Impact of Solubility and Dissolution Performance on Bioequivalence Recommendations for Immediate-Release Locally Acting Gastrointestinal Drug Products for Promoting Affordable Generic Drugs Available to American Public

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Statement of Purpose

Establishing bioequivalence (BE) for immediate-release (IR) locally acting gastrointestinal (LAGI) drug products is challenging for the following reasons: these products reach the site of action before entering systemic circulation; many have minimal systemic absorption that traditional in vivo BE studies with pharmacokinetics (PK) endpoints may not be feasible; and comparative clinical endpoint (CCEP) BE studies are generally insensitive to detect formulation differences and require a large sample size. Therefore, alternative approaches to establish BE for such products are warranted. Solubility and dissolution may predict in vivo performance and serve as a surrogate for in vivo BE assessment. The current research is to investigate the impact of solubility and dissolution on BE recommendations in FDA's published product-specific guidances (PSGs) for IR LAGI drugs.

Description of Methods & Materials

We collected data of solubility and dissolution in multiple pH media, and systemic absorption for 15 drug substances among 19 IR LAGI products to cover a variety of dosage forms including tablet, chewable tablet, capsule, suspension, and powder from new drug applications and abbreviated new drug applications. The corresponding BE recommendations in the total of 19 PSGs regarding qualitative (Q1) and quantitative (Q2) formulation, in vitro comparative dissolution testing, BE studies with PK or clinical endpoints were collected for each product. Based upon the in vivo absorption profiles, the 19 drug products were divided into a systemically detectable group for 11 products and a systemically undetectable group with approximately zero absorption for 8 products.

Data & Results

In the systemically undetectable group, six out of seven drug substances exhibit high solubility, as according to Biopharmaceutics Classification System criteria^, while in the systemically detectable group, only one out of eight drug substances has high solubility. For all seven highly soluble drugs, in vitro multi-media dissolution testing is recommended in the PSGs for Q1/Q2 sameness products, while for non-Q1/Q2 sameness products, additional BE studies with PK or clinical endpoints are recommended, except that for one product (magnesium sulfate; potassium chloride; sodium sulfate tablets) where only one medium dissolution testing is recommended. For the 12 drug products (2 systemically undetectable and 10 systemically detectable) containing the low soluble drug substances, the PSGs recommend additional in vitro BE studies (i.e., a binding study), in vivo BE studies with PK endpoints for Q1/Q2 sameness formulations, and additional CCEP BE studies for non-Q1/Q2 sameness formulations.

Interpretation, Conclusion & Significance

The solubility of drug substance was found as a critical physiochemical characteristics for in vitro and in vivo performance for IR LAGI drug products. As a result, for IR LAGI drug products with high solubility for Q1/Q2 sameness formulation, an in vitro multi-media or one medium dissolution testing may be sufficient to establish BE. However, for low soluble drugs, in vitro and in vivo performance were found to be less predictable based on in vitro data alone. Thus, additional in vitro BE studies (i.e., a binding study), and in vivo BE studies with PK and/or clinical endpoints should be recommended based on either Q1/Q2 or non-Q1/Q2 sameness formulations, in addition to in vitro multi-media dissolution testing. The science-based BE recommendations for IR LAGI drug products have facilitated the development of generic drug products, promoted affordable, high quality and safe medicines available to American public, and benefitted the public health.

^Guidance for Industry, *M9 Biopharmaceutics Classification System-Based Biowaivers (2021)*

Instrumental Findings for Optimal BE Recommendations for IR LAGI Products

The solubility of drug substance was found as a critical physiochemical characteristics for in vitro and in vivo performance. For IR LAGI drug products with high solubility for Q1/Q2 sameness formulation, an in vitro multi-media or one medium dissolution testing may be sufficient to establish BE. However, for IR LAGI drug products with low solubility, in vitro and in vivo performance were found to be less predictable based on in vitro data alone. Thus, additional in vivo BE studies with PK and/or clinical endpoints should be recommended based on either Q1/Q2 or non-Q1/Q2 sameness formulations, in addition to in vitro multi-media dissolution testing.

Absorption	Solubility	PSG Recommendations	Drug Products
Systemically Undetectable	High	In vitro comparative dissolution testing in one media	Magnesium Sulfate; Potassium Chloride; Sodium Sulfate Tablets
		For Q1/Q2 sameness formulations: In vitro comparative dissolution testing ***For non-Q1/Q2 sameness formulations:*** In vivo comparative clinical endpoint BE study	Acarbose Tablets Ferric Citrate Tablets Vancomycin HCl Capsules Plecanatide Tablets Linaclotide Capsules
	Low	***Option 1***: In vitro comparative dissolution testing **+** In vitro phosphate binding study ***Option 2***: In vivo comparative clinical endpoint BE study	Lanthanum Chewable Tablets Lanthanum Powder
Systemically Detectable	High	***For Q1/Q2 sameness formulations:*** In vitro comparative dissolution testing ***For non-Q1/Q2 sameness formulations:*** In vitro comparative dissolution testing **+** In vivo BE with PK endpoints	Sodium Phosphate, Dibasic, Anhydrous; Sodium Phosphate, Monobasic, Monohydrate Tablets
	Low	***For Q1/Q2 sameness formulations:*** In vitro comparative dissolution **+** In vivo BE with PK endpoints ***For non-Q1/Q2 sameness formulations:*** In vivo comparative clinical endpoint BE study Or In vitro comparative dissolution + in vivo BE with PK endpoints + Comparative clinical endpoint BE study Or In vivo BE with PK endpoints + comparative clinical endpoint BE study	Fidaxomicin Tablets Fidaxomicin Suspension Lubiprostone Capsules Mebendazole Tablets Nitazoxanide Tablets Nitazoxanide Suspension Rifaximin Tablets
		In vitro comparative dissolution testing **+** In vivo BE with PK endpoints	Balsalazide Tablets Balsalazide Capsules
		In vivo comparative clinical endpoint BE study	Orlistat Capsules

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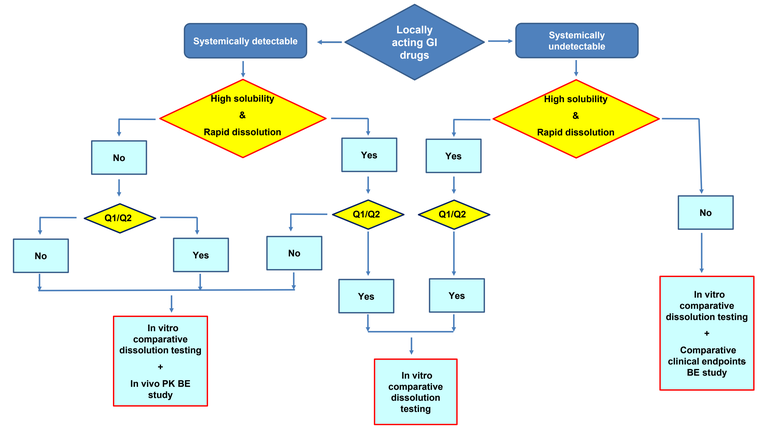
Table 1. Clinical effect classification for locally acting GI drugs (A total of 19 drug products)

Categories	Drug Substances	Dosage Forms
Laxative agent (5)	SPD; anhydrous; SPM; monohydrate,* Linaclotide, Lubiprostone, Plecanatide, and MS; PC; SS**	Tablet and capsule
Anti-parasite (3)	Nitazoxanide & mebendazole	Tablet and suspension
Antibiotics (3)	Fidaxomicin, vancomycin hydrochloride, and rifaximin	Tablet, capsule, and suspension
Anti-diabetic (1)	Acarbose	Tablet
Anti-inflammatory (2)	Balsalazide disodium	Tablet and capsule
Dialysis for phosphate (3)	Ferric citrate & lanthanum carbonate	Tablet and powder
Lipase inhibitor (1)	Orlistat	Capsule

* SPD-sodium phosphate, dibasic, anhydrous; SPM-sodium phosphate, monobasic, monohydrate tablets

** MS-magnesium sulfate; PC-potassium chloride; SS-sodium sulfate tablets,

Preliminary decision framework for BE recommendations for locally acting GI drugs in PSGs



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Disclaimer

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