M-CERSI Workshop: Drug Permeability: Best Practices for BCS-based Biowaivers

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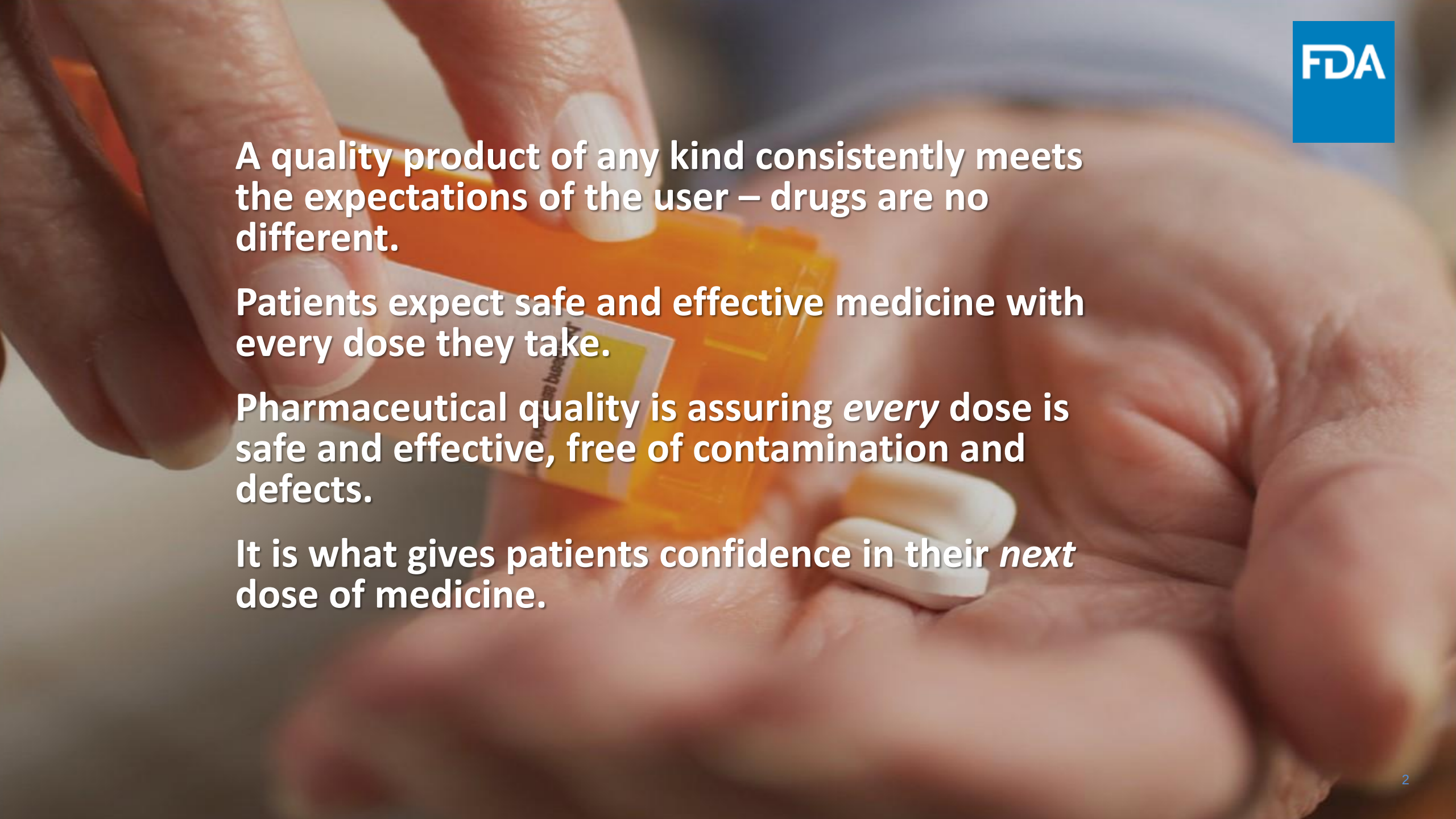
Typical Deficiencies relating to permeability assessment supporting BCS Biowaiver



A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

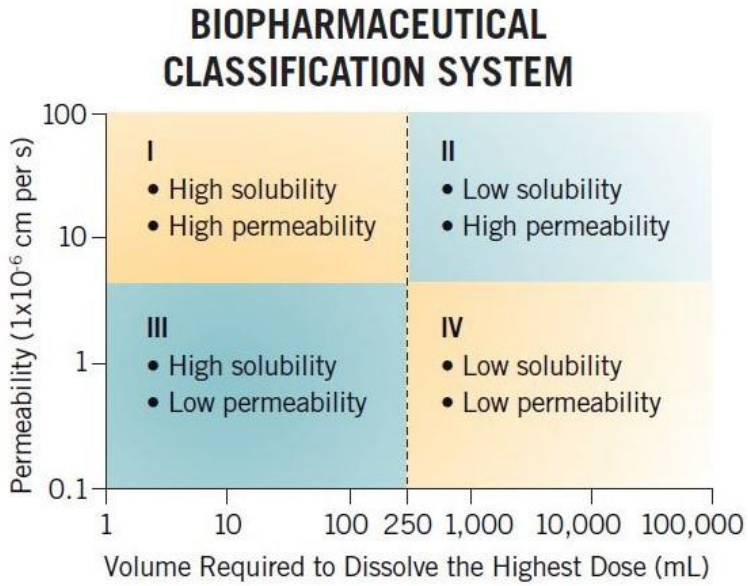
Outline

- Background on BCS classification criteria
- Permeability measurements
- Criteria and support of permeability
- Case studies
- Typical deficiencies related to permeability measurements

BCS Classification Criteria

The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substances, resulting in four classes:

- **Class I: high solubility, high permeability**
- **Class II: low solubility, high permeability**
- **Class III: high solubility, low permeability**
- **Class IV: low solubility, low permeability**



Permeability Measurements

- **Extent of absorption from Human PK studies**
  - **Absolute bioavailability**
  - **Mass balance studies**
- **Human In vivo data from published literature (product knowledge and bioavailability studies) may be acceptable***
- **In vitro methods using Caco-2 cells#**

***Peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.**
#Acknowledges other in vitro/in situ methods but agreement to rely on method with most experience. Other methods are for future consideration upon standardization.

Criteria and support of permeability

- A drug substance is considered highly permeable if
- absolute BA ≥ 85%.
- ≥ 85% of the administered dose is recovered in urine as unchanged drug (parent) or sum of parent drug, phase 1 oxidative and Phase 2 conjugative metabolites.
- Metabolite in feces – only oxidative and conjugative metabolites.

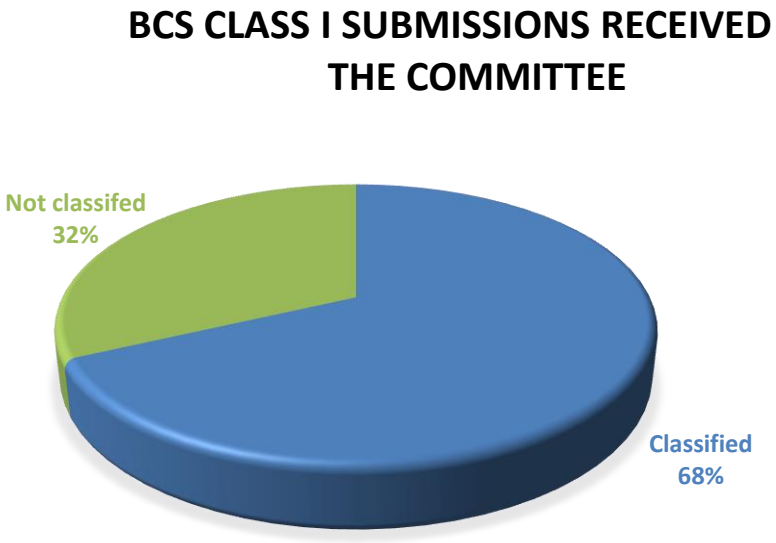
  (Metabolites formed through reduction or hydrolysis should not be included (unless it is demonstrated that it is not produced prior to absorption – microbial action); Unchanged drug in feces cannot be included for extent of absorption (unless data supports biliary excretion, intestinal secretion).

- Results indicating high permeability from validated in vitro Caco-2 permeability assays.
- Discuss Caco-2 results in context of available human PK data.
- Limited to passively absorbed compounds.

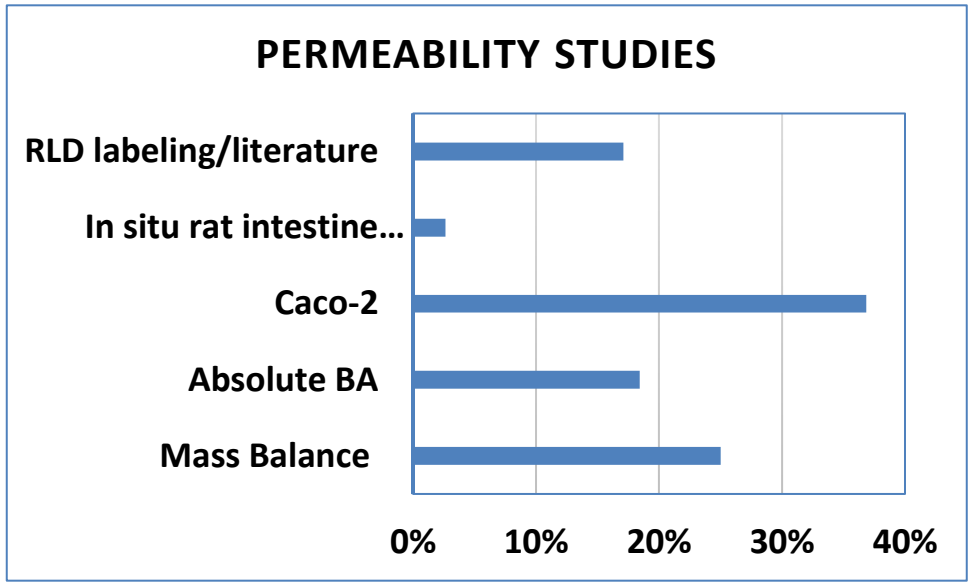
Stability in the GI tract

- If mass balance or Caco-2 studies are used, data to support drug substance stability in the GI tract should be provided.
- However, stability data are not required if mass balance study shows ≥ 85% of the administered dose recovered as unchanged drug in urine.
- GI stability: Documented using compendial or simulated gastric and intestinal fluids.
- Other relevant methods with appropriate justification.
- Drug solution incubated at 37°C (1 h in gastric fluid and 3 h in intestinal fluid).
- Significant degradation (> 10%) of a drug suggest potential instability.

BCS Class I Classified Products



- Reviewed: 97
- Classified: 66
- Not classified: 31



- RLD Labeling/Literature: 13
- In situ rat intestine perfusion: 2
- Caco-2: 28
- Absolute BA: 14
- Mass Balance: 19

Case Studies

Case Study 1-IND (Mass Balance Study)

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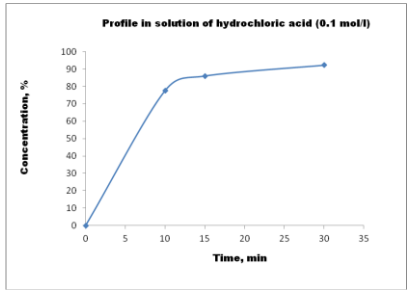
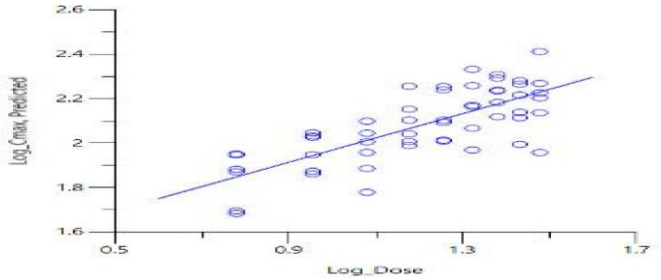
- Applicant submitted solubility, dissolution, Caco-2 in vitro permeability studies, mass balance studies, and gastric stability studies
- Compound A demonstrated high solubility and rapid dissolution
- However, permeability based on Caco-2 in vitro cell culture system was moderate (in comparison to model compounds), saturable transport and active efflux.
- Cmax was dose proportional within the range of doses tested
- Demonstrated adequate gastric stability

Dissolution Data

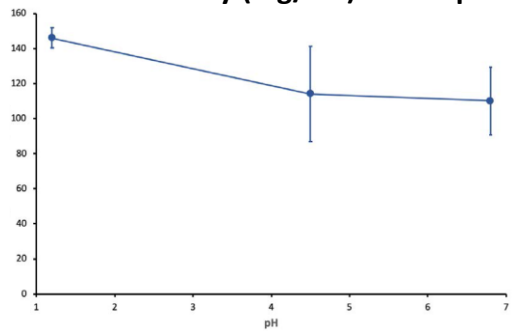
USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling points
2 (Paddle)	50	Hydrochloric acid solution (0.1 M); Acetate buffer pH 4.5; Phosphate buffer pH 6.8; Water /37.0 ± 0.5°C	500	10, 15, 30, and 45 min



Log Cmax versus Log Dose



Solubility (mg/mL) versus pH



AB permeability and BA Permeability (pH 6.5/7.4)

Compound A	Permeability (10^{-6} cm/s)			Recovery (%)		
	1st	2nd	Mean	1st	2nd	Mean
0.6 µM	3.34	3.75	3.5	84	82	83
6 µM	1.36	1.28	1.3	81	85	83
60 µM	1.38	1.33	1.4	86	86	86

Compound A	Permeability (10^{-6} cm/s)			Recovery (%)		
	1st	2nd	Mean	1st	2nd	Mean
0.6 µM	27.06	22.94	25.0	88	93	90
6 µM	3.84	3.62	3.7	93	89	91
60 µM	3.59	3.39	3.5	94	91	92

Gastric Stability

System	Initial pH	End pH	HPLC Purity (%) and Concentration (mg/mL)			
			1 h	3 h	8 h	24 h
FaSSGF	1.5	8.41	99.92% 19.22	99.83% 17.29	99.86% 19.57	99.66% 21.28
FeSSIF	5.0	8.36	99.81% 19.81	99.83% 19.34	99.86% 18.96	99.66% 20.37
FaSSIF	6.5	8.83	99.91% 17.67	99.86% 18.67	99.86% 17.18	99.86% 18.86

Case Study 1-IND Contd….

- Mass balance study: Open-label, randomized single-dose crossover Phase 1 study conducted in healthy subjects . Plasma and urine samples were collected pre-dose and up to 48 hrs post-dose. 13 subjects were randomized , 1 subject withdrew and 12 subjects completed the study.
- Total amount of Compound A excreted in the urine was greater than 85% of the administered dose.
- However, though the total amount of compound A excreted in the urine was greater than 85% of the administered dose, the variability of the measured concentrations in urine was very high based on the available data in the study report
- The applicant was, therefore, requested to submit the entire urine datasets as well as provide their explanation regarding this high variability.
- The Applicant noted that of the 12 subjects, only 2 individual subjects had less than 85% urine recovery: one subject was close at 82.8% recovery, and another was a clear outlier who had only 50.9%.
- When the excretion outcomes are recalculated excluding outlier, the mean excretion is 2.78 mg (representing 92.7% of the administered dose of 3 mg), with a standard deviation of 0.210, yielding a CV% of 7.5%. This reduction in the SD and CV% shows that the variability was heavily influenced by the data from the outlier.
- Compound A was classified as BCS Class I drug substance and BCS class I drug product.

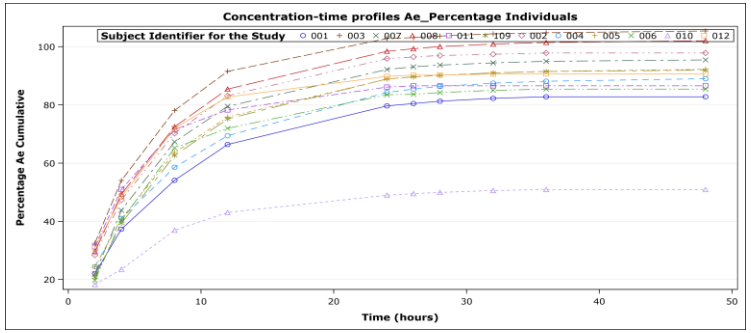
PK parameters

C_{max} (ng/mL)	Geo. Mean	32.9
T_{max} (h)	Median	0.750
$t_{½}$ (h)	Geo. Mean	4.71
λ_z (1/h)	Geo. Mean	0.147
AUC_{0-t} (h.ng/mL)	Geo. Mean	173
$AUC_{0-\infty}$ (h.ng/mL)	Geo. Mean	179
AUC_{extrap} (%)	Geo. Mean	3.11
CL/F (mL/h)	Geo. Mean	16700
Vd/F (mL)	Geo. Mean	114000
Total Ae_{0-48h} (mg)	Median Mean ±SD CV (%) Min, Max Geo. Mean	2.74 2.68±4.13 15.4 0.965, 3.10 2.64
Total Ae_{0-48h} (%)	Median Mean ±SD CV (%) Min, Max Geo. Mean	91.30 89.22±13.777 15.4 50.9, 105.4 87.98

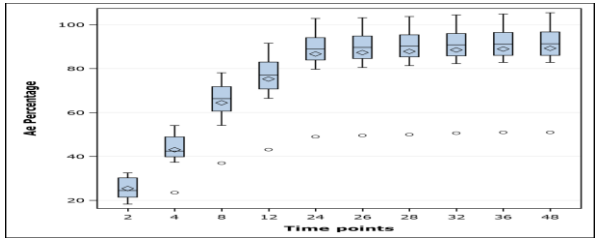
[1] Calculated using the PK set, with the exception of total amount excreted (Ae) and total Ae% calculated using the urine excretion set.

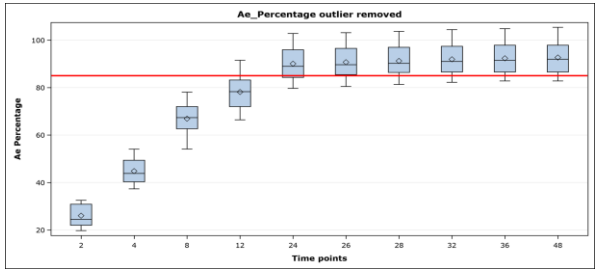
CV = coefficient of variation, PK = pharmacokinetic, SD = standard deviation

Cumulative percentage Ae-time profiles of individuals



Cumulative Urinary Excretion with and without the outlier subject





Case Study 2-ANDA (First Pass Effect)

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- Compound B demonstrated high solubility in the range of pH 1-6.8
- Rapid dissolution was observed with ≥ 85% of the labeled amount dissolved in 30 minutes
- RLD labeling indicated that absolute bioavailability of compound B when compared to IV infusion is 25% due to extensive first-pass metabolism. Also there exists linear relationship across a dose range.
- High permeability is supported by in vitro permeation studies across Caco-2 cell monolayers and stability data in the GI tract. Compound B showed greater permeability than high permeability model compound minoxidil at all the tested concentrations.
- Deficiencies pertaining to method validation in initial submission.
- No significant degradation was observed from the stability studies.
- Compound B was classified as a BCS class I drug substance and BCS class I drug product.

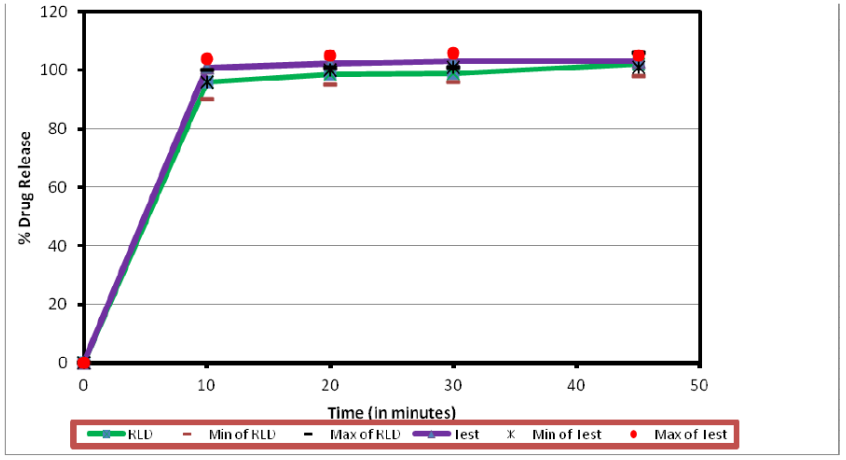
Solubility Data

No.	Buffer	Initial Drug Concentration (mg/mL)	Mean Drug Solubility (mg/mL)	CV%
1	pH 1.0 KCl/HCl	5	4.53	4.66
2	pH 3.0 potassium biphthalate buffer	5	4.31	6.71
3	pH 5.0 potassium biphthalate buffer	5	3.23	4.73
4	pH 6.8 potassium phosphate buffer	5	1.30	8.78

Permeability Data

Nominal Dosing Concentration[a]	Basis of Normalization	A-to-B		B-to-A		Efflux Ratio*
		P_{app} (10^{-6} cm/s)[b]	Recovery[c] (%)	P_{app} (10^{-6} cm/s)[b]	Recovery[c] (%)	
32.9 µM	Nominal Dosing	13.2 ± 1.39	105 ± 5.58	25.3 ± 3.76	108 ± 2.59	1.92
329 µM	Nominal Dosing	14.8 ± 0.615	116 ± 3.55	17.9 ± 1.82	114 ± 6.71	1.20
	Measured Donor	11.8 ± 0.870	91.9 ± 6.16	15.1 ± 1.26	96.0 ± 4.58	1.28
2.47 mM	Nominal Dosing	18.8 ± 0.450	91.2 ± 0.723	18.2 ± 1.47	90.4 ± 3.47	0.969

Dissolution Data



Case Study 3-ANDA (Food Excipient Interaction)

- Compound C was classified as BCS class I based on solubility, dissolution and mass balance of RLD application.
- Later in the year few other ANDA applications did not pass 90% criteria for fed BE studies
- Data indicated excipient-food interactions
- High proportion of microcrystalline cellulose and swelling of MCC matrix under fed conditions could lower the rate of absorption.
- Waiver of fasting BE study was granted but fed BE study was required

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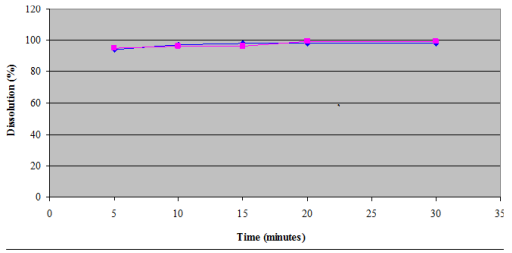
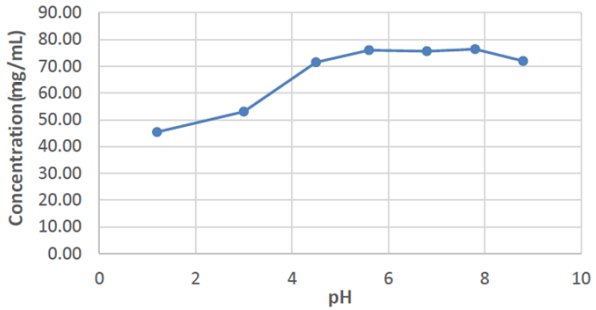
Solubility Data

Highest Strength	10 mg
Required conc. to be considered highly soluble	0.04 mg/mL

Dissolution Data





- USP apparatus II (Paddle)
- 50 rpm
- 900 ml of 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer
- Very rapid dissolving

Mass Balance Study

- Single dose study in 6 healthy male subjects .
- Mass balance following IV and oral administration of radioactive compound
- Total radioactivity was measured in blood, urine and feces for up to 7 days.
- Following oral dose 93% was recovered in urine.
- Highly permeable drug substance and drug product.

Case Study 4-ANDA (In situ rat intestine perfusion method)

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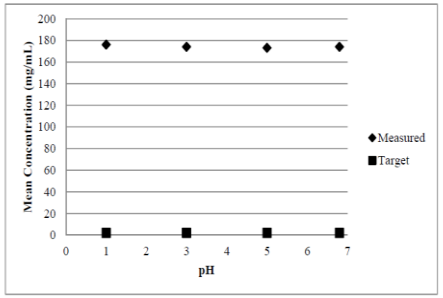
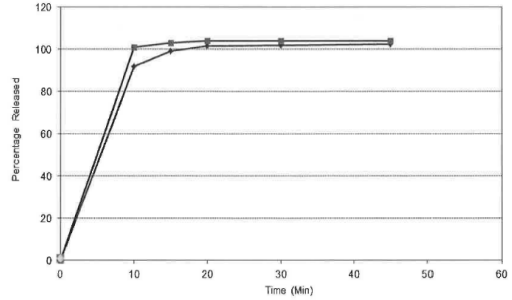
- Compound D demonstrated high solubility in aqueous medium over pH range of 1-6.8.
- Multimedia dissolution data demonstrated rapid dissolution with ≥85% dissolved in 30 minutes
- Data from Caco-2 study shows moderate permeability (previous NDA).
- In vivo human pharmacokinetic information and scientific literature indicated that the bioavailability is high.
- In this ANDA, applicant conducted in vitro permeability using in-situ rat intestine perfusion method.
- Cytotoxic causing loss of integrity and hence Caco-2 is not an appropriate model.

Solubility Data



Dissolution Data



In-situ rat intestine perfusion method

Drug	Parameter	20.0 µg/mL (263 µM)	200 µg/mL (2.63 mM)	2.00 mg/mL (26.3 mM)
Test Compound	P_{eff} (mean ± SD)*	0.690 ± 0.121	0.459 ± 0.125	0.657 ± 0.134
	Recovery (%)	N/A	N/A	N/A
High Internal Standard (Metoprolol, 50 µM)	P_{eff} (mean ± SD)*	0.573 ± 0.141	0.370 ± 0.0913	0.506 ± 0.155
	Recovery (%)	N/A	N/A	N/A

Instability in the Gastrointestinal Tract

Medium	Time of Incubation (min)	Incubation Temperature (°C)	Concentration (mg/mL) Before Incubation	% Recovery After Incubation[a]	*% Degradation
Simulated Gastric Fluid	60	37.0	2.00	99.9	0.1
Simulated Intestinal Fluid	180	37.0	2.00	98.9	1.1

Typical Deficiencies: Absolute bioavailability and Mass Balance studies

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- Lack of study reports, validation reports and other procedural documents
- Unexplained high variability in the measured urine concentrations, request for complete datasets along with calculations.
- Missing GI stability data to support <85% of the unchanged parent drug excreted in urine.

Typical deficiencies : Caco-2 studies

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Pre-study Model compound Validation studies

- Missing Standard operating procedures
- Missing validation data with model compounds
- Missing calibration curve and quality control data including linearity, slope, precision, and accuracy for all analytical runs used in the permeability study.
- Missing data on zero permeability model drug

Permeability study

- Missing non-specific binding (cell free) permeability study
- Missing procedures to ensure pH 7.4 was maintained during the course of the study.
- Missing data to demonstrate stability of stock solutions
- High recovery rates of internal standards and differences in recoveries between A-B/B-A directions.
- Permeability measurements influenced by presence of internal standards.
- Difference in permeability measurements of internal standards between validation and pivotal studies

Typical Deficiencies/concerns: Literature based, labeling

- Lack of necessary testing details for peer reviewed Journals
- Unreliable RLD label data (large variability, fewer subjects etc)

Typical deficiencies: Instability in GI Tract

- Missing procedural SOPs (study conduct, preparation of buffers etc).

References

- M9 Biopharmaceutics Classification System-Based Biowaivers, Guidance for Industry, May 2021 (FDA, ICH)

Acknowledgements

- Kimberly Raines
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- Office of Bioequivalence, Generic Drugs
- Office of Clinical Pharmacology/OTS/CDER/FDA

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Thank you !