
Your Generics & Biosimilars Industry

# FY 2019 Generic Drug Regulatory Science Initiatives Public Workshop

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# BCS Class Waivers: Expansion Beyond Q1/Q2?

# Framework

Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of BCS Class 3 biowaivers to non-Q1 and non-Q2 generic formulations to RLD.

# Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

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**Biopharmaceutics**

# BCS Class 3:  Definition

Class 1:  High Solubility – High Permeability
Class 2:  Low Solubility – High Permeability
Class 3:  High Solubility – Low Permeability
Class 4:  Low Solubility – Low Permeability

# What Are the Requirements for Submitting ANDA for a BCS Class III Drug Products?

For BCS class 3 DP, the following should be demonstrated:

1. The DS is highly soluble
2. The DP (test and RLD) is very rapidly dissolving and
3. The test product formulation is *qualitatively the same and quantitatively very similar to RLD*

# Define *"Qualitatively the Same and Quantitatively Very Similar to RLD"*

- 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 RLD.
- 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* and should be *quantitatively* very similar to the RLD.



*except for a different color, flavor, or preservative that could not affect the BA

# “Quantitively Very Similar”

Quantitatively very similar includes the following allowable differences:

1. Changes in the technical grade of an excipient
2. Changes in excipients (% w/w) of the total formulation ≤ following % 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%)
3. The total additive effect of all excipient changes should be NMT 10%

# Current Approach vs. Proposed Approach

Current Approach by FDA:  Excipients can have a greater impact on absorption of low permeability drugs.

Alternate Proposed Risk-Based Approach: Allow justification for "*qualitatively and quantitatively not similar excipient*" based on the "*sponsor's prior knowledge*" and the "*scientific literature that the excipient has no impact on the absorption of the drugs*".

Exceptions:

- Excipients, such as, Mannitol, may alter the absorption of drugs.
- Such excipients require q1/q2 sameness between Test & RLD.

- Comparative physico-chemical tests, i.e., permeability, on test & RLD can be developed to alleviate the concerns of quantitative differences in the excipients.
- Study the drug transportation and the excipient transportation from mechanistic point of view and / or  from empirical studies available in the published literature.
- Based on the broad evidence, many of the common excipients do not impact the permeability of drugs in GI tract.

# Literature Evidence (1):

**1. Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir;** Vaithianathan S, Haidar SH, Zhang X, Jiang W, Avon C, Dowling TC, Shao C, Kane M, Hoag SW, Flasar MH, Ting TY, Polli JE.; J Pharm Sci. 2016 Feb;105(2):996-1005. doi: 10.1002/jps.24643. Epub 2016 Jan 12.

**Objective:** To assess the impact of larger than conventional amounts of 14 commonly used excipients on BCS class 3 drug absorption in humans.

**Methods:** Cimetidine and acyclovir were used as model class 3 drugs across three separate 4-way crossover BE studies (n = 24 each) in healthy human volunteers. Total # of excipients used: 14.

**Outcome:**

1. In general, 12 common excipients were found in large amounts did not impact BCS class 3 drug absorption in humans, such that these excipients need not be qualitatively the same nor quantitatively very similar to reference.

# Literature Evidence (1):

1. Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir; Vaithianathan S, Haidar SH, Zhang X, Jiang W, Avon C, Dowling TC, Shao C, Kane M, Hoag SW, Flasar MH, Ting TY, Polli JE.; J Pharm Sci. 2016 Feb;105(2):996-1005. doi: 10.1002/jps.24643. Epub 2016 Jan 12

**Outcome (Continued)….**

2. Capsule formulations that incorporated HPMC or magnesium stearate exhibited lower absorption.

3. Cimetidine commercial solution contained sorbitol and also resulted in lower absorption.

4. For each HPMC and MCC, BCS class 3 biowaivers require these two excipients to be qualitatively the same and quantitatively very similar to the reference.

5. Lactose is a disaccharide from galactose and glucose. Hence, lactose has potential to inhibit a sugar transporter that the drug depends upon for its absorption. However, most drugs are absorbed by passive diffusion, rather than by transporter mediated uptake.

# Literature Evidence (2):

2. The Effect of Excipients on the Permeability of BCS Class III Compounds and Implications for Biowaivers.
Parr A, Hidalgo IJ, Bode C, Brown W, Yazdanian M, Gonzalez MA, Sagawa K, Miller K, Jiang W, Stippler ES.
Pharm Res. 2016 Jan;33(1):167-76. doi: 10.1007/s11095-015-1773-4. Epub 2015 Aug 19.

**Objective:** To study the effect of Excipients on the permeability of BCS Class III Compounds.

**Methods:**
1. Permeability of **4** BCS Class III & a single Class I compound in the presence / absence of five excipients was assessed (*HPMC, Povidone, PEG-400, SLS & Lactose*).
2. Permeability was assessed at various concentrations, with each excipient in two models: Caco-2 cell monolayers & *in-situ* rat intestinal perfusion.

**Outcome:**
1. No substantial increases in the permeability of any of the compounds were observed in the presence of any of the tested excipients in either of the models. Only exception is: disruption of Caco-2 cell monolayer integrity by sodium lauryl sulfate at 0.1 mg/ml and higher.
2. Absorption of these **4** BCS Class III compounds is not greatly affected by tested excipients.

# Literature Evidence (3):

3. Biowaiver monographs for IR solid oral dosage forms based on BCS literature data: Verapamil hydrochloride, propranolol hydrochloride, and atenolol; H.Vogelpoel, J. Welink, G.L. Amidon H.E.Junginger, K.K. Midha ,H. Möller ,M. Olling, V.P. Shah, D.M.Barends. 2004,Wiley Inter Science (www.interscience.wiley.com). DOI 10.1002/jps.20131.

**Objective:** Scientific literature data search for creation of biowaiver monographs for IR dosage forms of 3 molecules with high solubility and rapid dissolution.

**Methods:** Literature search for three BCS molecules was presented (verapamil HCl and, propranolol HCl and atenolol). Data on the qualitative composition of IR tablets containing these API with a Marketing Authorization (MA) in the Netherlands (NL) were also provided.

**Outcome:** The authors concluded Atenolol BCS III drug, can be considered a candidate for a biowaiver, as excipient interaction appeared not to be critical with regard to the absorption of atenolol, show rapid *in vitro* dissolution, and meet the dissolution profile comparison criteria, *provided that tablets are formulated with well-known excipients.*

# Literature Evidence (4):

4. The BCS: class III drugs - better candidates for BA/BE waiver?
Blume HH1, Schug BS. European Journal of Pharmaceutical Sciences 9 (1999) 117–121

**Objective:** Authors have proposed waiver of BA/BE studies for Class III compounds in fast dissolving products without excipients which may modify GI transit or membrane permeation. This type of API may be an even better candidate for a waiver as, in this case, bioavailability will not so much depend on the formulation characteristics, as on drug substance properties (e.g. permeability).

**Outcome:** Authors conclude extending the existing biowaiver to be granted for rapidly dissolving oral IR products containing Class III API with supposition that the products do not contain excipients which may modify GI transit or the absorption process.

# Literature Evidence (5):

5. The effect of pharmaceutical excipients on GIT Metabolic Enzymes & Transporters – an update; Zhang W, Li Y, Zou P, Wu M, Zhang Z, Zhang T, AAPS J. 2016 Jul;18(4):830-43.

**Objective:** Authors have summarized the recent findings of excipient effects on gastrointestinal (GI) absorption, focusing on their interactions with the metabolic enzymes and transporters in the GI tract, in particular with reference to extension of BCS biowaiver to BCS 3 drugs. A wide range of commonly used excipients such as binders, diluents, fillers, solvents, and surfactants (mainly) are discussed.

**Outcome:**

1. Authors have summarized the reported effects of those excipients on GI tract phase I and phase II enzymes, uptake and efflux transporters, and relevant clinical significance.
2. Majority of the studies are *in vitro* assays. Surfactants mainly were found to affect CYP450 enzymes (inhibited weakly) and transporters.
3. Overall, for a drug whose absorption is influenced substantially by an active transporter, caution should be taken in selection of excipients.

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# Thank You

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