Essential Elements of BCS III-Based Biowaiver Request

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Learning Objectives

- To discuss essential elements of Biopharmaceutics Classification System (BCS) III-based biowaiver as an alternative bioequivalence (BE) approach
- To share research results on potential BCS III drug products
- To investigate formulation impact on BCS III-based biowaiver

Guidance for BCS-Based Biowaiver

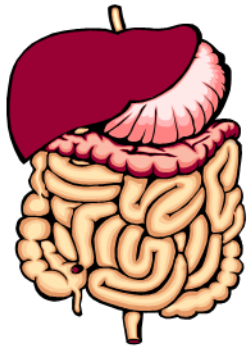
- *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021) located at https://www.fda.gov/media/148472/download

Scientific Basis for BCS

- A scientific framework for classifying drug substances based on

Aqueous Solubility

Intestinal Permeability



BCS Class Boundaries

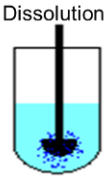
Class	High Permeability (≥85%)	Low Permeability (<85%)
High Solubility (BCS Volume≤250 mL)	I	III
Low Solubility (BCS Volume>250 mL)	II	IV

Product-Specific Guidance (PSG) for BCS Biowaiver

- Agency's General Practice for PSGs
  - Recommends BCS biowaiver as one of BE options once the drug has been classified by the Agency
- BCS Biowaiver Option not in PSG
  - Not classified
  - Applied with sufficient supportive data
- BCS Biowaiver Eligibility
  - Many IR drugs with high solubility are potentially eligible for BCS biowaiver (I or III)

Essential Elements for BCS III-Based Biowaiver

- Highly soluble
- Very rapidly dissolving (VRD) across multiple pH media
  - Determine VRD for the reference product
  - Demonstrate VRD for the test product



- Qualitatively (Q1) the same and Quantitatively (Q2) similar to the reference product except for
  - Film coating
  - Capsule shell excipients

High Solubility

- Drug Amount: Highest single therapeutic dose (HSTD)
- BCS Volume:
  - HSTD (mg)/Solubility (mg/mL)
  - No more than 250 mL
- Media: Aqueous
- pH range: 1.2 - 6.8
- Temperature: 37 ± 1 °C

Very Rapid Dissolution

- USP apparatus:
  - I (Basket)
  - II (Paddle)
- Agitation:
  - 100 rpm for basket
  - 50 rpm for paddle
- Temperature: 37 ± 1 °C

Very Rapid Dissolution

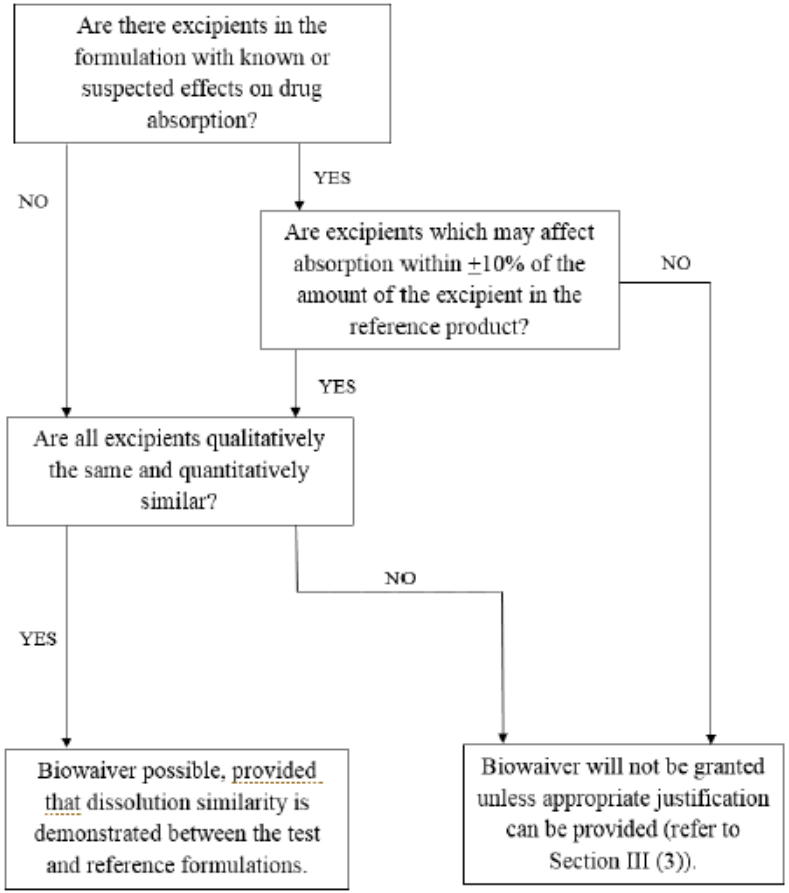
- Volume of Dissolution Media: 900 mL or less
- Dissolution Media:
  - pH 1.2 buffer
  - pH 4.5 buffer
  - pH 6.8 buffer
- Dissolution Specification: NLT 85% within 15 minutes in all three buffers
  - Fixed Dose Combination:
    - Contain only BCS III drug substances
    - Contain both BCS I and BCS III drug substances

Formulation Similarity Assessment

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III drugs should not exceed the following targets:	
Excipient Class	**Percent of the Amount of Excipient in the Reference**
Excipients which may affect absorption	
Per excipient:	10%
Sum of differences:	10%
	Percent Difference Relative to Core Weight* (w/w)
All excipients:	
Filler	10%
Disintegrant	
Starch	6%
Other	2%
Binder	1%
Lubricant	
Stearates	0.5%
Other	2%
Glidant	
Talc	2%
Other	0.2%
Total % change permitted for all excipients (including excipients which may affect absorption):	10%

*Note: Core does not include tablet film coat or capsule shell.

Determination of Formulation Similarity



Challenges in BCS Class III Biowaiver

- Two key limiting factors are subjects of research
  1. Meet the criteria for very rapid dissolution
     a. Solubility and multi-pH media dissolution testing data for BCS III potential products
  2. Meet the criteria for formulation similarities
     a. Expanding BCS Class III biowaivers for Generic Drugs to Non-Q1/Q2 Formulations
     b. Excipients Impact on Bioavailability of BCS Class III Drugs
     c. Assessment on the Formulation Similarity of Approved Generic Drug Products with BCS Class III Potential
     d. Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling as an Alternative BE Approach to Support BCS Class III Biowaiver
     e. Effect of Excipient Transporter Interactions on BCS Class III Drugs
     f. Effect of Excipients on the Oral Absorption of Fexofenadine in Humans (Just initiated)

Multi-pH Dissolution Study of Potential BCS III Drugs (1a)

Drug Product	NDA/ANDA	Formulation	Strength	% of Meeting NLT 85% in 15 mins	% of Meeting NLT 85% in 30 mins
Atenolol Tablet	ANDA1	Q1 different	25 mg	61.11	100
	ANDA2	Q1/Q2 similar	50 mg 100 mg	88.89	100
Acyclovir Tablet	ANDA1 (RS)		400 mg 800 mg	100	100
	ANDA2	Q1 different		100	100
	ANDA3	Q1 different		83.33	100
Metformin Hydrochloride Tablet	ANDA1	Q1 different	500 mg	0	33.33
	ANDA2	Q1/Q2 similar	850 mg 1000 mg	0	50
	ANDA3	Q1 different		61.11	100
Hydroxychloroquine Sulfate Tablet	NDA (RLD/RS)		200 mg	50	100
	ANDA1	Q1 different		0	66.67
	ANDA2	Q1 different		0	0
Tenofovir Disoproxil Fumarate Tablet	NDA (RLD/RS)		300 mg	100	100
	ANDA1	Q2 different		100	100
	ANDA2	Q2 different		100	100

Reference: Daniela Selaya, Robert Hunt, Ping Ren, David Li, Haiou Qu, Wen Cheng Yang, Jiang Wang, Theresa Chan, Myong-Jin Kim, Patrick Faustino, Yi Zhang: Evaluation of the Dissolution Drug Release Profiles of Approved Generic Formulations in Multiple pH Media for Putative Biopharmaceutics Classification System Class III Drugs, Atenolol Tablets and Acyclovir Tablets. AAPS Poster 2021

Results of Multi-pH Dissolution Test

- The majority of the dissolution studies demonstrated very rapidly dissolving in all dissolution media as well as meeting BCS Class III biowaiver dissolution criteria.
- The small percentage of dissolution studies that did not meet the BCS Class III biowaiver dissolution criteria may be due to the dose strength or minor differences in manufacturing procedure, such as the tablet hardness.
- Our data showed that different dissolution rates, either very rapidly or rapidly dissolving, did not appear to impact the in vivo performance of these approved generic drug products.

Impact of Excipients on Non-Q1/Q2 Formulations (2a)

- Effects of common excipients on the dissolution and permeation of BCS Class III drug products evaluated by in-vitro dissolution absorption system (IDAS)
  - Simultaneous measurement of dissolution and permeation of finished drug products (tablets and capsules)
  - Four pairs of reference listed and generic drug products that had previously demonstrated bioequivalence in clinical studies
    - Acyclovir
    - Cimetidine
    - Ranitidine
    - Atenolol

Reference: Chris Bode, Sid Bhoopathy, Blair Miezeiewski, Fang Wu, Ping Ren, Zhong Wang, Liang Zhao: Biowaivers to Non Q1/Q2 BCS Class In vitro Comparative Dissolution and Permeation Testing Using the In vitro Dissolution Absorption System (IDAS) for Expanding III Products. AAPS Abstract 2022

Study Scope for Impact of Excipients

- Used a novel in vitro product characterization tool to assess the impact of excipients on the dissolution and permeation of BCS Class III model drugs
- Investigated the potential to expand BCS Class III biowaivers for non-Q1/Q2 generic drugs by varying the amounts of excipients

Reference: Chris Bode, Sid Bhoopathy, Blair Miezeiewski, Fang Wu, Ping Ren, Zhong Wang, Liang Zhao: Biowaivers to Non Q1/Q2 BCS Class In vitro Comparative Dissolution and Permeation Testing Using the In vitro Dissolution Absorption System (IDAS) for Expanding III Products. AAPS Abstract 2022

Results of Impact of Excipients on Permeation

Effects	Excipients	Change in Permeation
None	Hydroxypropyl methylcellulose (two viscosities) Microcrystalline cellulose Croscarmellose sodium Talc Mannitol Silicon dioxide	No effects on permeation of any model drugs
Have effect on one or two model drugs	Povidone K30	Decrease in permeation of acyclovir and ranitidine
	Magnesium stearate	Decrease in permeation of acyclovir
	Lactose Calcium phosphate Pregelatinized starch PEG-400	Increase in permeation of cimetidine and ranitidine
Inconsistent effect	Sorbitol	Have effects on permeation of all model drugs, but different directions in two tests
Consistent effect	Sodium lauryl sulfate (SLS)	Dose-dependent increase in permeation of all model drugs

Reference: Bode C. Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Products Podium Presentation, CRCG PBPK Workshop, 2021

Excipients Impact on Bioavailability (2b)

- Cimetidine and acyclovir were used as model BCS Class III drugs in four-way crossover BE studies in healthy subjects
  - Twelve common excipients in large amounts do not impact BCS class III drug absorption in vivo
  - The Q1 sameness and Q2 similarity of test products to the reference product with regard to excipients of hydroxypropyl methylcellulose and microcrystalline cellulose seem essential

Reference: Soundarya Vaithianathan, Sam H. Haidar, Xinyuan Zhang, Wenlei Jiang, Christopher Avon, Thomas C. Dowling, Changxing Shao, Maureen Kane, Stephen W. Hoag, Mark H. Flasar, Tricia y. Ting, James E. Polli: Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir Solubility and multiple-media dissolution testing for IR drug products with BCS 3 potentials, 2015, Journal of Pharmaceutical Sciences https://doi.org/10.1002/jps.24643

Formulation Assessment of Approved Generic Drug Products with Potential for BCS Class III Biowaiver (2c)

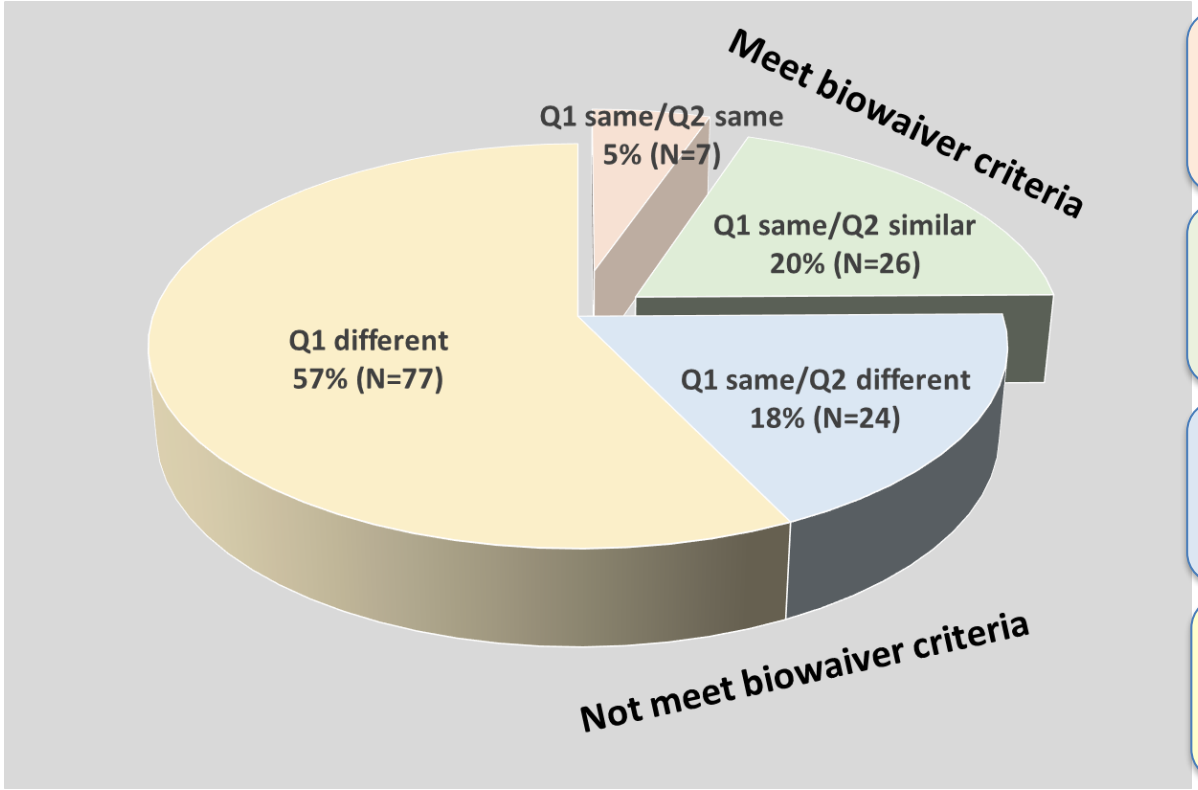
- Collected formulation data in approved generic products that successfully demonstrated vivo BE (potential for BCS class III biowaiver)
- Compared compositions between generic and reference drug products
- Explored impact of excipient changes on in vivo BE outcome

Reference: American College of Clinical Pharmacology (ACCP) Poster on Assessment on the Formulation Similarity of Approved Generic Drug Products and their Respective Reference Products Which are Considered as Potential BCS Class 3 Drugs

Drug Substances Assessed

Permeability Class	Drug Substance	Absorption	Efflux Transporter (P-gp (P-glycoprotein), BCRP (Breast Cancer Resistance Protein))	Method for Permeability Determination	Permeability
Low	Acyclovir	Slow, variable, incomplete	Not a substrate	Absolute Bioavailability (BA)	10-30%
	Pravastatin	Rapid but incompletely absorbed	Not a substrate	Absolute BA	~17-34%
	Tenofovir	--	A substrate of P-gp and BCRP	Absolute BA	~25%
	Nadolol	--	Not a substrate	Absolute BA	35%
	Rasagiline	Rapid	Not a substrate	Absolute BA	36%
	Penicillamine	Rapid	Not a substrate		40-70%
	Colchicine	Rapid	Substrate of P-gp	Absolute BA	45%
Moderate	Atenolol	Rapid and consistent	Substrate of P-gp	Absolute BA	50%
	Ranitidine	Rapid	Substrate of P-gp	Absolute BA	50%
	Metformin	Rapid	Not a substrate	Absolute BA	50-60%
	Hydroxychloroquine		Not a substrate	Absolute BA	67-74%
	Oseltamivir	Rapid	Not a substrate	Absolute BA	~80%
	Abacavir	Rapid	Not a substrate	Absolute BA	~83%

Results of Formulation Analysis



Q1 same/Q2 same

Same ingredients

Each excipient change stays within 5%*

Q1 same/Q2 similar

Same ingredients

Total excipient change is no more than 10%**

Q1 same/Q2 different

Same ingredients

Total excipient change exceeds 10%**

Q1 different

Different ingredients

*[(RLD – Test)/RLD]x100

Reference: ACCP Poster
(Total No. of ANDAs=134; Total No. of APIs=13)

**Based on Scale Up Post Approval Change definition of total excipient change

Common Excipients

Subcategory	Excipients	No. of ANDA	% of Total ANDAs	% Range (w/w)
Filler	Microcrystalline Cellulose	77	57.89	1.83 - 58.22
	Lactose	51	38.35	2.40 - 85.31
	Dibasic Calcium Phosphate Dihydrate	7	5.26	11.53 - 34.29
	Mannitol	4	3.01	8.94 - 52.00
Disintegrant	Sodium Starch Glycolate	45	33.83	1.00 -10.00
	Starch	43	32.33	0.30 - 40.87
	Croscarmellose Sodium	34	25.56	1.36 - 10.00
	Crospovidone	13	9.77	0.20 - 15.93
Binder	Povidone	52	39.1	0.27 - 25.81
	Pregelatinized Starch	33	24.81	2.46 - 57.02
	Hypromellose	6	4.51	0.50 - 6.25
Lubricant	Magnesium Stearate	115	86.47	0.25 - 2.82
	Sodium Lauryl Sulfate	20	15.04	0.10 - 1.67
	Sodium Stearyl Fumarate	9	6.77	0.24 - 3.00
	Stearic Acid	8	6.02	0.81 - 3.50
Glidant	Colloidal Silicon Dioxide	44	33.08	0.16 - 3.50
	Talc	14	10.53	0.15 - 3.50
Stabilizer	Magnesium Oxide	4	3.01	2.50 - 3.38
Buffer agent	Citric Acid	6	4.51	1.08 - 4.76

Reference: ACCP Poster (Total No. of ANDAs=134)

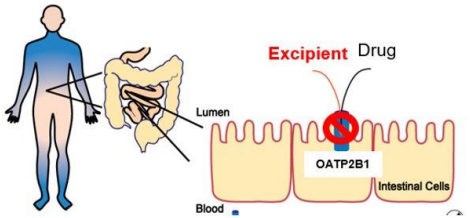
PBPK Absorption Modeling in BCS Class III Drugs (2d)

- Explored impact of gastric pH on absorption of weak base drugs such as saxagliptin
- Conducted virtual BE simulations to establish dissolution safe space for oseltamivir phosphate and its metabolite oseltamivir carboxylate in both adult and pediatric populations

Reference1: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541
Reference2: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. Using a physiologically-based pharmacokinetic absorption model to establish dissolution bioequivalence safe space for oseltamivir in adult and pediatric populations. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Effect of Excipient Transporter Interactions on BCS Class III Drugs (2e)

- Screening excipients that are potential inhibitors for intestinal absorptive transporters in membrane vesicles and cells
  - P-glycoprotein (P-gp)
  - Breast Cancer Resistance Protein (BCRP)
  - Organic Anion Transporting Polypeptide 2B1 (OATP2B1)



Reference: Grant on Effects of Excipients in Generic Drug Products on Intestinal Drug Transporters
Giacomini, K. The Effects of Excipients on Intestinal Drug Transporters. Presentation at ACCP Annual Meeting. Bethesda, MD, Sept. 22, 2018

Preliminary Assessment

- Meeting the criteria for BCS class III-based biowaiver does ensure bioequivalent performance in vivo
- An observation of changes in excipients is based upon the approved generic drug product formulations
- The research outcome does not mean these excipients in the stated amounts can be used in all BCS class III drug products

Summary

- Refer to the ICH M9 Guidance on BCS-based biowaiver to assess if the drug may be eligible for BCS class III biowaiver
- BCS class III biowaiver can be applied with sufficient supportive data even though the current PSG does not include this option
- Controlled Correspondence can be submitted to request if the proposed test formulation is eligible for BCS class III waiver
- Research on dissolution, modeling, and excipients continues to provide more insight to promote using BCS class III waiver as an alternative BE approach in the future

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