Biopharmaceutics Classification System Class 3 Waiver

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 4: Practical Considerations in the Study Design and Data Evaluation Recommended in PSGs

Topic 1: Oral Products

Yi Zhang, Ph.D.

Commander, U.S. Public Health Service

Office of Research and Standards, Office of Generic Drugs

CDER | U.S. FDA

September 30, 2020

Disclaimer

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Learning Objectives

- To elaborate the current Biopharmaceutics Classification System (BCS) class 3 waiver as an alternative bioequivalence (BE) approach
- To discuss research related to future BCS class 3 waiver expansions

Guidance for BCS-based Waiver

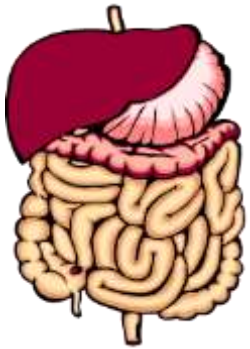
- FDA Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release (IR) Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (2017)
- The International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M9 Guideline: *Biopharmaceutics Classification System-Based Biowaivers* (2019)

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

BCS Waiver and Product-Specific Guidance (PSG)

- General Practice for PSG
  - Add BCS waiver recommendation to the PSG when the drug is classified
  - BCS Class 1 drug substances
  - BCS Class 3 drug substances
- BCS Waiver Option not in PSG
  - Not classified
  - BCS waiver can be requested
- BCS Waiver in Future
  - Many drugs with high solubility are potentially eligible for BCS waiver
  - Applicants should show their due diligence

BCS Class 3-based Biowaiver

- For BCS class 3 drug products, the following should be demonstrated:
  - 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) very similar to the reference product

BCS 3 Formulation Similarity Assessment

- Allowable differences for Q2 very similar:
  - Changes in the technical grade of an excipient
  - Changes in excipients as %(w/w) within the following % ranges
  - Total additive effect of all excipients within 10%

- 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%)

Regulatory Route for BCS Class 3 Waiver

- Submit controlled correspondence for eligibility of BCS class 3 waiver
  - **Do:** request if your proposed formulation is eligible for BCS class 3 waiver
  - **Don't**: ask if your proposed formulation is Q1 the same/Q2 very similar to the reference product

Potential Challenges in Applying BCS Class 3 Waiver

- Two key limiting factors are subjects of research
  - Meet the criteria for very rapid dissolution
    - Solubility and multi-pH media dissolution testing data for IR drug products with BCS 3 potential
  - Meet the criteria for formulation similarities
    - Contract with Absorption Systems: Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Formulations
    - Physiologically Based Pharmacokinetic Absorption Modeling as an Alternative BE Approach to Support BCS Class 3 Waiver
    - Assessment on the Formulation Similarity of Approved Generic Drug Products with BCS Class 3 Potential

Excipients in BCS Class 3 Drugs

- Cimetidine and acyclovir were used as model BCS Class 3 drugs in four-way crossover BE studies in healthy subjects
  - 12 common excipients in large amounts do not impact BCS class 3 drug absorption in vivo
  - Hydroxypropyl methylcellulose and microcrystalline cellulose need to be Q1 the same and Q2 very similar to the reference product

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

Transporter Interactions with Excipients

- Screening of excipients that are potential inhibitors for intestinal 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

Formulation Assessment Research Project

- Collected formulation data in approved generic products that successfully demonstrated vivo BE (potential BCS class 3 drugs)
- Compared compositions between generic and reference drug products
- Explored impact of excipient changes on in vivo BE outcome

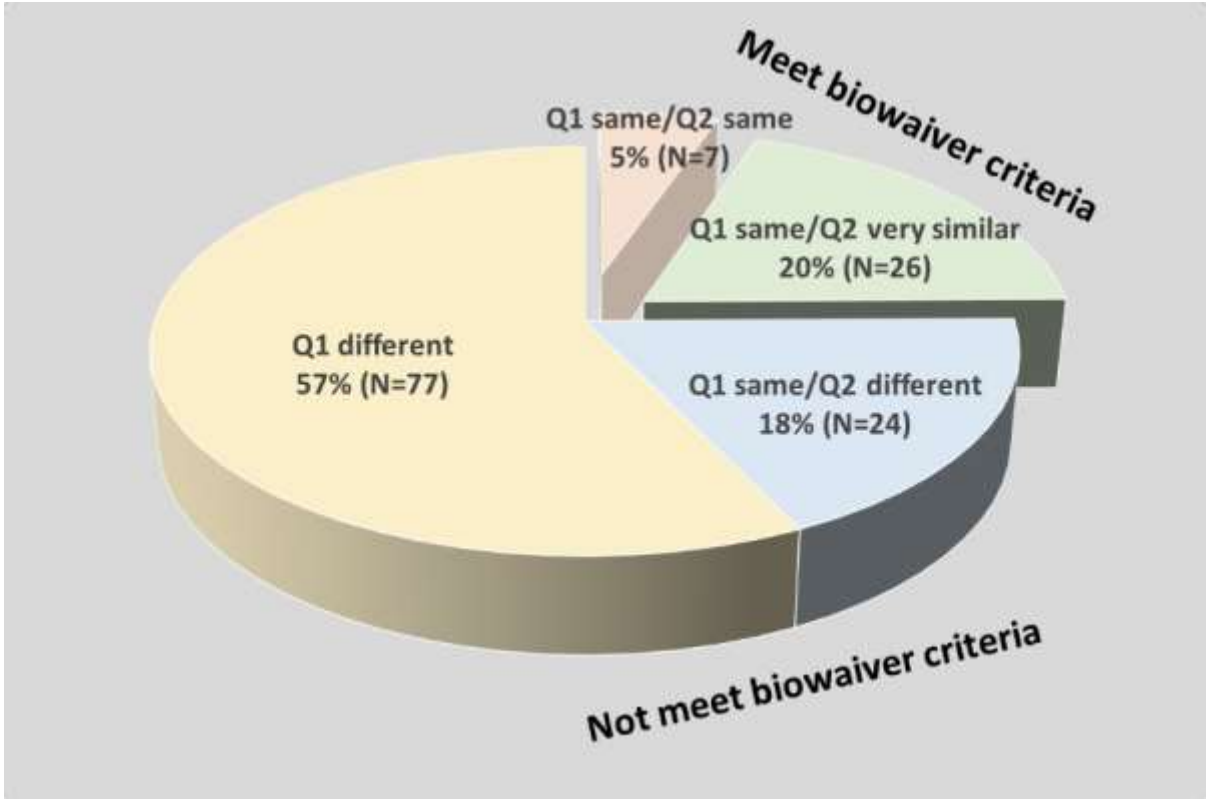
Reference: American College of Clinical Pharmacology (ACCP) Poster on Assessment on the Formulation Similarity of Approved Generic Drug Products and their Respective Reference Products Which are Considered as Potential BCS Class 3 Drugs

Drug Products Used in Project

Permeability Class	Drug	Absorption	Efflux Transporter (P-gp (P-glycoprotein), BCRP (Breast Cancer Resistance Protein))	Method for Permeability Determination	Permeability
Low	A	Slow, variable, incomplete	Not a substrate	Absolute Bioavailability (BA)	10-30%
	B	Rapid but incompletely absorbed	Not a substrate	Absolute BA	~17-34%
	C	--	A substrate of P-gp and BCRP	Absolute BA	~25%
	D	--	Not a substrate	Absolute BA	35%
	E	Rapid	Not a substrate	Absolute BA	36%
	F	Rapid	Not a substrate		40-70%
	G	Rapid	Substrate of P-gp	Absolute BA	45%
Moderate	H	Rapid and consistent	Substrate of P-gp	Absolute BA	50%
	I	Rapid	Substrate of P-gp	Absolute BA	50%
	J	Rapid	Not a substrate	Absolute BA	50-60%
	K		Not a substrate	Absolute BA	67-74%
	L	Rapid	Not a substrate	Absolute BA	~80%
	M	Rapid	Not a substrate	Absolute BA	~83%

Reference: : ACCP Poster

Result for Formulation Analysis



Q1 same/Q2 same

Same ingredients

Each excipient change stays within 5%*

Q1 same/Q2 very similar

Same ingredients

Total excipient change is less 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)

Preliminary Assessment

- Meeting the criteria for BCS class 3-based waiver does ensure bioequivalent performance in vivo
- An observation of changes in excipients is based upon the approved generic drug product formulations
- Not mean these excipients in the stated amounts can be used in all BCS class 3 drug products
- Ongoing project to determine if more general conclusions could be drawn from this dataset

Summary

- BCS Guidance should be referred to assess if the drug may be eligible for BCS class 3 waiver
- BCS class 3 waiver can be requested even though the current PSG does not include such recommendation
- Controlled Correspondences can be submitted to request if the proposed test formulation is eligible for BCS class 3 waiver
- Research on dissolution, modeling, and excipients continues to provide more opportunities in the future for using BCS class 3 waiver as an alternative BE approach

Challenge Question

If the current PSG does not include the recommendation on BCS class 3 waiver, can the generic firm submit its waiver request?

A. Yes

B. No

Acknowledgement

- Ping Ren, MD, Ph.D.
- Theresa Chan, Pharm.D.
- Wen Cheng Yang, MD
- Myong-Jin Kim, Pharm.D.
- Lei Zhang, Ph.D.
- Robert Lionberger, Ph.D.