Assessment on the Formulation Similarity of Approved Generic Drug Products and their Respective Reference Products Which are Considered as Potential BCS Class 3 Drugs

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Purpose

A biowaiver of in vivo bioequivalence (BE) studies for Biopharmaceutics Classification System (BCS) Class 3 drugs may be considered provided that formulations are qualitatively (Q1) the same and quantitatively (Q2) very similar to the reference drug product as per the U.S. FDA BCS guidance[1]. However, the formulation development remains a major challenge for generic drug applicants when pursing this approach due to the challenges in meeting the Q1/Q2 and dissolution criteria recommended in FDA's guidance. The Q1/Q2 criteria for biowaiver for BCS Class 3 drugs are mainly used to address concerns on the potential effects of excipients on drug absorption. The purposes of this study were to investigate the impact of formulation similarity on the drug absorption through assessing BE study results of the approved generic (test, T) products that are potential BCS Class 3 drugs and to explore the flexible space of formulation similarity for BCS Class 3 drugs that may not impact BE outcome.

Method(s)

A total of 110 approved abbreviated new drug applications (ANDAs) were examined for 11 potential BCS Class 3 drug substances formulated as immediate-release oral solid dosage forms (e.g., tablets and capsules). For each ANDA, the formulation compositions from both T and reference drug products (reference, R) were compared and categorized based on Q1 and Q2. The excipients used in these formulations were analyzed based upon the function and percent of total weight (%w/w). In addition, the pharmacokinetic (PK) parameters (i.e., $AUC_{0\text{-}t}$, $AUC_{0\text{-}i}$ and C_{max}), T/R ratios of these PK parameters, and 90% confidence intervals (CIs) of these T/R geometric mean ratios were collected from a total of 210 BE studies (115 fasting and 95 fed BE studies).

Results

1. General Information

As per the published literature, World Health Organization (WHO) BCS 3 list[2], internal assessments, and reference listed drug labeling, 11 drug substances (A - K) were selected as potential BCS 3 drug candidates. Their formulations and PK data were retrospectively collected from a total of 110 approved ANDAs with fasting and fed BE studies.

2. Solubility and Permeability

All 11 drug substances were characterized with high solubility and low permeability (<85%) as defined by the FDA BCS guidance. Their permeability ranged from 10 to 83%. Based on the permeability data, two sub-groups were further divided, one is for low (fa<50%) permeability and the other is for moderate (fa=50-84%) permeability as shown in Table 1.

Table 1: BCS 3 Permeability and Absorption Characteristics

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	Absolute BA	40 - 70%
Moderate	G	Rapid and consistent	A substrate of P-gp	Absolute BA	50%
	H	Rapid	A substrate of P-gp	Absolute BA	50%
	I	Rapid	Not a substrate	Absolute BA	50 - 60%
	J	Rapid	Not a substrate	Absolute BA	~83%
	K	Rapid	Not a substrate	Absolute BA	~80%

Results (cont.)

3. Formulation Assessment

The comparative formulation evaluation between the test and reference products was classified into four groups:

- **Q1/Q2 same** contains the same inactive ingredients with individual excipient difference within ±5%;
- **Q1 same/Q2 similar** has a total additive effect of all excipient changes that is less than or equal to 10%;
- **Q1 same/Q2 different** has a total additive effect of all excipient changes that is greater than 10%;
- **Q1 different** contains different excipient(s)

The results of the comparative formulation evaluation are described in Figure 1.

4. Q1 and Q2 Different Formulation Assessment

The excipient changes were calculated based on the FDA BCS criteria as shown in Table 2. In particular for Q2 similar and Q2 different formulations, the excipient categories in which changes that were out of range were mostly lubricant, binder, disintegrant, and glidant as shown in Figure 2.

Figure 1: Comparative Formulation Assessment between the Test and Reference from U.S. FDA Approved ANDAs (N = 110)

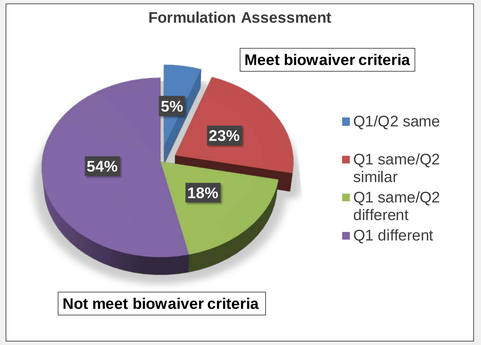
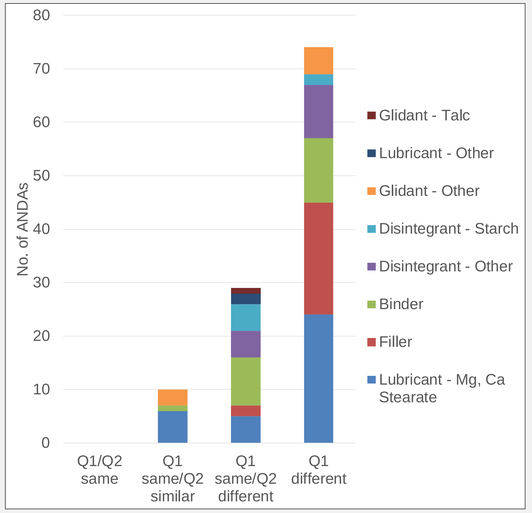


Table 2: Excipient Allowable Differences

Excipient class	Percent difference relative to core weight (w/w)
Filler	10%
Disintegrant	
Starch	6%
Other	2%
Binder	1%
Lubricant	
Mg, Ca Stearates	0.5%
Other	2%
Glidant	
Talc	2%
Other	0.2%

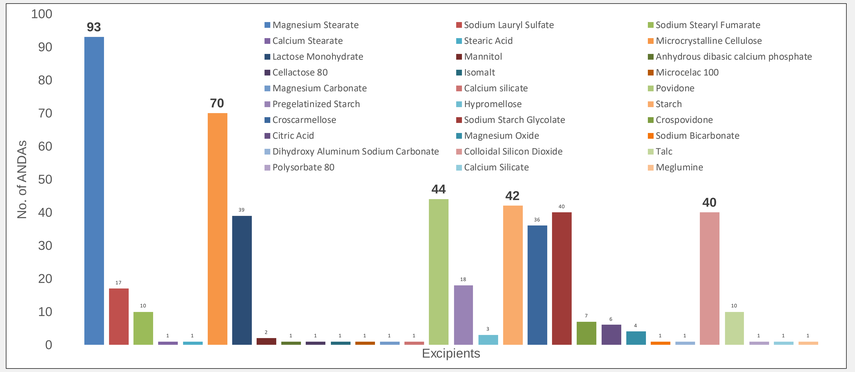
Figure 2: Summary of Excipient Changes (w/w%) among Approved ANDAs by Q1/Q2 Classification



5. Common Excipients by Function

In these formulations, a total of 30 excipients of various amounts were used – none of which were novel or in atypically large amounts. The top five common excipients were magnesium stearate, microcrystalline cellulose, povidone, starch, and colloidal silicon dioxide as shown in Figure 3.

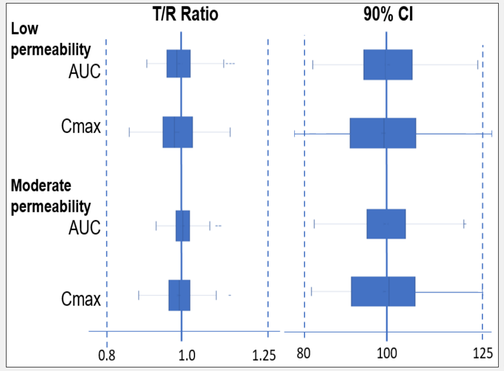
Figure 3: Top Twenty Common Excipients



6. In Vivo BE Studies

For all ANDAs referencing these 11 drug substances, the range of T/R ratios and 90% CI values for all PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}i}$, and C_{max}) are shown in Figure 4, demonstrating that the area under the curve and maximum plasma/serum concentration are in accordance with the BE acceptance criteria. The sample size includes 110 ANDAs from 11 drug substances in which the formulation assessments were conducted.

Figure 4: In Vivo BE studies



We collected all T/R ratios and 90% CI of C_{max} and AUC for each drug candidate from all ANDAs. We used those data to construct box plot (or box-and-whisker plot) to show the distribution of each drug T/R ratios and 90% CI PK parameters located within 0.8-1.25 (as shown by the vertical dashed lines). Each box contains upper (75%) and lower (25%) quartiles and the lines indicate variability outside the upper and lower quartiles. Based on the box plot, T/R ratio and 90% CI for all approved ANDA meet BE criteria (80-125%) except for 3 ANDAs (under fed conditions)*.

AUC = Data from $AUC_{0\text{-}t}$ and $AUC_{0\text{-}i}$ were combined in the box-and-whisker plots

**Note: The data points shown outside 80-125% range in the right column in Figure 4 were from three ANDAs (approved prior to Year 2000), in which meeting 80-125% criteria was not required at the time of review.*

Conclusions

Although the majority of formulations (~72%) in our study may not be eligible for BCS Class 3 biowaiver as per the FDA BCS Guidance, the in vivo BE study results suggested that the observed Q1/Q2 differences may not impact in vivo BE. In addition, the identified excipients (30 in total assessed in the study) do not seem to affect the absorption of these potential BCS Class 3 drugs. Because there is a potential limitation of our dataset on only formulations that passed BE, future studies, combining data-driven and mechanistic approaches, are warranted to further investigate the potential allowable flexibility for formulation criteria as defined in the current FDA BCS Guidance.

Acknowledgements

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References: (1) FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Dec 2017) **(2)** Lindenberg M, Kopp S, Dressman, JB. Classification of Orally Administered Drugs on the World Health Organization Model List of Essential Medicines according to the Biopharmaceutics Classification System. Eur J Pharm Biopharm. 2004;58(2):265-278.

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