Current Knowledge Gaps and Regulatory Challenges in the Evaluation of Biowaivers for Biopharmaceutical Classification System (BCS) Class III-“like” Drugs.

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Abstract

BACKGROUND: The current FDA guidance recommends that for a waiver of in vivo bioequivalence (BE) study to be justified, a Biopharmaceutical Classification System (BCS) class III generic product must contain qualitatively (Q1) the same and quantitatively (Q2) very similar excipients when compared to the reference listed drug (RLD), and the drug product dissolution must meet the “very rapidly dissolving” criteria. There has been minimal regulatory precedence on granting biowaiver for BCS class III drugs. **PURPOSE:** The purpose of this project is to study the relationship between formulation Q1/Q2 similarity and in vivo bioequivalence outcome in a group of BCS class III-“like” drugs, as well as to investigate whether the dissolution rate of these products meet the "very rapidly dissolving" criteria. **METHODOLOGY:** A total of nine BCS class III-“like” drugs were identified from ~70 Abbreviated New Drug Applications (ANDAs). An assessment on the formulation composition and the dissolution data of the generic and RLD products were conducted. **RESULTS:** The results show that bioequivalence between the generic and RLD products are demonstrated when critical excipients (i.e., croscarmellose sodium, magnesium stearate, povidone, corn starch and lactose) in the generic drug product are not Q1/Q2 the same/similar to the RLD. Majority of BCS class III-“like” drug products demonstrated >85% drug-release within 15 min. **CONCLUSIONS:** The result that bioequivalence is demonstrated for products with excipient differences beyond Q1/Q2 the same/similar (in conjunction with very rapid dissolution) provides supporting evidence for a possibility for the Agency to re-consider its “Q1/Q2 similarity” criteria set in the current guidance for BCS class III biowaiver. Additional investigation is needed if further guidance advancement is warranted.

Introduction

- The BCS is a framework for classifying drug substances based upon their aqueous solubility and intestinal permeability across biological membranes.
- The FDA BCS guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), ANDAs, and supplements to these applications (sNDA) who wish to request a waiver of in vivo BE studies for immediate-release (IR) solid oral dosage forms.
- Drug substances are classified based on their intestinal permeability (or the fraction of oral dose absorbed), aqueous solubility, and dissolution rate at multiple pH values covering the range found in the gastrointestinal (GI) tract.

Introduction

- Class I drugs have high permeability, high solubility, and rapid dissolution (>85% drug-release within 30 min) at all pH values between 1.0 and 6.8. On the other hand, Class III drugs have low permeability, high solubility, and very rapid dissolution (>85% drug-release within 15 min) at all pH values between 1.0 and 6.8.
- Class I drugs can be granted waiver from in vivo BE testing due to their consistently high fraction absorbed, regardless of the formulation. Unlike waiver of BE studies for BCS class I drugs, for a biowaiver to be scientifically justified, a BCS class III drug product must contain Q1 the same and Q2 very similar excipients when compared to the RLD. This is due to limited data documenting the potential impact of excipients on the absorption of drugs in humans and due to the concern that excipients can have a greater impact on absorption of low permeability drugs.
- Based on public comments in the 2017 FDA BCS guidance, there is concern in the pharmaceutical industry that the recommendation for excipients for the generic product to be Q1/Q2 same/similar in comparison to the RLD and “very rapidly dissolving” criteria are conservative and may be a barrier for BCS class III waivers.
- The purpose of this project is to study the relationship between formulation Q1/Q2 similarity and in vivo bioequivalence outcome in a group of BCS class III-“like” drugs, as well as to investigate whether the dissolution rate of these products meet the "very rapidly dissolving" criteria.

Materials and Methods

As shown in the **Table 1** below, a total of nine (9) BCS class III-“like” drugs were identified based on literature search. Subsequently, an assessment of in vivo BE and in vitro dissolution studies along with formulation data of the generic and RLD products from ~70 in-house ANDAs were conducted. All the ~70 in-house ANDAs contained only passing pivotal BE studies and failed BE studies were not observed.

Acyclovir
Atenolol
Enalapril maleate
Methotrexate
Ranitidine
Lamivudine
Metformin
Sofosbuvir
Cimetidine

Table 1. List of BCS class III-“like" drugs obtained from literature.

Results and Discussion

- Data from the current study shows that when the generic product is not Q1/Q2 same/similar to the RLD, excipients commonly used in IR drug products do not affect demonstration of bioequivalence between the generic and RLD products.
- Results, similar to the current study were also observed in studies conducted by *Parr, A., et al* and *Vaithianathan, S., et al* using in vitro Caco-2 cell model and in vivo BE study, respectively. In these two studies, the authors demonstrated that excipients commonly used in IR drug products do not impact in vitro permeability and in vivo absorption in humans.
- As shown in Figure 2, many BCS class III-“like” drug products have >85% drug-release within 15 min (i.e., many of the BCS class III-“like” drug products meet the “very rapidly dissolving” criteria).
- However, for Metformin and Ranitidine, there are greater number of ANDAs that do not meet the “very rapidly dissolving” criteria. For the ANDAs with less than 85% drug-release within 15 min, there is no observation of bio-**in**equivalence.

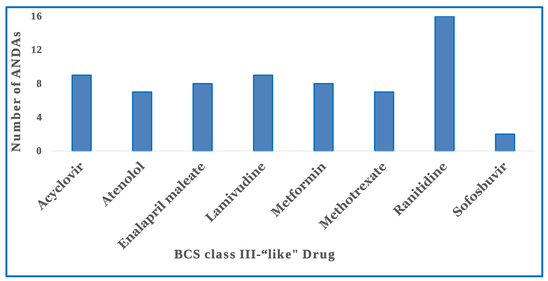

Figure 1. Number of ANDAs evaluated for each BCS Class III-“like" drug. ANDAs for Cimetidine were not investigated due to unavailability of data in electronic format.

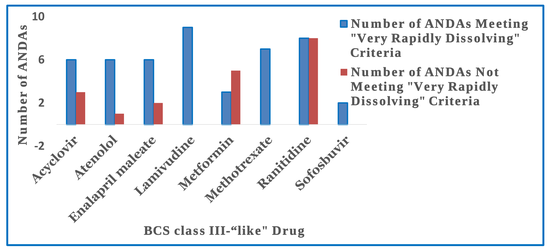

Figure 2. Number of ANDAs Meeting the “Very Rapidly Dissolving” Criteria for each BCS class III-“like" drug.

Table 2. Excipients commonly used in Immediate-release BCS class III-“like" drug products.

Excipient	Function
Croscarmellose sodium	Disintegrant
Lactose	Diluent/Filler
Magnesium stearate	Lubricant
Microcrystalline cellulose	Binder/Diluent
Povidone/Crospovidone	Binder
Starch (Corn and Pregelatinized)	Diluent/Disintegrant
Silicon dioxide	Glidant
Sodium starch glycolate	Disintegrant

Conclusion

- Till date, there is very limited data in humans documenting the impact of excipients on the bioequivalence of BCS class III-“like” drugs.
- The data collected in the current study on nine (9) literature-reported BCS class III-“like" drugs provides in vivo evidence that excipients commonly used in Immediate-release BCS class III-“like" drug products (and excipients investigated in the current study) may not impact in vivo drug disintegration, dissolution, GI tract motility, drug permeation, & absorption of BCS class III drugs in humans.
- Results from this study show that “very rapidly dissolving” criteria for dissolution testing may not be a barrier for BCS class III waivers and there is no risk of bio-**in**equivalence when drug products do not meet the “very rapidly dissolving” criteria.
- The results from this study mirrors literature reports demonstrating no impact of excipients on in vitro permeability and in vivo absorption of BCS class III drugs in humans.
- The result that bioequivalence is demonstrated for products with excipient differences beyond Q1/Q2 the same/similar (in conjunction with very rapid dissolution) provides supporting evidence for the Agency to re-consider its “Q1/Q2 same/similarity” criteria set in the current guidance for BCS class III based biowaivers. Additional investigation is needed if further guidance advancement is warranted.
- A potential limitation of the current study is that conclusions from this project were based on ANDAs with only passing BE studies. ANDAs with failed BE studies (due to excipient related BE study failures) were not available for inclusion in this project.

References

- The Effect of Excipients on the Permeability of BCS Class III Compounds and Implications for Biowaivers. *Parr, A., et al, Pharm Res (2016) 33:167–176.*
- Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. *Vaithianathan, S., et al, Journal of Pharmaceutical Sciences 105 (2016) 996-1005.*