GPhA
Generic Pharmaceutical Association

# Modeling and Simulations for Development and Bioequivalence Evaluation of a Generic Drug Product

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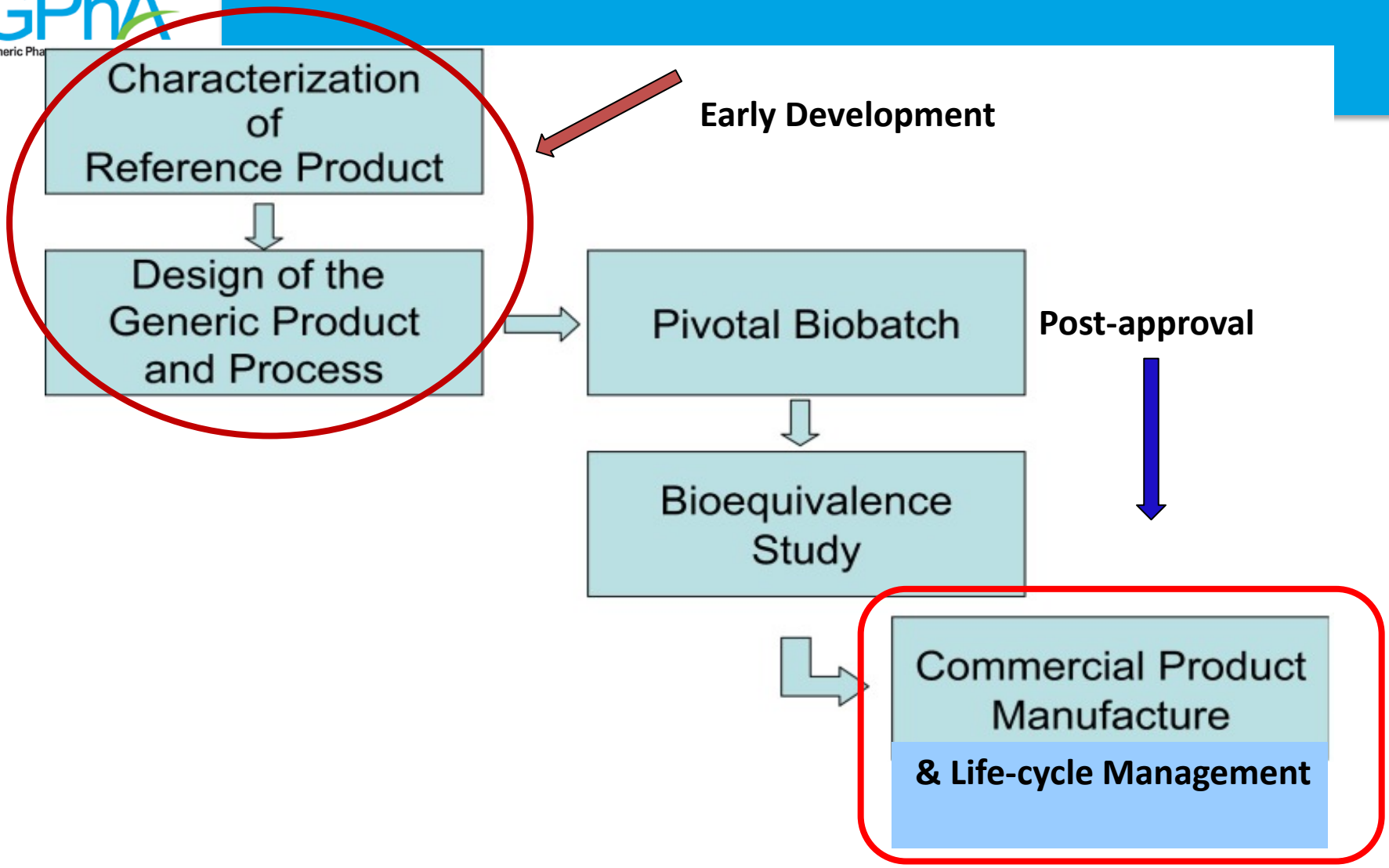
# About GPhA

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Generics represent greater than 88% of all prescriptions dispensed in the U.S. but only 28% of the expenditures of prescription drugs.

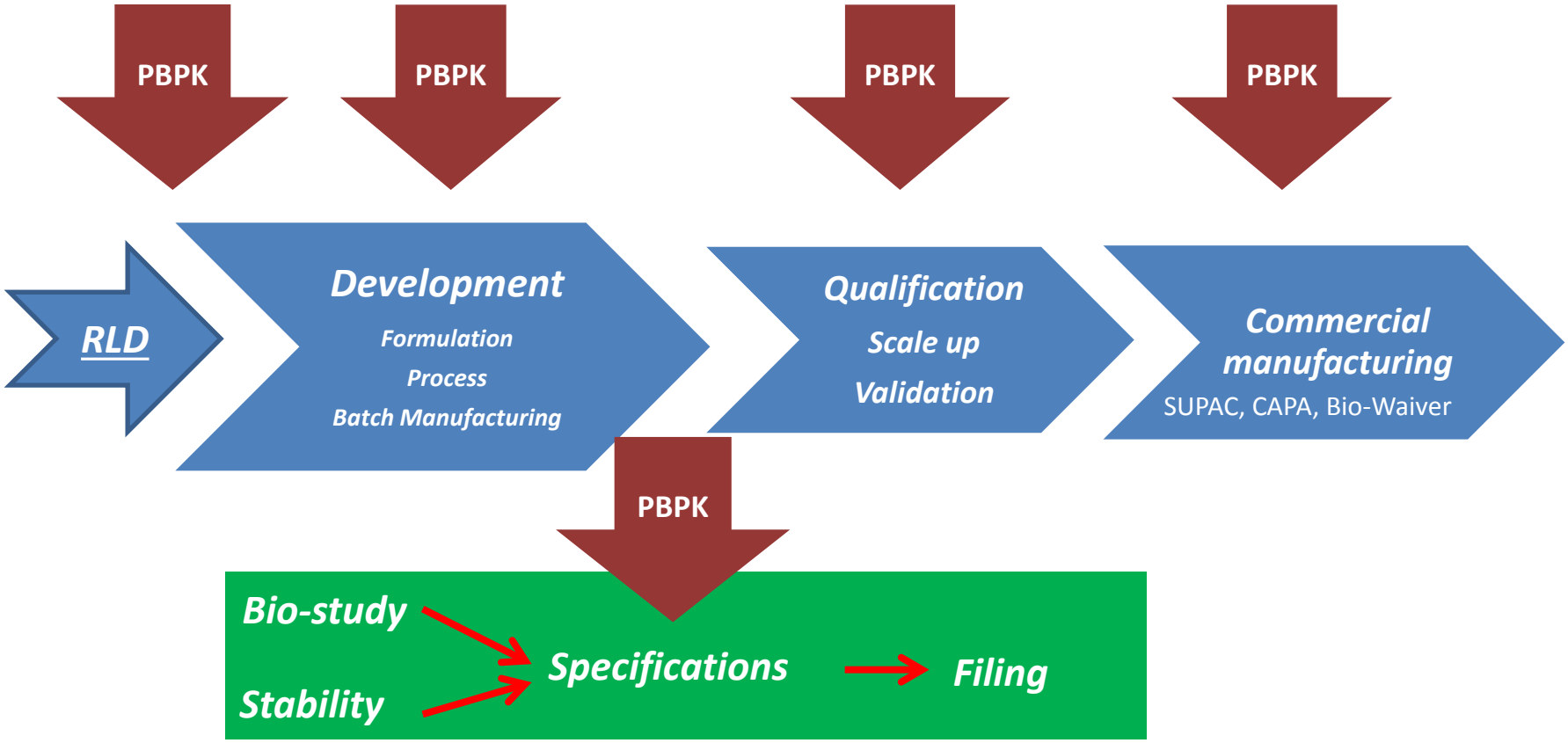



(Lionberger, The AAPS Journal, Vol. 10, No. 1, March 2008)

# Outline

- **Roles of PBPK modeling and simulation**
  - **Early development**
    - Reference List Drug (RLD) characterization;
    - Establishing Quality Target Product Profile (QTPP);
    - Formulation design and product development of to achieve bioequivalence
  - **Life-cycle and Quality Risk Management (QRM)**
    - Bio-indicative dissolution test conditions and clinically meaningful specification limits;
    - Bio-study waiver for the additional strengths and SUPAC;
    - Critical material attributes (CMA) and boundaries for a rate–controlling excipient**;**

# Product Life-cycle: Opportunities for PBPK Modeling & Simulations



# GPhA Survey:
# Do We Use the Opportunities?

| Are you using PBPK modeling for any of the following? | % Yes |
|---|---|
| Formulation and process development to understand the critical performance of the RLD? | 75 |
| Establishing the QTPP? | 0 |
| Design of the product to meet bioequivalence? | 75 |
| Developing the manufacturing process? | 50 |
| QRM Process to establish CQA, CMA and CPP? | 0 |
| Establishing specifications for the dissolution drug release? | 0 |
| Scale up for QRM? | 0 |
| Ensuring performance of the scaled up product? | 0 |
| Changes/Continual Improvement? | 0 |
| CAPA? | 0 |

# Early Development

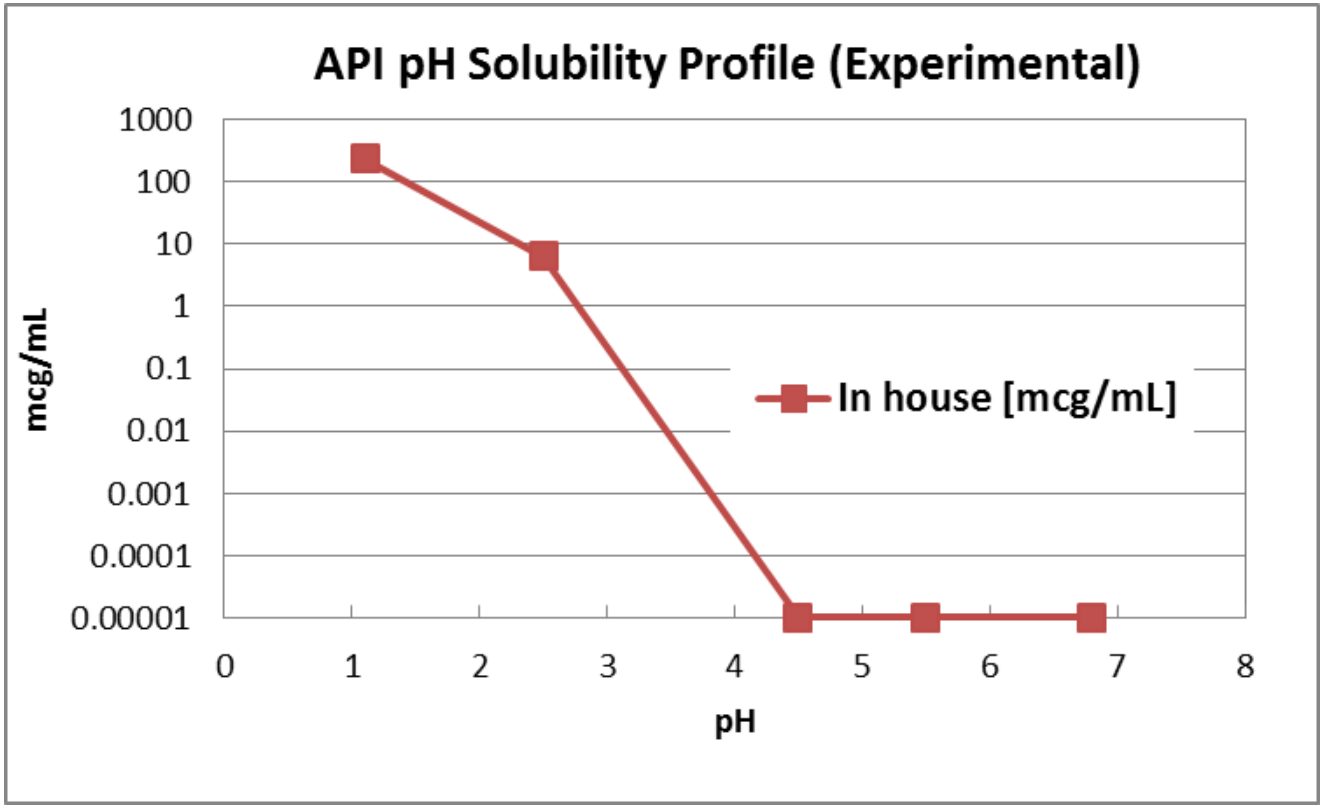
- **Characterize RLD in terms of the attributes critical for *in vivo* performance;**
- **Define Quality Target Product Profile (QTPP);**
- **Facilitate formulation design and define development strategy to achieve BE with RLD**

# RLD Characterization: Tools & Input Info

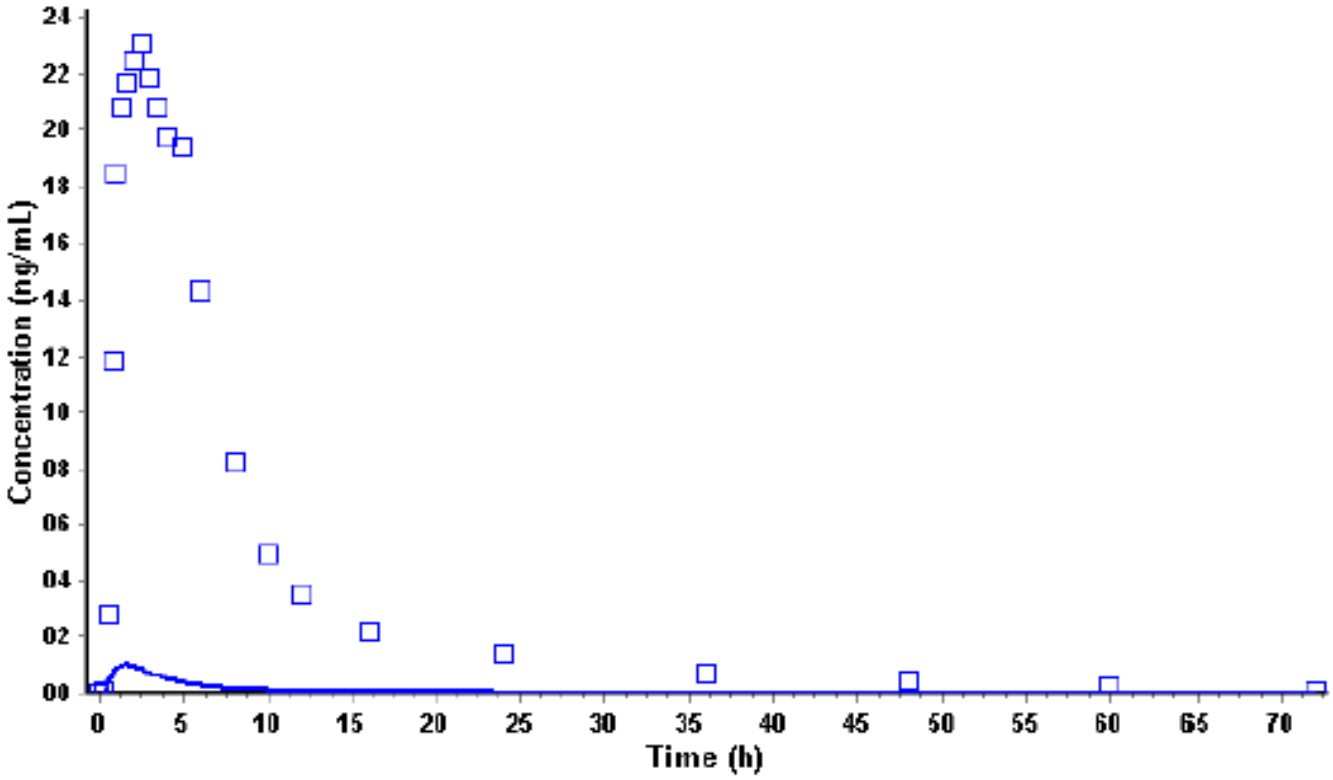
- **GastroPlus v.8** (SimulationsPlus Inc)
- **Input info for RLD:**
  - **Physico-chemical and PK properties of the API;**
  - **Dosage form and dosage strength;**
  - **Route of administration;**
  - **API pH solubility profile;**
  - **Plasma concentration *versus* time data or PK parameters;**
  - ***In vitro* release profile (optional)**

# Example
# API – Steroid, BCS 4: Input Info

- **Dosage form/strength: IR tablet, 250 mg**
- **Molecular formula/weight:** $C_{26}H_{33}NO_2$; 391.55
- **API: Log D, pKa, Caco-2 permeability**
- **API: pH solubility profile (in house generated)**
- **PK parameters: $C_{max}$, $T_{max}$, AUC, Vd, CL, plasma protein binding**
- **Plasma concentration *versus* time profile**
- ***In vitro* dissolution profile** (for information purpose)


API pH Solubility Profile (Experimental)
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
mcg/mL
0
1
2
3
4
5
6
7
8
pH
In house [mcg/mL]

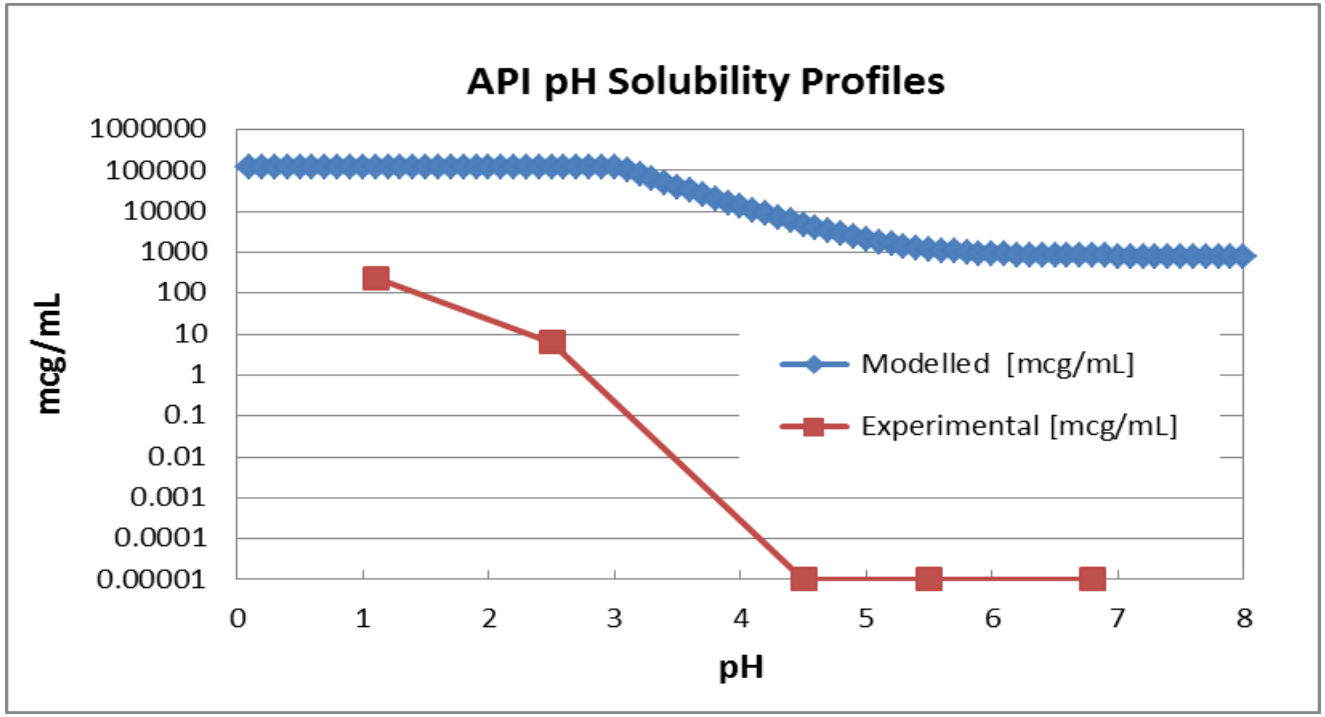
# RLD Characterization: PK Profile



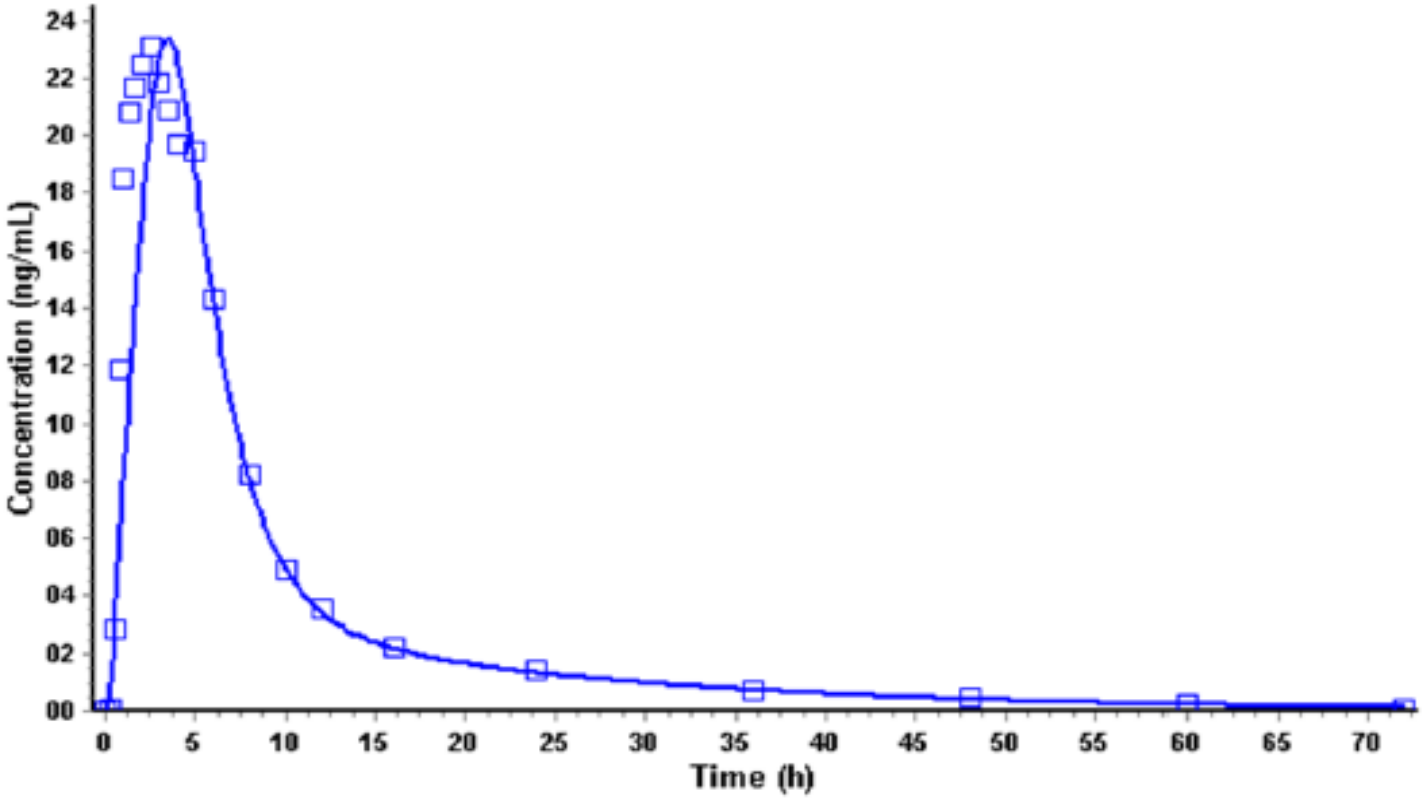

Simulated (line) *versus* Observed (empty squares) Plasma Concentration *versus* Time Profile

# Profiles are not Matching. Why?

- Parsimony Principle (William Ockham, 1287-1347)



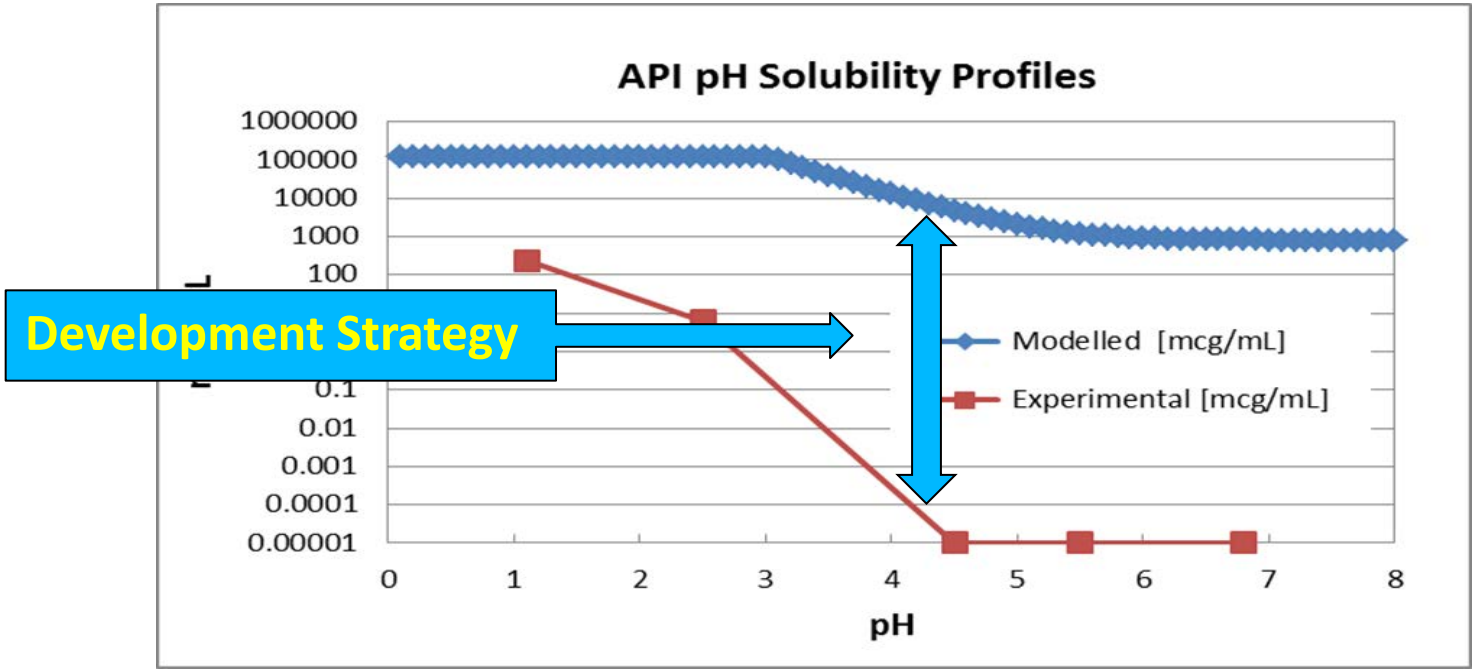
# RLD Characterization: Target PK Profile




Plasma Concentration *versus* Time Profile Simulated (line) using Theoretical pH Solubility Profile *versus* Observed (empty squares)

# Development Strategy & Formulation Design to Achieve BE

- **Solubility enhancement, based on the modeling results**




**Bioequivalence achieved!**

# Commercial Product Manufacture & Life-Cycle Management: Modeling & Simulations to Ensure QRM

# Our Product

- A BCS 1 API formulated as an extended-release, matrix based formulation in multiple strength, linear PK.
- Bioequivalence *versus* reference product proved for the lowest and highest strengths.
- Formulations subjected to bio-studies exhibited different release rates in one of the test media. Is this relevant to the product's *in vivo* performance?
- Biowaiver justification for the intermediate strengths is challenged due to the release differences. Is a science-based approach that employs modeling and simulations applicable?

# PBPK Modeling and QRM

- **Bio-indicative dissolution test conditions and clinically relevant specification limits to ensure BE;**

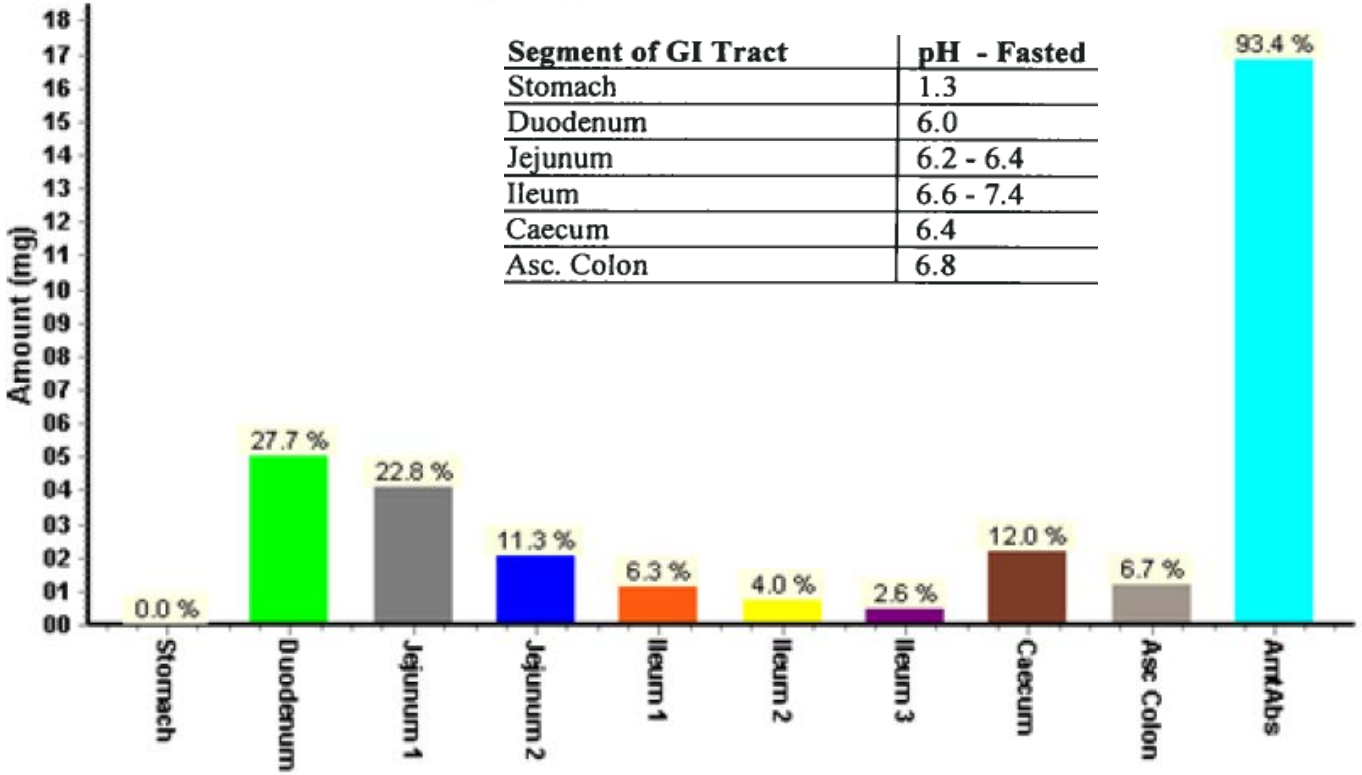
- **Bio-study waiver for the intermediate strengths and/or SUPAC (IVIVC Level A);**

- **Boundaries for critical material attributes (CMA) of a rate–controlling excipient to ensure *in vitro* release within clinically relevant specification limits.**

# Bio-indicative Dissolution Test Conditions & Specification Limits to Ensure BE

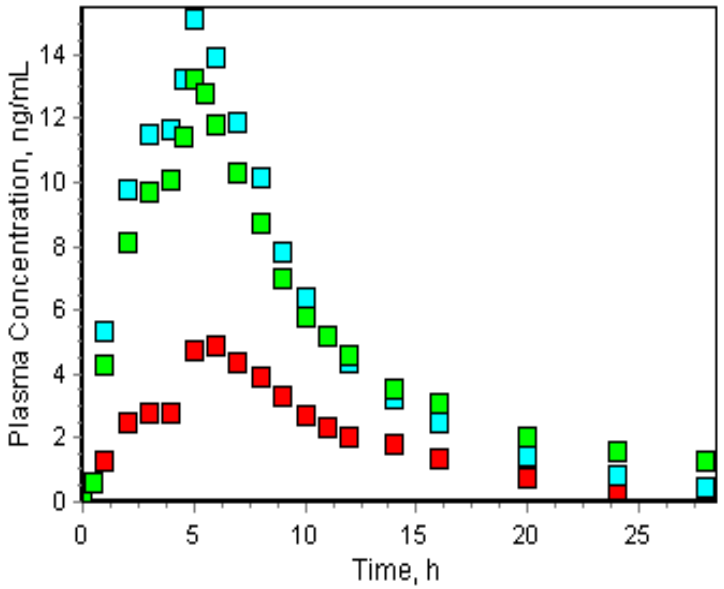
# Regional GI Absorption Profile

| Segment of GI Tract | pH - Fasted |
|---|---|
| Stomach | 1.3 |
| Duodenum | 6.0 |
| Jejunum | 6.2 - 6.4 |
| Ileum | 6.6 - 7.4 |
| Caecum | 6.4 |
| Asc. Colon | 6.8 |

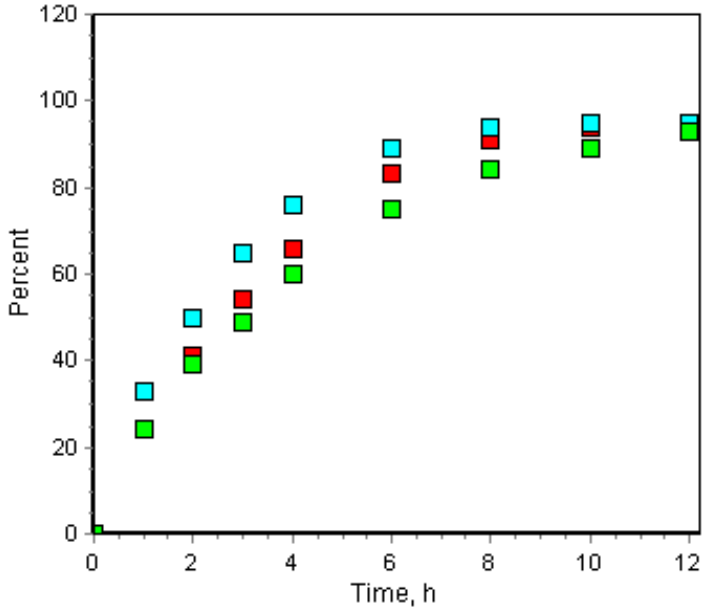


# Bio-Lots

**PK Profiles (not dose-normalized)**




***In Vitro* Release Profiles**

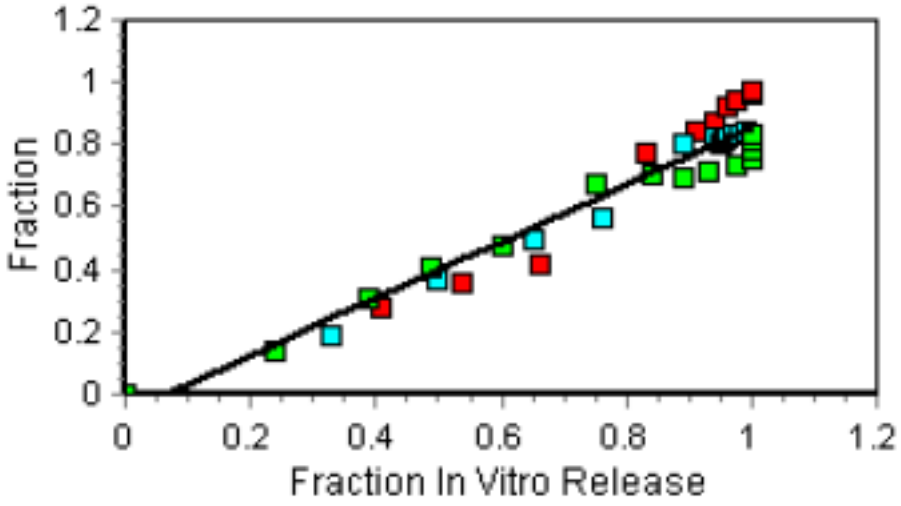



The lowest strength -bioequivalent

The highest strength -bioequivalent

The highest strength –bioequivalent (“border-line” confidence)

# In Vitro-In Vivo Correlation- Level A




Correlation between fraction of dose released *in vitro* and absorbed *in vivo*. The linear function is: y = - 0.058 + 0.914x, where x is the fraction *in vitro* released, and y is the fraction absorbed *in vivo*. Rsq = 0.955

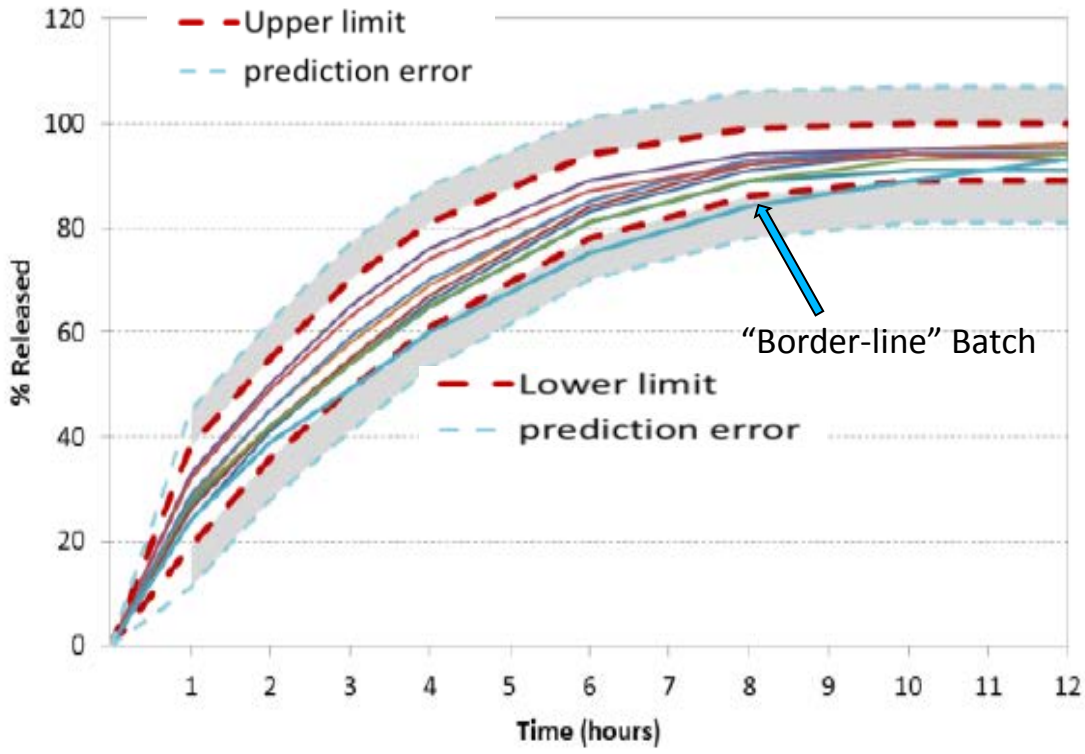
# Dissolution Test Method: IVIVC Based Specification Limits

- A series of simulations, conducted to predict the PK parameters for hypothetical batches exhibiting different *in vitro* release profiles.

- Acceptance criteria, proposed based on the simulation results, ensure discrimination between bioequivalent and "border-line" bioequivalent batches.

- The proposed acceptance criteria are in agreement with the actual data for the "border-line" batch (marginally outside the limits).

# IVIVC Based Specification Limits for Bio-Relevant Dissolution Test Method

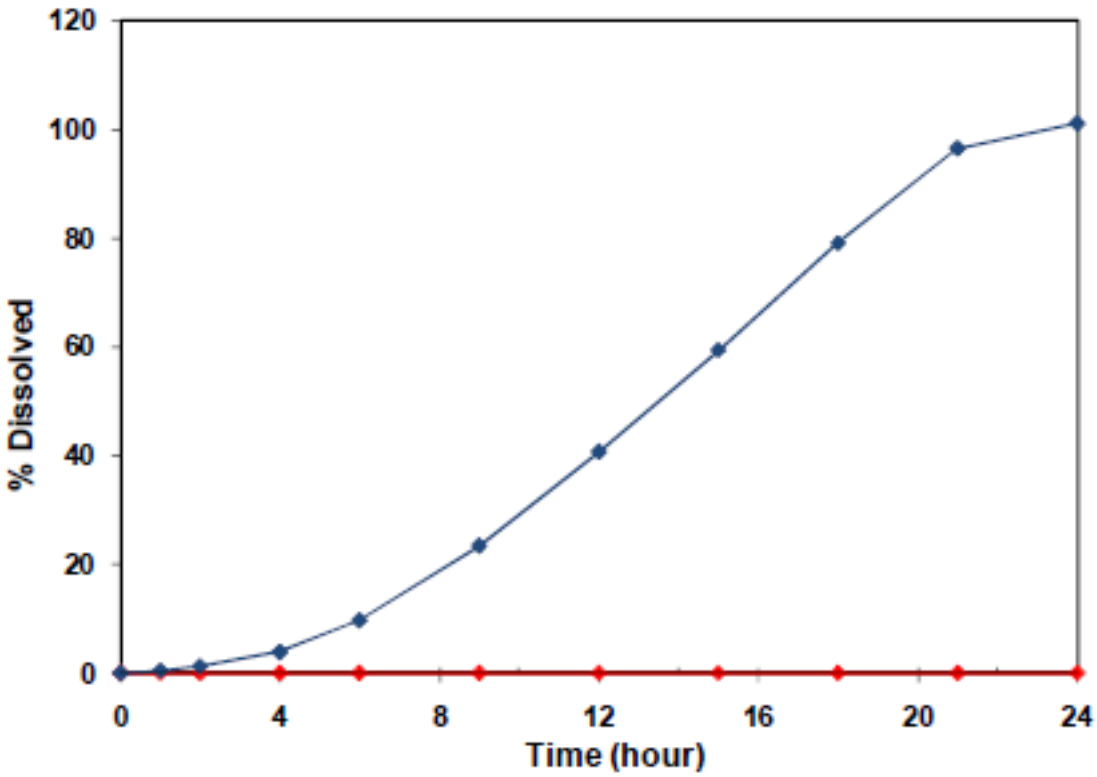



Grey Area (prediction error)

# Bio-Relevant vs QC Dissolution

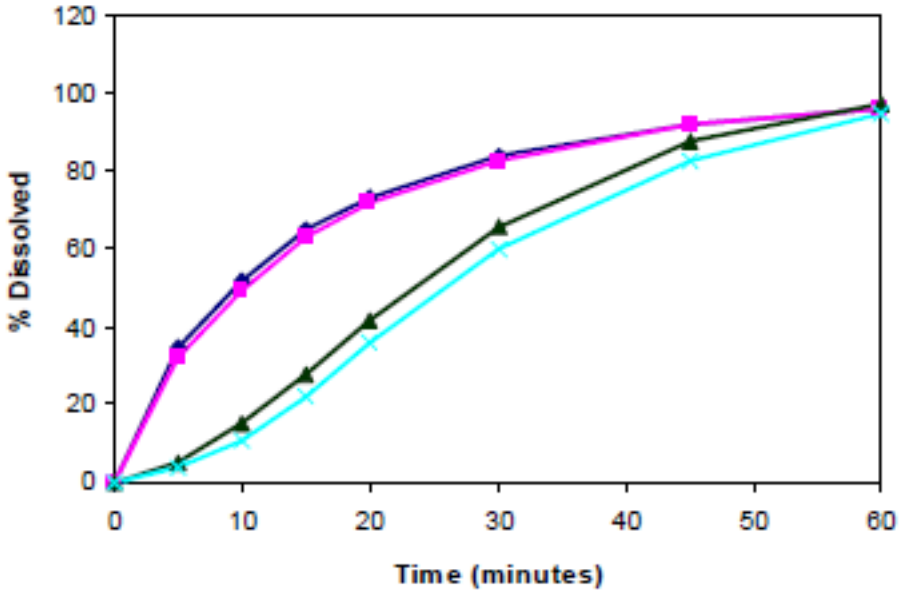
- May be different methods
- QC method  is used routinely; could be overly discriminating and bio-irrelevant
- Bio-relevant method may be impractical for routine applications
- Complement each other
- Impact of changes (SUPAC etc.) or out-of-spec results at stability (generated by QC method) on the product BA/BE is assessed by bio-relevant dissolution test method

# FDA-OGD Dissolution Methods: Does One Size Fit All?




Two bioequivalent drug products with generic drug showing no release

# FDA-OGD Dissolution Methods: Does One Size Fit All?




Two bioequivalent products with different release characteristics in FDA-OGD recommended test conditions

# Bio-study Waiver for Intermediate Strengths

- Bio-study waiver is justified based on the PK profiles simulated for the intermediate strengths using validated Level A IVIVC.

- *In vitro* release profiles generated for the intermediate strengths by the bio-indicative test method are incorporated into simulation.

- Test/Reference ratios are predicted for $C_{max}$ and AUC

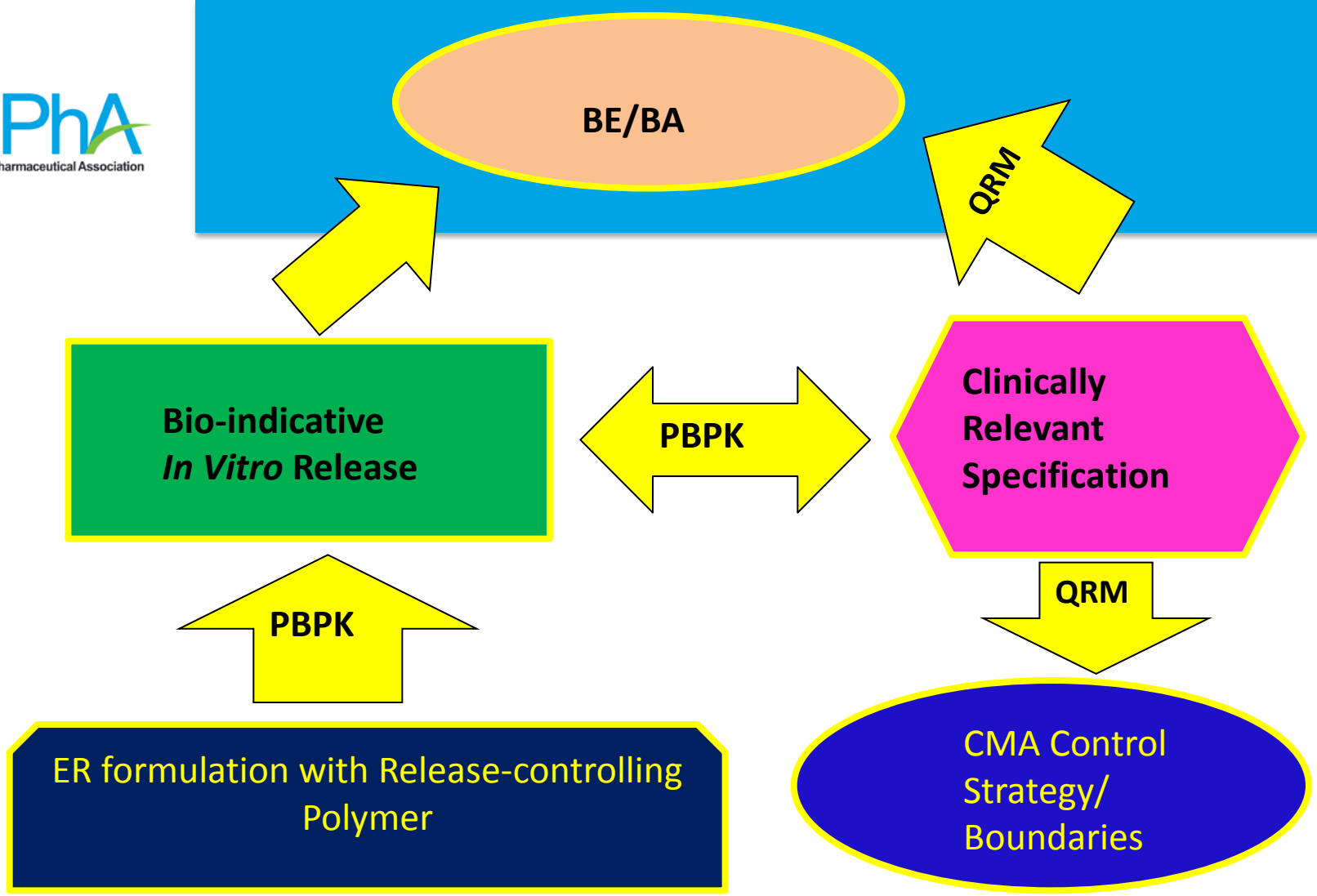
# Boundaries for Critical Material Attributes of Release Controlling Polymer

- A polymer material attributes may have impact on the release of the active ingredient and consequently on the bioavailability.

- What are the boundaries of the polymer CMA?

- Boundaries are defined to ensure BE.

- BE is ensured by clinically relevant specification for release testing conducted using bio-indicative test method.




Boundaries for the polymer CMA are defined by the product ability to meet clinically relevant specification when tested using bio-indicative *in vitro* release method.

# Summary

- At early product development stage PBPK modeling  is a proven toll to characterize RLD, facilitate product development to define formulation strategy and achieve bioequivalence;

- During life-time cycle management, QRM is ensured by implementing adequate controlled strategies (i.e. test methods and specification limits);

- Controlled strategy, established to ensure BE, is developed based on PBPK modeling;

- PBPK Modeling and Simulation is a powerful but underused tool to facilitate development and ensure QRM of a generic drug product.

# References


- Zhang X., Lionberger R.A., Davit B.M. and Yu L.X. (2011): "Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development", AAPS Journal.13: 59-71

- Mirza T., Bykadi S.A., Ellison C.D. Yang Y., Davit B.M. and Khan M.A. (2013): "Use of *In Vitro-In Vivo* Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices", Pharm. Res. 30: 179-190

- Roudier B., Davit B.M., Beyssac E. and Cardot J-M. (2013): "*In Vitro-In Vivo* Correlation's Dissolution Limits Setting", Pharm. Res. 31:2529-2538

- http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf

- Mattocks D: A Strategy for Dissolution Method Development: A Risk-Based QbD Approach, The AAPS In Vitro Release and Dissolution Testing (IVRDT) Focus Group had a Face-to-Face (F2F) Meeting on November 19, 2015

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# Thank you!