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Excipient Similarity in Generic Formulations Containing Biopharmaceutics Classification System 3 Drugs

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PURPOSE

~~The~~ FDA's final guidance on "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)" (referred to as "BCS Waiver Guidance for Industry" in this poster) (December 2017) describes the possibility of waivers of conducting pharmacokinetic (PK) bioequivalence (BE) studies for BCS 3 drugs (high solubility, low permeability, and very rapid dissolution) in addition to BCS 1 drugs (high solubility, high permeability, and rapid dissolution) if certain formulation similarity criteria are met. The purpose of the present study is to investigate the formulation similarity found in the generic (test) product formulations of approved Abbreviated New Drug Applications (ANDAs) of selected potential BCS 3 candidate drug products by comparing test and reference product formulations qualitatively and quantitatively.

METHOD(S)

The collective data for a total of 57 approved ANDAs were examined for 6 potential BCS 3 candidate drug substances with high solubility and different permeability delivered via immediate-release dosage forms (tablets and capsules). The PK parameters (AUC_{0-t}, AUC_{0-i} and C_{max}) were collected for a total of 97 BE studies, including 57 fasting and 40 fed BE studies. The distribution of the Test/Reference (T/R) ratios and 90% confidence intervals (CIs) of the test/reference geometric mean ratios for AUC_{0-t}, AUC_{0-i} and C_{max} were evaluated. In addition, the formulation compositions from both generic (test) and reference drug products were compared qualitatively (Q1) and quantitatively (Q2) for each ANDA submission. The sameness, similarities, and differences of the generic drug formulations to their corresponding reference products were categorized into four groups: Q1/Q2 same (individual excipient difference between test and reference products stays within ±5%), Q1 same/Q2 similar (criteria defined by "BCS Waiver Guidance for Industry"), Q1 same/Q2 different, and Q1 different. The excipients used in these potential BCS 3 candidate drug formulations were analyzed based upon the function, frequency of use, and percent of total weight (%w/w).

RESULT(S)

1. General Information

As per the published literature, WHO BCS 3 list, internal assessments, and reference listed drug labels, six drug products (A – F) were selected as potential BCS 3 candidates. Their formulations and PK data were retrospectively collected from a total of 57 approved ANDAs with fasting and fed BE studies.

2. Solubility and Permeability

All six drugs were characterized as having high solubility and low permeability (<85%) as defined by the "BCS Waiver Guidance for Industry". Their permeability ranged from 17 to 60%. Based on the permeability data, two sub-groups were further divided into low (fa<50%) and moderate (fa=50-84%) permeability.

Permeability Class	Drug	Absorption	Efflux transporter (P-gp, BCRP, MRP2)	Method	Permeability
Low-Low	A	Rapid but incompletely absorbed	Not a substrate of P-gp	Absolute BA, Human Fa	~17%, 34%
	B		A substrate of P-gp and BCRP	Absolute BA	~25%
	C	Rapid	Not a substrate of P-gp	Absolute BA	36%
Low-Moderate	D	Tablet and Capsule: Tmax: 2 to 3 hrs.	A substrate of P-gp	Absolute BA	50%
	E	Rapid	Not a substrate of P-gp	Absolute BA	50-60%
	F	Rapid and consistent	A substrate of P-gp	Absolute BA	50%

RESULT(S) CONT.

3. Formulation Evaluation

The comparative formulation evaluation between the test and reference 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 10 percent;
Q1 same/Q2 different has a total additive effect of all excipient changes that is greater than 10 percent;
Q1 different contains different excipient(s), either added or substituted.
The results of the comparative formulation evaluation of these 57 ANDAs showed that 15.8% (9/57) generic drug products were Q1/Q2 same, 5.3% (3/57) generic drug products were Q1 same/Q2 similar, 15.8% (9/57) generic drug products were Q1 same/Q2 different, and 63.2% (36/57) generic drug products were Q1 different.

Drug	Q1/Q2 same	Q1 same/Q2 similar	Q1 same/Q2 different	Q1 different	Total
A	0	1	2	4	7
B	3	0	3	4	10
C	0	0	1	5	6
D	1	1	0	9	11
E	3	0	0	5	8
F	2	1	3	9	15
Total Percentage	15.8% (9/57)	5.3% (3/57)	15.8% (9/57)	63.2% (36/57)	100% (57)

4. Q1 and Q2 Different Excipients

The following table lists the specific excipients in Q1 and Q2 different generic drug formulations. The excipients identified in Q1 and Q2 different formulations were mostly disintegrant, diluent (or filler), and binder.

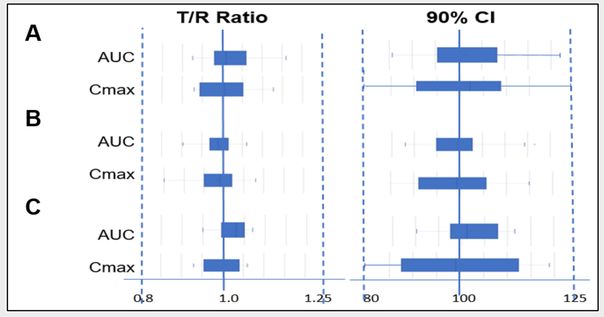
Excipient Changes	Excipient Category	Total # of ANDAs	Specific Excipient
Q1 different	Glidant	17	Colloidal Silicon Dioxide
	Disintegrant	18	Starch, Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium
	Diluent	12	Microcrystalline Cellulose, Lactose, Mannitol, Cellactose 80, Anhydrous dibasic calcium phosphate, Isomalt, Magnesium Carbonate, Calcium Silicate
	Binder	5	Hypromellose, Pregelatinized Starch, Povidone
	Lubricant	8	Sodium Lauryl Sulfate, Sodium Stearyl Fumarate, Calcium Stearate, Magnesium Stearate
	Acidifying Agent	2	Citric acid
	Buffering Agent	2	Dihydroxy Aluminium Sodium Carbonate, Sodium Bicarbonate
	Emulsifier	1	Polysorbate 80
Q2 different	Diluent	7	Microcrystalline Cellulose, Lactose Monohydrate
	Disintegrant	3	Sodium Starch Glycolate
	Binder	1	Pregelatinized Starch

5. Common Excipients by Function

A total of 27 different excipients with various amount contained in the current FDA-approved immediate-release solid oral dosage forms were used to formulate 57 generic drug products in ANDAs. The top five common excipients were Magnesium Stearate, Microcrystalline Cellulose, Povidone, Croscarmellose, and Sodium Starch Glycolate. There were no novel excipients or atypically large amounts of commonly used excipients in these ANDAs.

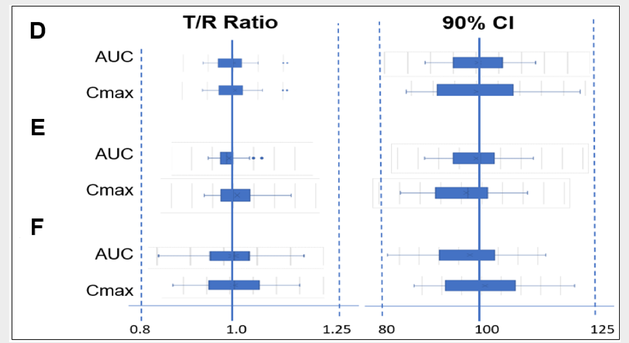
Function	Excipient	Total (out of 57)
Lubricant	**Magnesium Stearate**	**48 (84%)**
	Stearic Acid	5 (9%)
	Talc	4 (7%)
	Sodium Lauryl Sulfate	3 (5%)
	Sodium Stearyl Fumarate	3 (5%)
	Calcium Stearate	1 (2%)
Diluent/Filler	**Microcrystalline Cellulose**	**40 (70%)**
	Lactose Monohydrate	17 (30%)
	Mannitol	2 (4%)
	Anhydrous dibasic calcium phosphate	1 (2%)
	Cellactose 80	1 (2%)
	Magnesium Carbonate	1 (2%)
	Isomalt	1 (2%)
	Microcelac 100	1 (2%0
	Calcium Silicate	1 (2%)
Glidant	**Colloidal Silicon Dioxide**	**25 (44%)**
Binder	**Povidone**	**24 (42%)**
	Pregelatinized Starch	13 (22%)
	Hypromellose E5	2 (4%)
Disintegrant	**Croscarmellose**	**20 (35%)**
	Sodium Starch Glycolate	**20 (35%)**
	Starch	12 (21%)
	Crospovidone	6 (11%)
Stabilizer/Buffering Agent	Magnesium Oxide	4 (7%)
	Sodium Bicarbonate	1 (2%)
	Dihydroxy Aluminum Sodium Carbonate	1 (2%)
	Citric Acid	3 (5%)
	Sodium Bicarbonate	1 (2%)
Emulsifier	Polysorbate 80	1 (2%)
Counterion	Meglumine	1 (2%)

6. In vivo BE studies – Low Permeability



RESULT(S) CONT.

7. In vivo BE studies – Moderate Permeability



Note: For all six drug products, T/R ratios and 90% CI for all PK parameters (AUC and Cmax) in all in-vivo BE studies met BE criteria (80-125%). In terms of dissolution, most of the ANDAs demonstrated very rapid dissolution.

CONCLUSION

The majority (about 80%) of the surveyed formulations in these six oral dosage form ANDAs does not meet the criteria for BCS 3 waivers according to the current FDA "BCS Waiver Guidance for Industry". This indicates a potential barrier to a more extensive use of BCS 3 waivers in ANDAs. Although all the non-Q1 same/Q2 similar formulations in this survey had acceptable BE studies, FDA's data on the PK study results for these non-Q1 same/Q2 similar formulations are biased to some extent because failed BE studies were not always submitted to FDA. Our future work will focus on identifying what conclusion can be drawn on the 27 excipients used to formulate these six potential BCS 3 generic drug products based on the observations in acceptable BE studies. This will involve a more in-depth consideration of the metabolism and transport pathways of these BCS 3 drug substances. The goal of our future work is to combine data-driven and mechanistic approaches to better define the specific excipient space within which the non-Q1 same/Q2 similar BCS 3 products shall stay bioequivalent to their corresponding reference products.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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Disclaimer: The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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