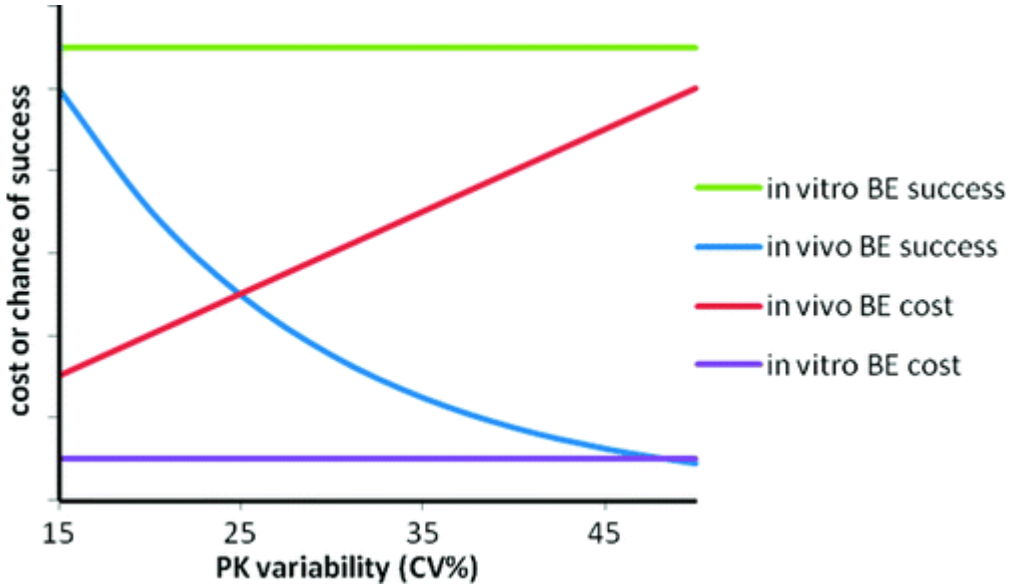
Impact of Excipients

BCS Class 3 Drug Product Dissolution and Permeability

Sid Bhoopathy, PhD
Chief Operating Officer

BCS Class 3 drugs

The value to the generic industry in expanding BCS class 3 waivers to non-Q1/Q2 formulations

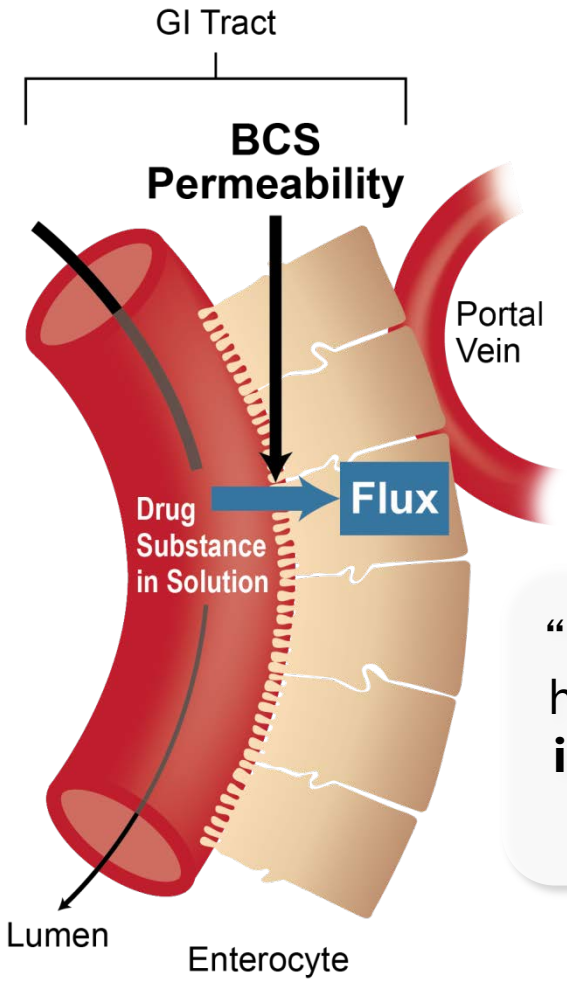


- BCS Class 3 drugs constitute 25% of drugs marketed in the United States
- Almost 40% of orally administered drugs on the WHO Model List of Essential Medicines are BCS Class 3 drugs.

Impact of Biopharmaceutics Classification System-Based Biowaivers[‡]
Jack A. Cook[‡]*, Barbara M. Davit*[§]*, and James E. Polli*[*,∥]

Vaithianathan, et al., J Pharm Sci. 2016; 105:996-1005

The Science of BCS Biowaivers



Absorptive Flux (J)

$= C_{int} \bullet P_{wall}$

P_{wall} = **effective or BCS permeability**

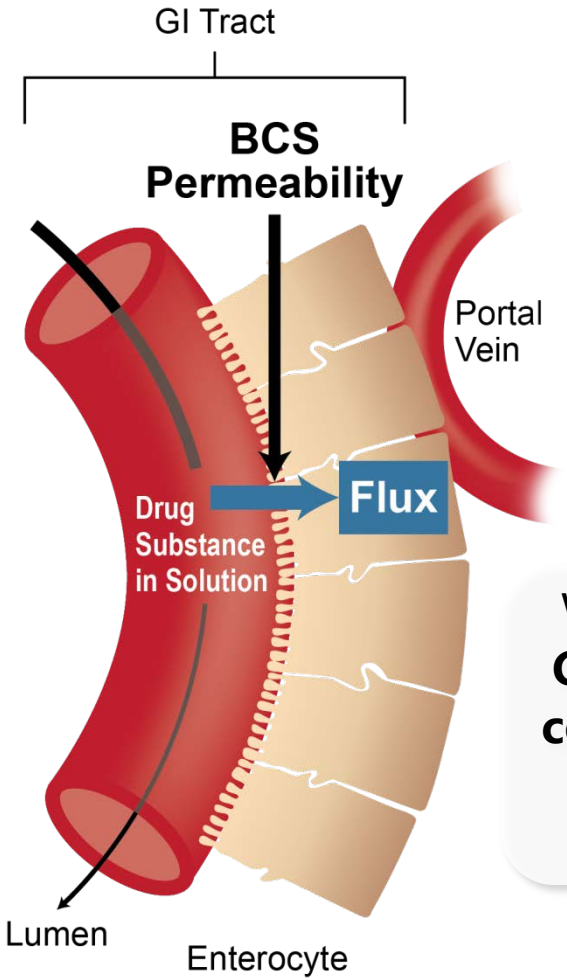
C_{int} = **concentration in lumen**

Which implies…

"…If two drug products, containing the same drug, have the **same concentration time profile at the intestinal membrane surface** then they will have the same rate and extent of absorption"

Amidon.G et. al. A Theoretical Basis for a Biopharmaceutics Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability, Pharm Res (12) No. 3, 1995.

The Science of BCS Biowaivers



Absorptive Flux (J)

$= C_{int} \bullet P_{wall}$

P_{wall} = **effective or BCS permeability**

C_{int} = **concentration in lumen**

Which further implies…

When *in vitro* testing can demonstrate the same **GI concentration time profile under all luminal conditions**….it can serve as a reliable surrogate for judging **therapeutic equivalence** of pharmaceutically equivalent drug products

BCS 3 Biowaiver Eligibility

- The drug substance is **highly soluble**
  - The highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C.

- The drug product is very **rapidly dissolving**
  - A mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes using USP Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm in 500 mL or less in -

    (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;

    (2) a pH 4.5 buffer; and

    (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

- The test product formulation is **qualitatively the same and quantitatively very similar** to the RLD

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System - Guidance for Industry , December 2017

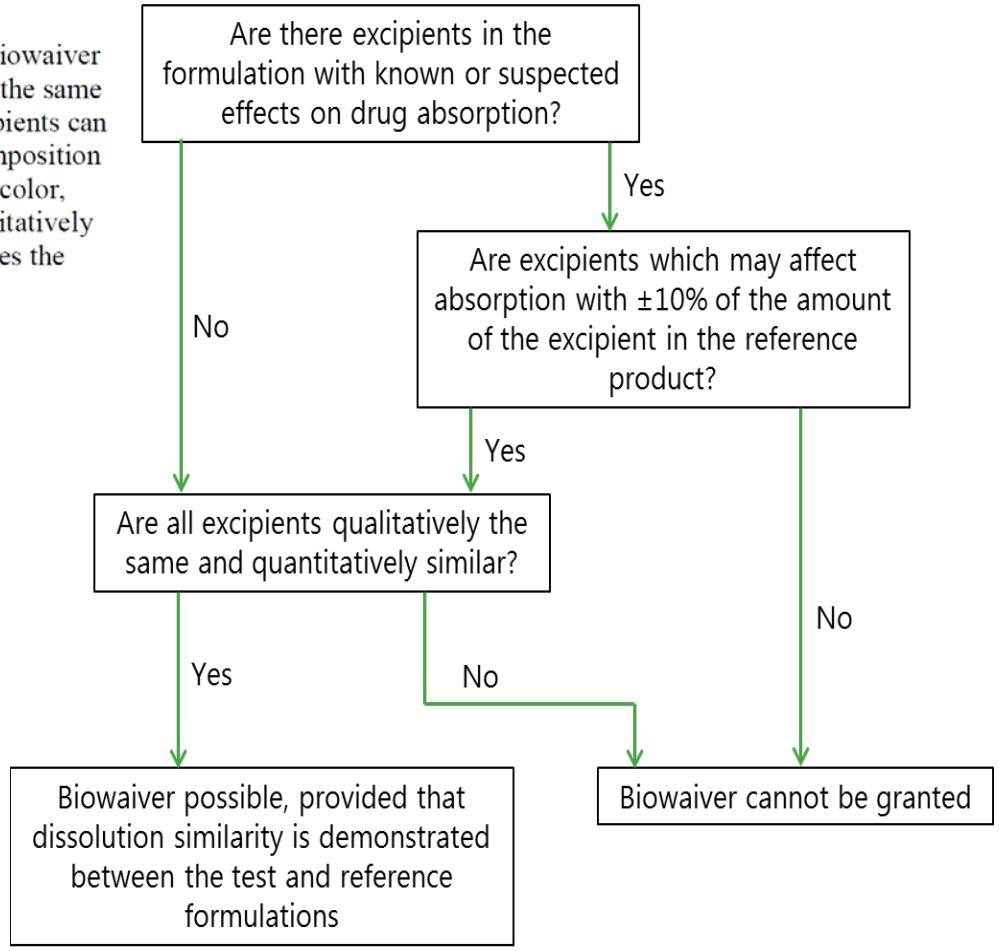
BCS Class 3 Drug Products

(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



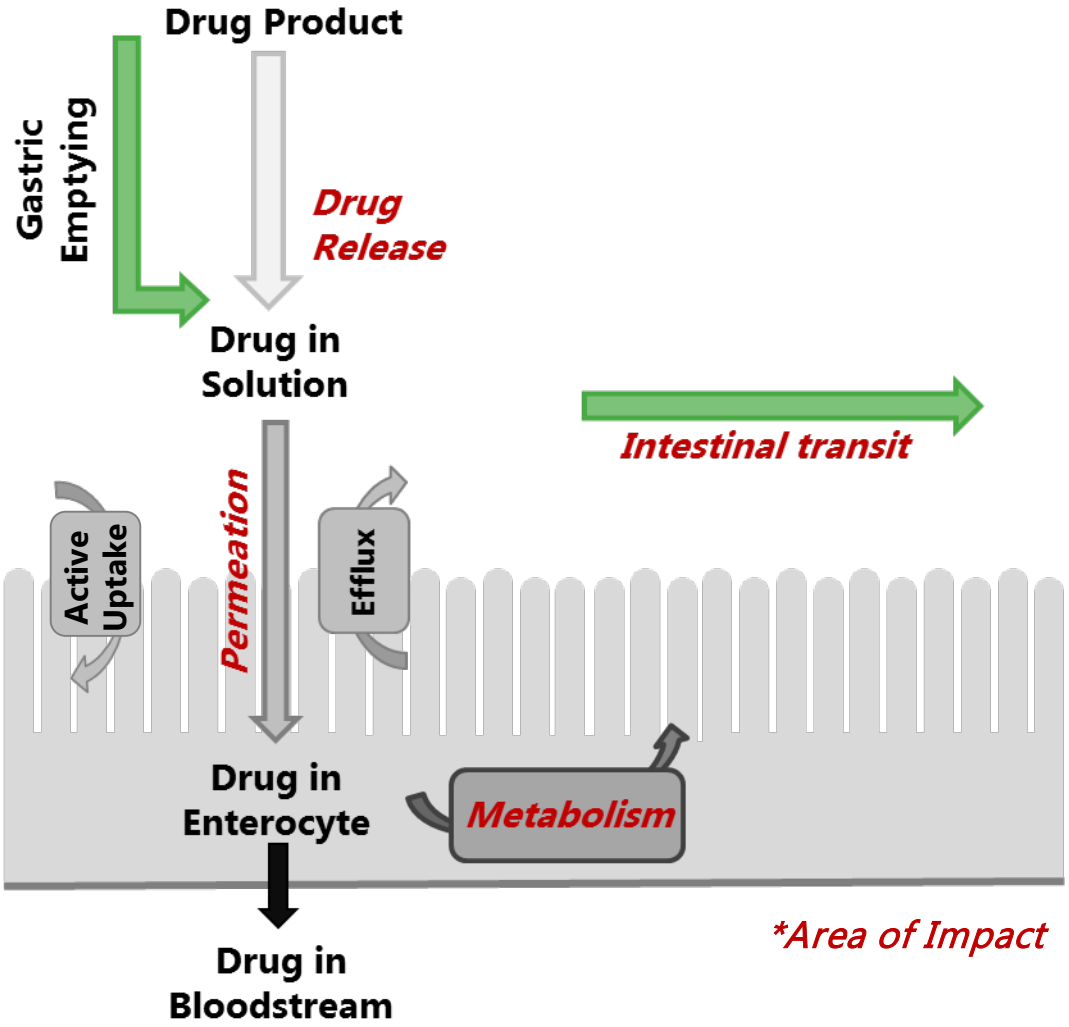
ICH Draft June 2018

Challenges

- 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*

How Excipients May Impact Absorption?



Release rate/amount of drug in solution
- Altered disintegration time
- Altered dissolution rate
- Altered local pH
- Complexation (excipient-drug complexes)

Transit and luminal volumes
- Faster gastric emptying
- Increased luminal volume (osmotic effect)
- Altered small intestinal transit time

Altered effective permeability
- Damage to intestinal surface/ tight junction modulation
- Inhibition of efflux
- Inhibition or enhancement of active uptake

Altered metabolism
- Inhibition of gut wall metabolism

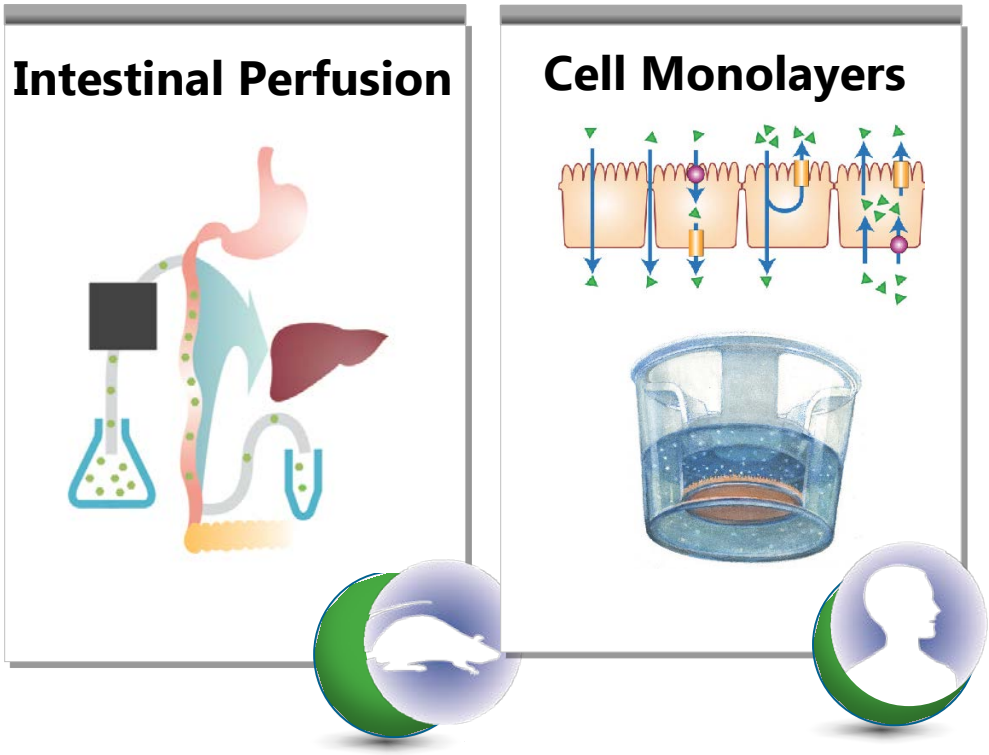
Ref. Dr. Talia Flanagan

Conventional Techniques

Dissolution

- Using USP Apparatus 1 or Apparatus 2
- In a volume of 500 mL to 900 mL
- Representative media:
  - 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;
  - pH 4.5 buffer
  - pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Permeability



Limitations with Conventional Techniques

- Dissolution testing - **insensitive** to excipient-drug complexation and impact of altered local pH

- Over-sensitivity of the cell monolayers to excipient effects –**model configuration?**

  Aungst BJ, J Pharm Sci. 2000; 89(4):429-442)

- Sensitivity to excipients such as SLS at concentrations known to be safe and widely used **– deviation from "real world" correlation**

  Rege, et al. (J Pharm Sci. 2001;90(11):1776-1786

- Same excipients tested in in situ rat intestinal perfusion model, with no obvious excipient-related effects outside the inherent variability of that model – **in vitro model over-discrimination or variability of in situ perfusion**

  Parr, et al. Pharm Res. 2016; 33(1):167-176

- BE studies in humans showed lack of excipient effect with two model BCS Class 3 compounds and 12 commonly used excipients – **Lack of in vivo correlation but in vivo can be difficult to deconvolute and/or scale**

  Vaithianathan, et al J Pharm Sci. 2016; 105:996-1005

Basis for Innovation: Biopharmaceutics

"The study of the chemical and physical properties of drugs and the biological effects they produce"

Using this principle:

- Develop tools that are more bio-relevant
- Link API and formulation to their effect

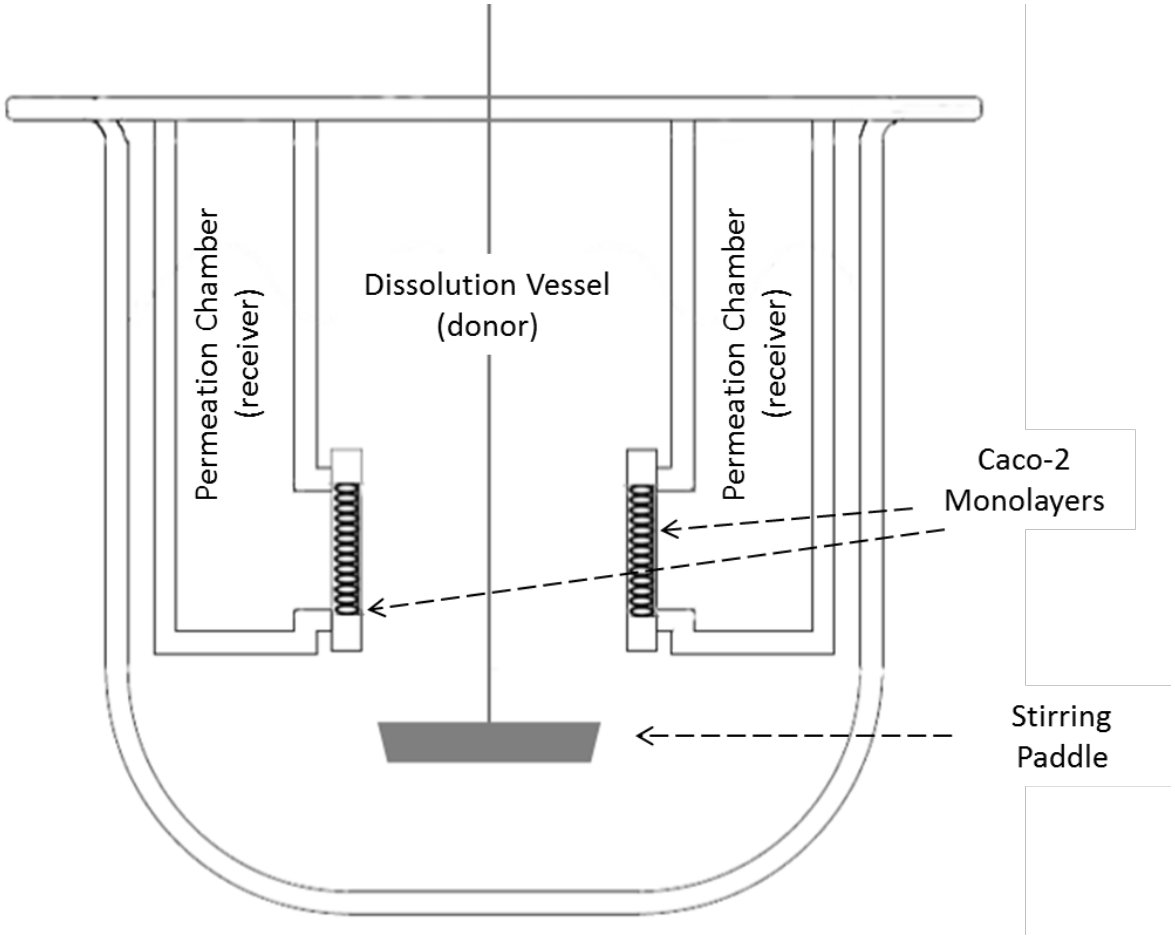
Applications

- Infer pharmaceutical and bioequivalence
- Performance testing of dosage forms
  - Predict and control BA & BE
  - Accelerate product development

Adapted from Robert Lionberger, "Biopharmaceutics of Non-Orally Administered Drugs"

Innovation: IDAS

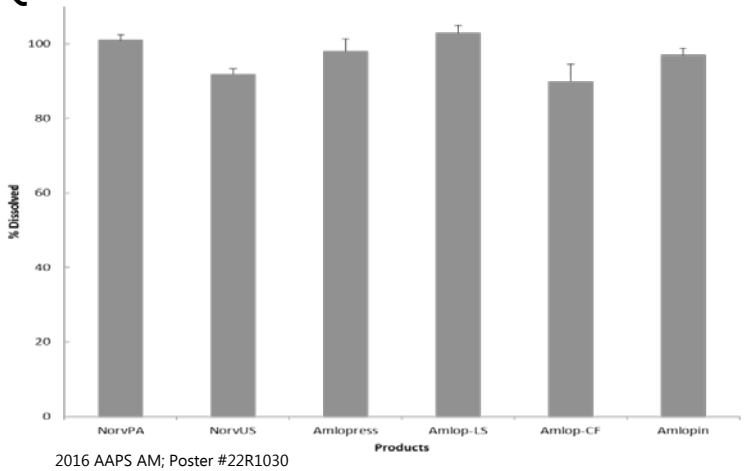
In Vitro **Dissolution Absorption System** combines traditional dissolution testing with a means to **determine and quantify** interactions with a bio-relevant membrane.



Biopharmaceutics Dissolution with Better *In Vivo* Correlation

Why IDAS?

Batch Release Data for Product A-
Q value was similar for different manufacturers



2016 AAPS AM; Poster #22R1030

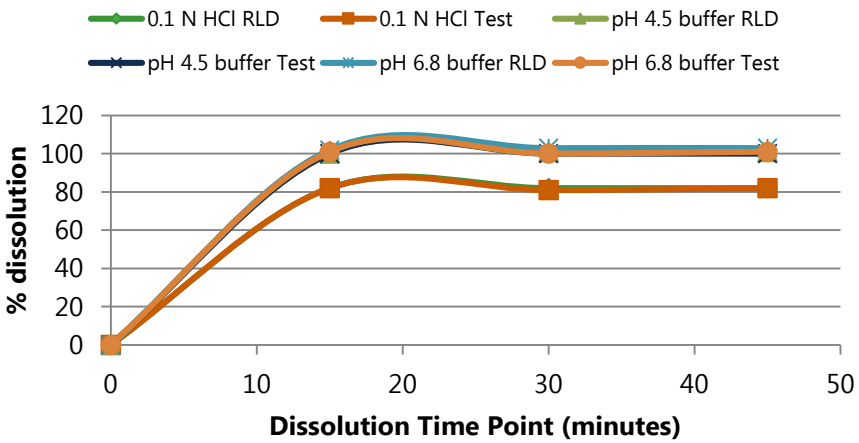
Data using IDAS shows marked differences in AUC and % permeated for different manufacturers

Product	AUC (0-2 hours)	% Permeation (0-2 hours)
FF15-025	**7304.8 ± 407.1**	**2.33 ± 0.52**
FF15-027	4001.3 ± 590.1*	0.25 ± 0.13*
FF15-028	2166.1 ± 756.8*	0.51 ± 0.16*
FF15-029	5043.8 ± 1157.7*	0.55 ± 0.35*
FF15-030	6477.0 ± 1031.9	0.51 ± 0.16*

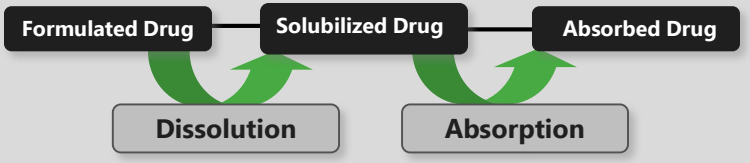
*: $p < 0.05$

IDAS Achieves Discrimination

Dissolution for Compound B [BCS III]



- The **test product failed bioequivalence.** for **C_{max} and AUC**
- IDAS – **dual gated process**



POTENTIAL

ABSORPTION SYSTEMS®

Why IDAS?

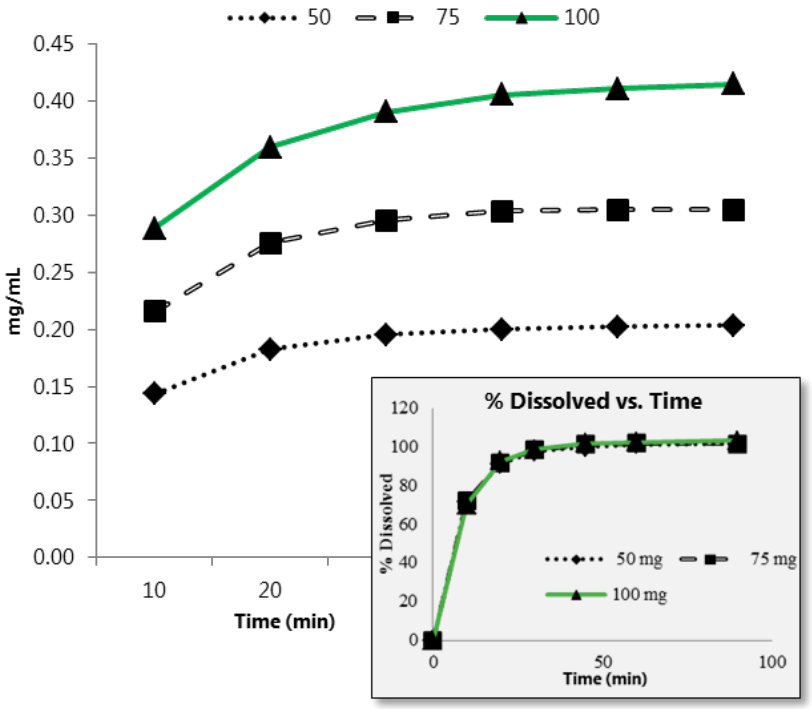
- Dissolution, solubility and permeability are routinely measured independently and under conditions that may have less physiologic relevance
- Poor discrimination, which impacts the link between *in vitro* drug product release characteristics and *in vivo* performance.
- Concomitant evaluation of bio-relevant processes

Application: Product Discrimination

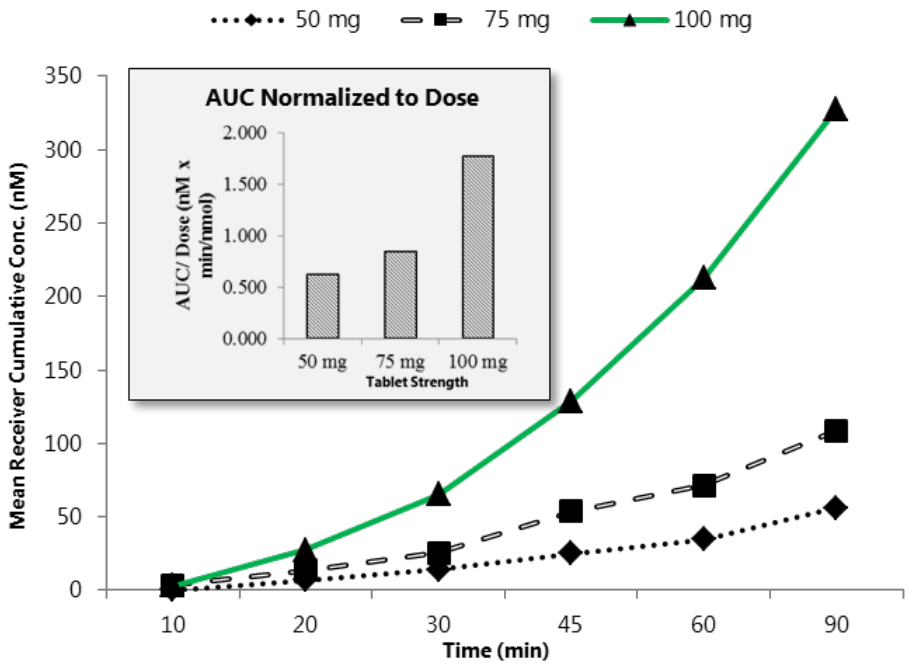
IDAS Achieves Improved Dose Discrimination:

Dissolution vs. permeability in fasted simulated intestinal fluid for a tablet with different strengths

Amount Dissolved vs. Time



Amount Permeated vs. Time



IDAS Resource Library

- Posters
  - **In Vivo Correlation:** Assessment of Drug Gastrointestinal Supersaturation Using a Two-Stage In Vitro Dissolution Absorption System 2 (CRS 2018)
  - **Supersaturation:** Assessment of drug gastrointestinal supersaturation using In Vitro Dissolution - Absorption System 2 (AAPS 2018)
  - **Food Effects:** Study of the Effect of Simulated Fast vs Fed State on the Dissolution and Permeation of BCS Class 1-4 Drugs Using the In-vitro Dissolution Absorption System 2 (AAPS 2018)
  - **In Vivo Correlation:** Evaluation of the In Vitro Dissolution and Absorption (IDAS2) as a potential surrogate for in vivo performance of drug formulations (AAPS 2018)
  - **Biowaivers:** Applications of the In vitro Dissolution and Absorption System 2 as a Bioequivalence Biowaiver Tool (AAPS 2018)
- Publications
  - **Supersaturation**: In Vitro and In Vivo Assessment of the Potential of Supersaturation to Enhance the Absorption of Poorly Soluble Basic Drugs (in progress, 2019)
  - **PSD:** Simultaneous Analysis of Dissolution and Permeation Profiles of Nanosized and Microsized Formulations of Indomethacin Using the *In Vitro* Dissolution Absorption System 2 (Li, et al., J Pharm Sci. 2019, in press)
  - **Biowaivers:** Innovative *in vitro* methodologies for establishing therapeutic equivalence (Murray, et al., Rev Panam Salud Publica. 2016; 40(1): 23-28)

Proposed Experimentation

- Use IDAS to evaluate excipients at 3 levels:

  Follow-up to Parr, et al. Pharm Res. 2016; 33(1):167-176

Excipient	Concentration (mg/mL)		
	Low	Medium	High[#]
HBSSg, pH 6.5 (control)	---	---	---
Lactose monohydrate	0.5	2.0	8.0
Povidone K30	0.05	0.2	0.81
Hypromellose 2910 (4000 mPa·s)	0.5	2.0	8.0
SLS	0.025	0.1	0.39
PEG-400	0.075	0.3	3.84

[#] Consistent with the Inactive Ingredients Database;

Expanded Utility of BCS Class 3 Biowaivers

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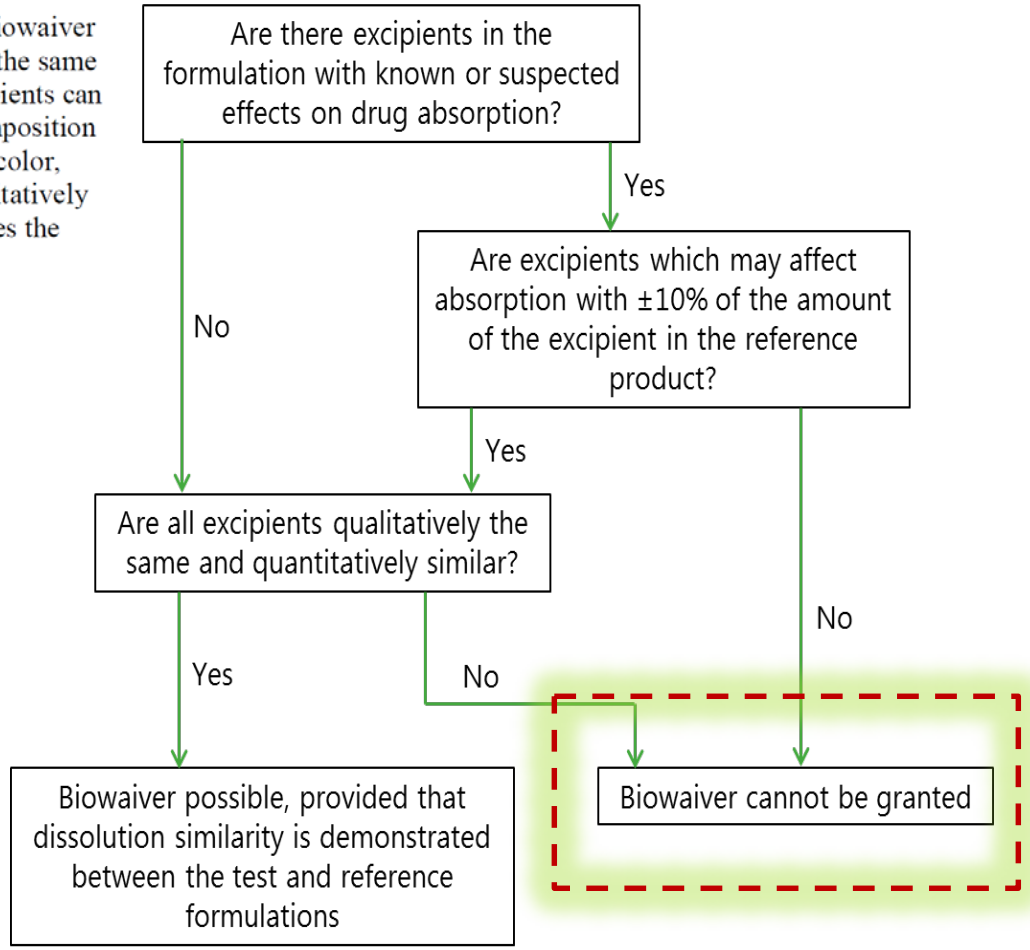
FDA Final Guidance December 2017



To works towards – Exception categories, alternative pathways for evaluation, expanded tolerance ranges