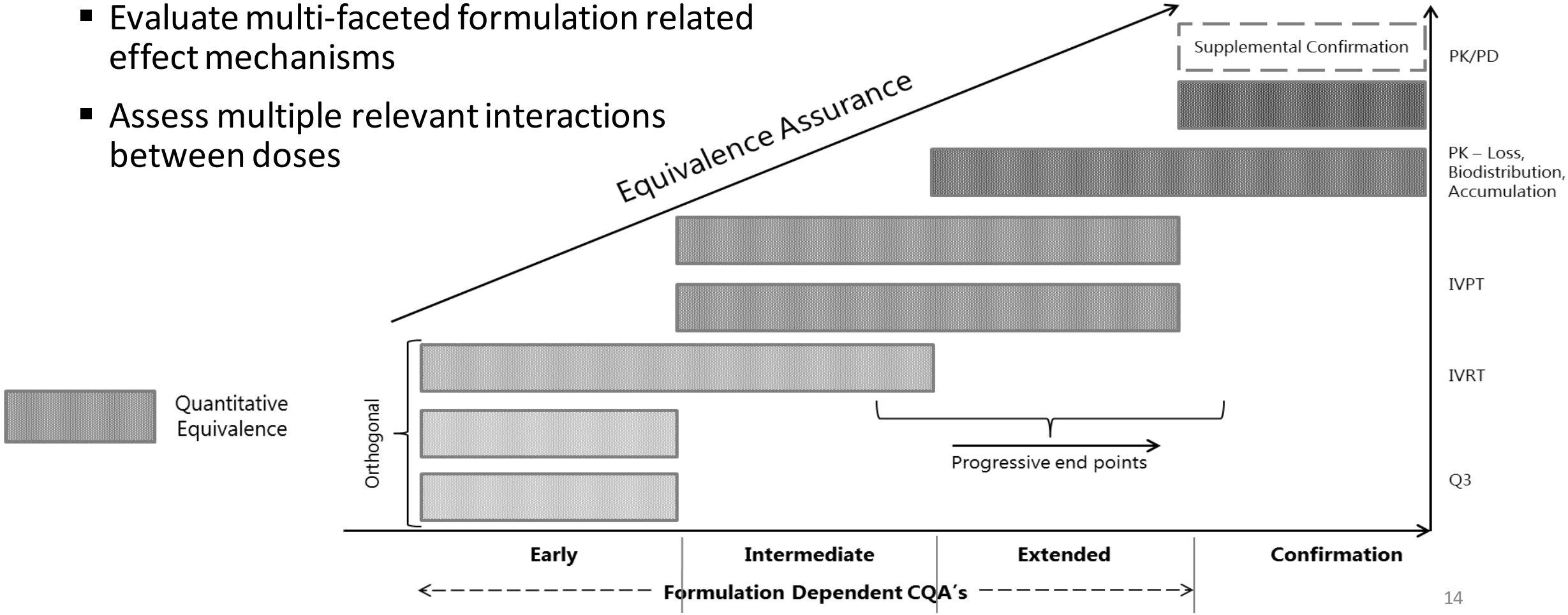




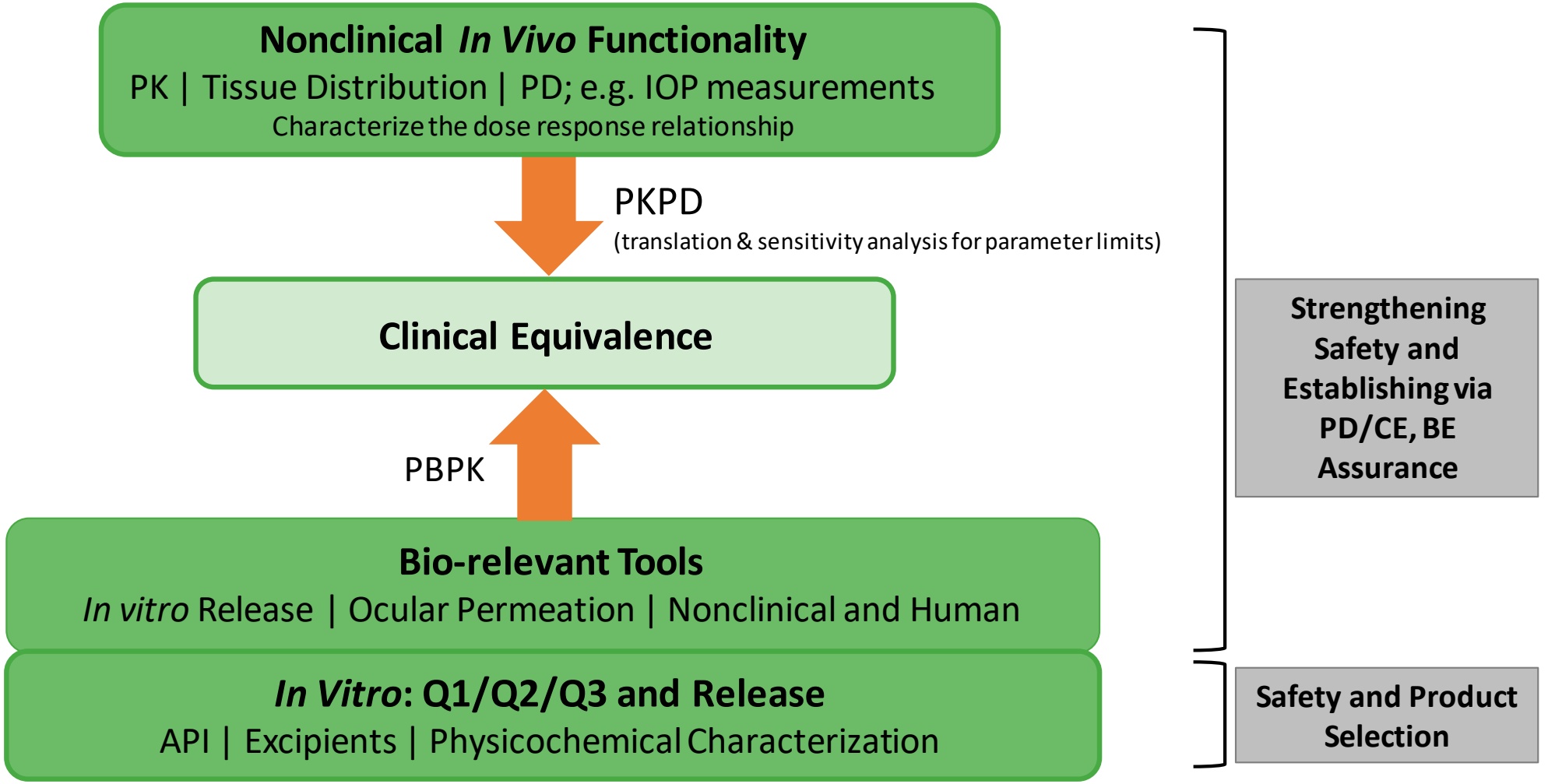
Adapted from Trabado et al. International Journal of Pharmaceutics. October 2017

How to elevate confidence in BE conclusions?

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



Chronic complex ophthalmics: Opportunity for Innovation



Potential outcomes and challenges

- An alternative in-vitro, model informed BE approach for chronic complex ophthalmic products

- *Establishing IVIVC for the identified ophthalmic product CQAs (lack of human in vivo data on local BA, what are possible surrogate measures, model validation for regulatory acceptance)?**

Potential areas for FY 2021 research priorities