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Reconciling sprinkle administration information in approved NDA labeling with sprinkle bioequivalence study recommendations in FDA product-specific guidances for generic drug development

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ABSTRACT

Objectives: Certain patient populations (e.g., children and the elderly) may not be able to swallow solid oral dosage forms. In the absence of availability of a dosage form that is appropriate for these patient groups, liquids and/or soft foods as described in the Food and Drug Administration (FDA)-approved product labeling can be used as a suitable vehicle(s) for oral administration of the specific drug product. The approved labeling of some new drug application (NDA) products contains information for sprinkle administration on liquids or soft foods. Since abbreviated new drug application (ANDA) products must demonstrate bioequivalence (BE) to the reference listed drug (RLD) products, and since the generic drug labeling is the same as RLD, generic applicants are recommended to conduct *in vivo* BE sprinkle study using one of the soft foods mentioned in RLD labeling. The current FDA guidance specifically recommends that generic applicants conduct a sprinkle BE study if the labeling of a modified-release (MR) RLD product states that the product can be administered sprinkled on soft foods. For ANDAs, such recommendations for *in vivo* BE sprinkle studies for MR products are routinely communicated in the respective product-specific guidance (PSG) published by FDA and readily available for prospective ANDA applicants. FDA guidance does not recommend sprinkle BE study for an immediate-release (IR) product since the formulation differences between IR generic and RLD products are not expected to impact administration with food vehicle.

Materials and Methods: FDALabel and PSG databases were searched for current NDAs with sprinkle labeling and individual PSGs with recommendations for an *in vivo* sprinkle BE study, respectively. Results from FDALabel were narrowed to NDAs for oral solid dosage forms with approved labeling for sprinkle administration on food vehicles. Only MR NDAs with sprinkle labeling were included in the final analysis as recommended by FDA for inclusion of *in vivo* sprinkle BE study recommendations in PSGs for generic products. We searched the FDA external PSG database for availability of respective PSGs containing *in vivo* sprinkle study recommendations for those MR products with approved NDA labeling for sprinkle administration.

Results: Of the 57 NDAs with FDA-approved drug products that are labeled to include sprinkle administration, 45 NDAs were MR (tablet, capsule, and granule) products. Forty-two (93%) of the 45 MR products have PSGs with *in vivo* sprinkle BE study recommendations. Standardized data extraction sheets created by Microsoft Excel 2019 for data extraction were utilized.

Conclusion: FDA has a sprinkle-study PSG for almost all currently approved MR NDAs. The results of our study show that *in vivo* BE study recommendations in PSGs closely match information in the approved drug labeling. Applicants who plan to develop MR generic products should visit the FDA public web page for the availability of the product-specific BE recommendations for the proposed products.

Keywords: Generic drugs, Modified-release drugs, Sprinkle, Product-specific guidance, Drug label, Soft foods

INTRODUCTION

Due to their ease of administration and high acceptability by patients, most drug products are administered through the oral route as solid dosage forms, mainly in the form of tablets and capsules. It is estimated that 50% of the population, including children and the elderly, have problems swallowing tablets.[1] In recent years, novel solid oral dosage forms, such as mini-tablets, chewable tablets, orally disintegrating tablets, orally disintegrating strips, orally disintegrating films, and sprinkle formulations, have been introduced to ease medication administration in patients with dysphagia.[2-6] Sprinkle formulations allow sprinkling of multi-particulate beads, pellets, granules, and crushable tablets on soft foods (commonly applesauce) before oral administration.

For sprinkle instructions to be included in the reference listed drug (RLD) labeling, the new drug application (NDA) applicant needs to demonstrate the absence of impact of food vehicles on bioavailability (BA) through an *in vivo* fasting sprinkle bioequivalence (BE) study. If the labeling of a modified-release (MR) RLD product states that the product can be administered by sprinkling, Food and Drug Administration (FDA) also recommends that the abbreviated new drug application (ANDA) applicant conducts an *in vivo* sprinkle BE study.[7,8] Sprinkle BE study is generally not recommended for an immediate-release (IR) solid oral dosage form since the formulation differences between IR generic and RLD products are not expected to impact administration with food vehicle.

During formulation development stage, NDA and ANDA applicants are recommended to perform *in vitro* and *in vivo* testing methods for selection and qualification of food, drug product, and food-drug mixture.[7-9] Sprinkle administration of drug product with foods should not significantly alter its potency and stability. The use of inappropriate food vehicles may affect the BA and stability of drugs. For example, sprinkling acid-sensitive drugs on acidic foods (e.g., applesauce, apple juice, and orange juice) may cause drug degradation or premature drug release. On the other hand, MR products with specialized coating designed to dissolve rapidly in the intestine should not be sprinkled on alkaline foods.[10,11]

Since 2007, FDA has implemented the product-specific guidance (PSG) program which reflects the regulatory agency's current thinking on the type of studies and information to support the development and approval of a generic drug product therapeutically equivalent to RLD product[12] [Figures 1 and 2]. The FDA recommends that ANDA applicants routinely access published PSGs when considering the appropriate BE study for a proposed drug product [Figure 3]. As of the third quarter (September) of 2022, FDA has published 2038 PSGs for individual products

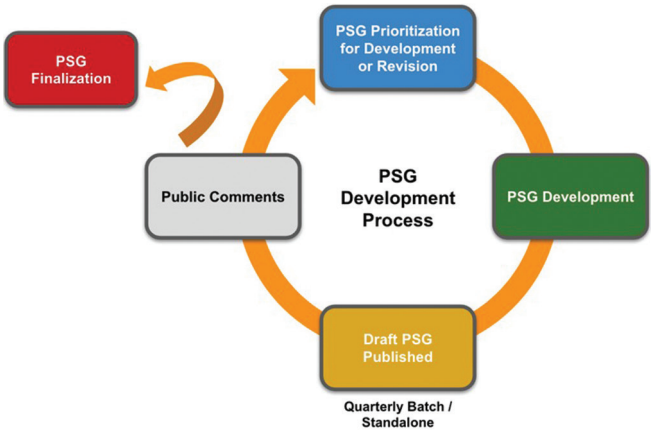

Figure 1: Product-specific guidance development process.

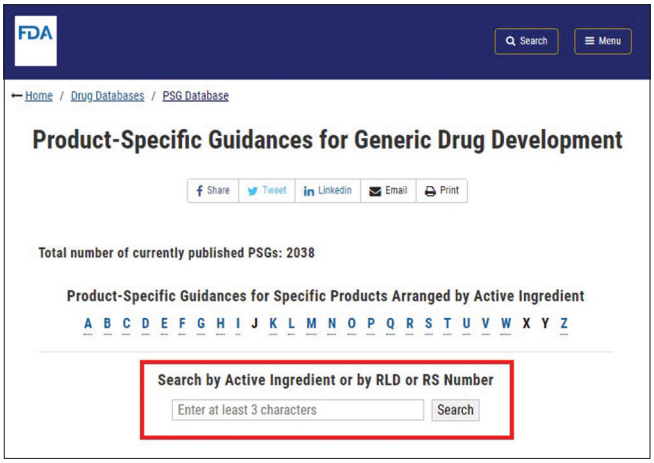

Figure 2: Food and Drug Administration product-specific guidances webpage (Adapted from https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm).

on its public webpage. For additional information on sprinkle administration of drug product, ANDA applicants should consult the "Dosing and Administration" section of the approved label of RLD.

FDALabel is a web-based application designed to allow users to perform customizable searches of thousands of "in use" labeling for human prescription drug, non-prescription drug (OTC), and biological products [Figure 4]. FDALabel database is updated weekly and contains the most recent labeling documents. Using FDALabel, one can perform: (1) full-text searches of the entire labeling or specific sections/subsections of the labeling; (2) narrow searches by application type (e.g., NDA, ANDA), by route(s) of administration, and to retrieve only RLD labeling; and (3) locate RLD labeling for most ANDA original holders.

The aim of this study was to investigate whether all MR NDAs approved for sprinkle administration have sprinkle BE study recommendations in their respective PSGs and to

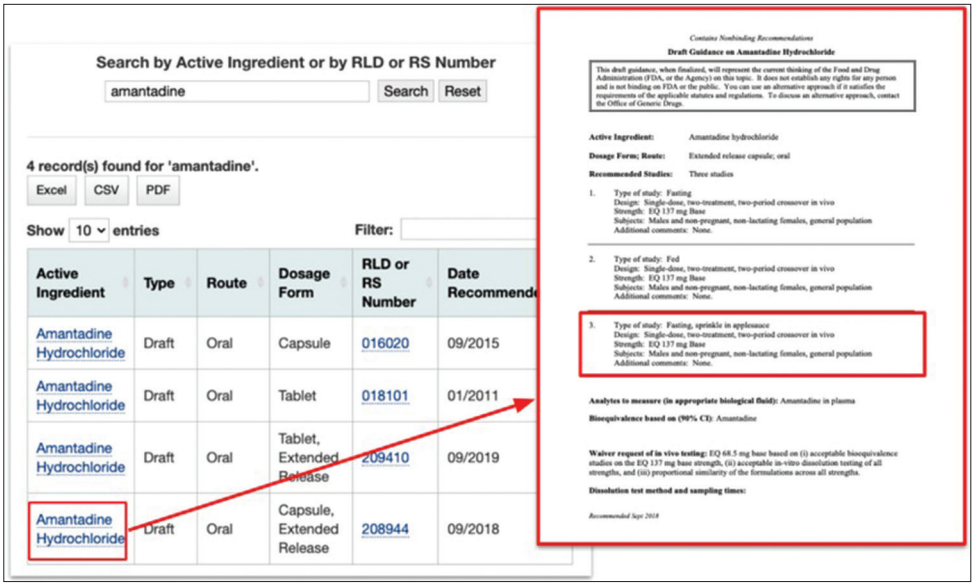

Figure 3: Illustration of steps for accessing individual product-specific guidances.

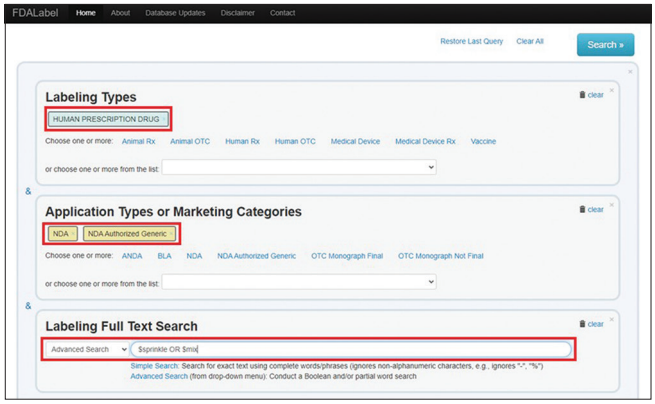

Figure 4: FDALabel database webpage (Adapted from https://nctr-crs.fda.gov/fdalabel/ui/search).

confirm that the food vehicle selected in the PSG is one of those mentioned in the approved RLD label.

MATERIALS AND METHODS

The external database, FDALabel (version 2.7), was used to search for current NDAs with sprinkle labeling.[13] We conducted the search up to October 2022. To capture all variations of administration instructions, a labeling full-text search was conducted for the root words "sprinkle" and "mix," using the Boolean operator $ ("$sprinkle OR $mix"). Labeling type was limited to human prescription drugs, and application type confined to NDAs. Query results were further filtered to include solid oral dosage forms (powders, granules, pellets, capsules, and tablets) with RLD labeling that mentions instructions for sprinkle administration on soft food or liquid. NDAs were excluded if they were non-solid oral dosage forms (e.g., intravenous solutions); required chewing, crushing, or dissolving in the vehicle; added to water only for nasogastric or enteral tube administration; labeling text specified "not to sprinkle or mix;" and discontinued products. Among NDAs with sprinkle administration labeling, only MR NDAs were included in the final evaluation since sprinkle BE study is exclusively recommended in PSGs of MR products. We, then, searched the FDA external PSG database for availability of respective PSGs containing *in vivo* sprinkle study recommendations for those MR products with approved NDA labeling for sprinkle administration. We used standardized data extraction sheets made by Microsoft Excel 2019 for data extraction. All the data generated and analyzed during the present study are publicly available.

RESULTS

FDALabel database search for human prescription NDAs containing iterations of the words "sprinkle" or "mix" returned 1114 results [Figure 5]. The list was further narrowed to 57 approved NDAs with sprinkle administration information in the label. Of the 57, 45 NDAs were MR (extended release [ER] and delayed release) [Table 1] and 12 NDAs were IR products [Table 2]. Out of the 45 MR NDAs, 42 had sprinkle BE study recommendations in their respective PSGs. The remaining 3 NDAs, including a recently approved drug (ranolazine [Aspruzyo Sprinkle]), may have their PSGs under development.

Among the 45 MR sprinkle formulation NDAs, 28 NDAs (62%) were ER capsules [Figure 6]. In PSG sprinkle BE study recommendations for MR sprinkle formulations, applesauce was the most used vehicle (89%), with a minority of study recommendations listing applesauce or yogurt (2%), or fruit

Table 1: 45 Modified-release NDAs approved for sprinkle administration.

Trade Name	Generic Name	Dosage form	Sprinkle Administration Instructions in Labeling	Sprinkle Study Recommendation in PSG
Gocovri	Amantadine	Capsule, Coated Pellets, Extended Release	✓	✓
Entocort EC	Budesonide	Capsule, Delayed Release	✓	✓
Dexilant	Dexlansoprazole	Capsule, Delayed Release	✓	✓
Drizalma Sprinkle	Duloxetine	Capsule, Delayed Release	✓	✓
Nexium	Esomeprazole Magnesium	Capsule, Delayed Release	✓	✓
Esomeprazole Strontium	Esomeprazole Strontium	Capsule, Delayed Release	✓	✓
Prevacid	Lansoprazole	Capsule, Delayed Release	✓	✓
Aciphex Sprinkle	Rabeprazole Sodium	Capsule, Delayed Release	✓	✓
Procysbi	Cysteamine Bitartrate	Capsule, Delayed Release Pellets	✓	✓
Verelan	Verapamil Hydrochloride	Capsule, Delayed Release Pellets	✓	✓
Carbatrol	Carbamazepine	Capsule, Extended Release	✓	✓
Equetro	Carbamazepine	Capsule, Extended Release	✓	✓
Coreg CR	Carvedilol Phosphate	Capsule, Extended Release	✓	✓
Amrix	Cyclobenzaprine Hydrochloride	Capsule, Extended Release	✓	✓
Focalin XR	Dexmethylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Mydayis	Dextroamphetamine Sulfate, Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, and Amphetamine Sulfate	Capsule, Extended Release	✓	✓
Adderall XR	Dextroamphetamine Sulfate, Dextroamphetamine Saccharate, Amphetamine Sulfate, and Amphetamine Aspartate	Capsule, Extended Release	✓	✓
Tiazac	Diltiazem Hydrochloride	Capsule, Extended Release	✓	✓
Rytary	Levodopa and Carbidopa	Capsule, Extended Release	✓	✓
Loreev XR*	Lorazepam	Capsule, Extended Release	✓	✓
Namenda XR	Memantine Hydrochloride	Capsule, Extended Release	✓	✓
Namzaric	Memantine Hydrochloride and Donepezil Hydrochloride	Capsule, Extended Release	✓	✓
Pentasa	Mesalamine	Capsule, Extended Release	✓	✓
Ritalin LA	Methylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Metadate CD	Methylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Aptensio XR	Methylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Jornay PM	Methylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Adhansia XR	Methylphenidate Hydrochloride	Capsule, Extended Release	✓	✓
Kapspargo Sprinkle	Metoprolol Succinate	Capsule, Extended Release	✓	✓
Embeda	Morphine Sulfate and Naltrexone Hydrochloride	Capsule, Extended Release	✓	✓
Avinza	Morphine Sulfate	Capsule, Extended Release	✓	✓
Kadian	Morphine Sulfate	Capsule, Extended Release	✓	✓
Xtampza ER	Oxycodone	Capsule, Extended Release	✓	✓
Micro-K 10 Extencaps; Micro-K Extencaps	Potassium Chloride	Capsule, Extended Release	✓	✓
Qudexy XR	Topiramate	Capsule, Extended Release	✓	✓
Effexor XR	Venlafaxine Hydrochloride	Capsule, Extended Release	✓	✓
Verelan PM	Verapamil Hydrochloride	Capsule, Extended Release	✓	✓
Qelbree	Viloxazine Hydrochloride	Capsule, Extended Release	✓	✓

(Contd...)

Table 1: *(Continued).*

Trade Name	Generic Name	Dosage form	Sprinkle Administration Instructions in Labeling	Sprinkle Study Recommendation in PSG
Depakote Sprinkles	Divalproex Sodium	Capsule, Pellets, Delayed Release	✓	✓
Procysbi	Cysteamine Bitartrate	Granule, Delayed Release	✓	✓
Protonix	Pantoprazole Sodium	Granule, Delayed Release	✓	✓
Doryx	Doxycycline Hyclate	Tablet, Delayed Release	✓	✓
Zenpep	Pancrelipase	Capsule, Delayed Release	✓	
Creon	Pancrelipase	Capsule, Delayed Release Pellets	✓	
Aspruzyo Sprinkle	Ranolazine	Granule, Extended Release	✓	

CD: Controlled delivery, CR: Continuous release, DR: Delayed release, EC: Enteric-coated, ER: Extended release, PM: Afternoon, XR: Extended release

Table 2: 12 Immediate-release new drug applications approved for sprinkle administration.

Trade name	Generic name	Dosage form	Sprinkle administration instructions in labeling
Colazal	Balsalazide Sodium	Capsule	✓
Celebrex	Celecoxib	Capsule	✓
Tasigna	Nilotinib	Capsule	✓
Altace	Ramipril	Capsule	✓
Azstarys	Serdexmethylphenidate and Dexmethylphenidate	Capsule	✓
Rapaflo	Silodosin	Capsule	✓
Bylvay	Odevixibat	Capsule, Coated Pellets	✓
Sustiva	Efavirenz	Capsule, Gelatin Coated	✓
Lyvispah	Baclofen	Granule	✓
Jadenu	Deferasirox	Granule	✓
Alkindi Sprinkle	Hydrocortisone	Granule	✓
Solosec	Secnidazole	Granule	✓

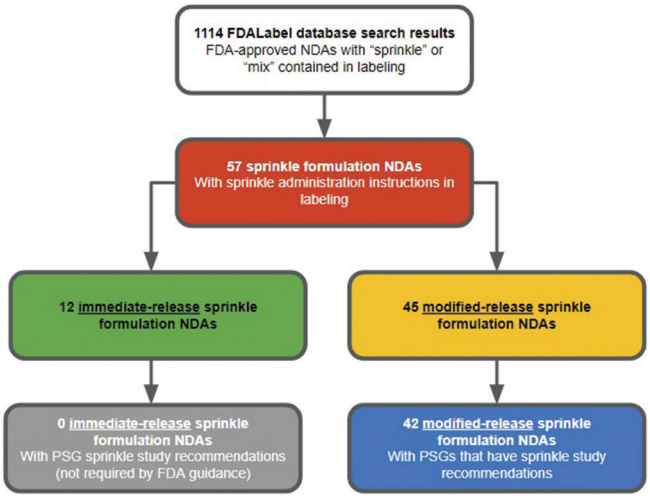

Figure 5: Flowchart of the search, selection, and inclusion of modified-release new drug applications approved for sprinkle administration.

juice (7%). One (2%) sprinkle BE study for carvedilol (Coreg CR) did not list a vehicle [Figure 7].

DISCUSSION

The "Dosage and Administration" section of approved RLD labeling includes directions for administering the drug using the recommended liquid or soft food vehicle. For sprinkle instructions to be included in "Dosage and Administration" section of RLD labeling, the NDA applicant needs to demonstrate the absence of impact of food vehicles on BA, typically through a fasting sprinkle BE study to compare the pharmacokinetics of the drug given as intact product to that of the dosage contents sprinkled on soft foods. If BA is comparable between the two ways of drug administration, the innovator may add instructions in the product label describing the drug product administration through sprinkling on the soft food used in the BE study. If a liquid or soft food is qualified as a vehicle(s) and recommended

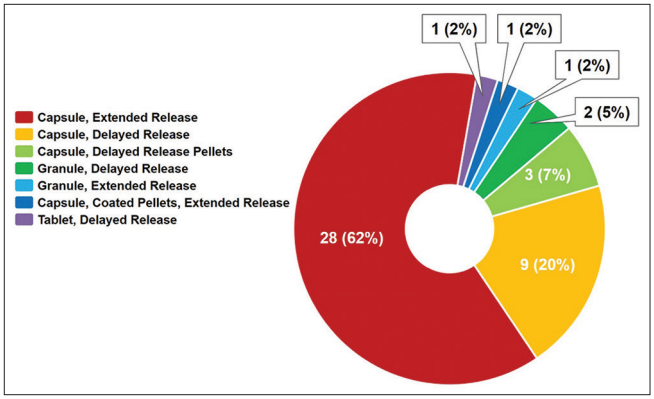

Figure 6: Types of solid oral dosage forms approved for sprinkle administration.

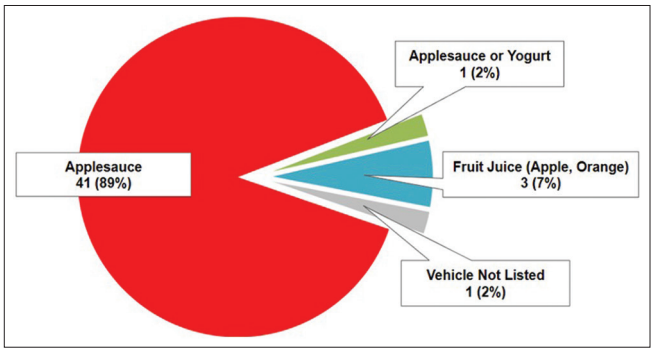

Figure 7: Commonly used soft foods and liquids for sprinkle administration.

for the administration of a drug, the labeling should include: (1) recommended type(s) of soft food or liquid vehicle(s); and (2) recommended critical manipulations, such as emptying capsule contents or crushing a tablet for ease of administration. If the labeling of a MR RLD product states that the product can be administered sprinkled, FDA also recommends that an ANDA applicant conducts an *in vivo* sprinkle BE study.[8]

A food vehicle is considered suitable for drug product administration when it has no appreciable effect on drug product stability or potency [Figure 8]. For instance, for drug products with an intact enteric protective coating suitable for an acidic environment with pH values 5 or below, the proposed vehicle should not have a pH value higher than 5, since exposing the coating to higher pH values will disrupt and remove the coating from the drug product. The types of food commonly used for sprinkle administration with their pH ranges are summarized in [Figure 8]. Applesauce, yogurt, fruit juice (apple juice, orange juice, etc.), pudding, jelly/jam, ice cream, syrup, mashed potato, puree, cheese, and baby food/infant formula/nutritional supplement have all been mentioned in MR products labeled for sprinkle administration.[9] Sovaldi (Sofosbuvir) is the only drug that

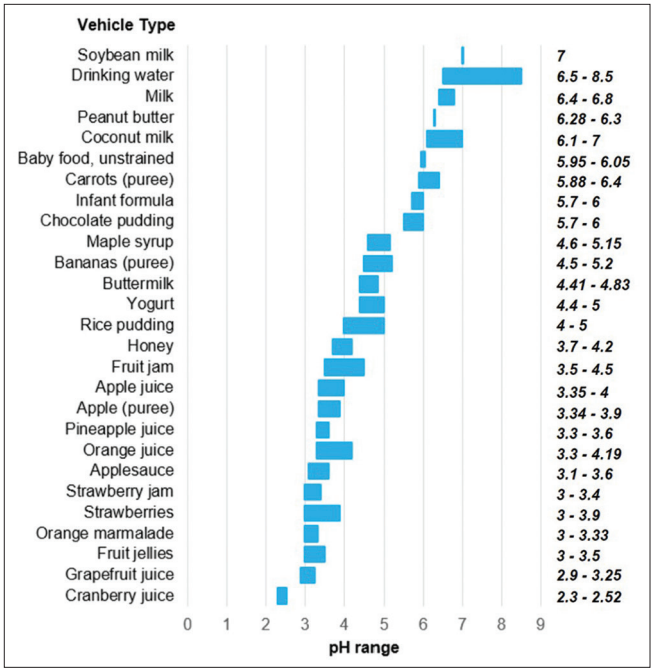

Figure 8: Food vehicles used in sprinkle administration and approximate pH ranges (Adapted from Ref. No. 9).

is indicated to be used with non-acidic soft foods (pudding, chocolate syrup, mashed potato, and ice cream), according to the applicant. Applesauce, yogurt, and fruit juice are commonly used foods for sprinkle administration.

A generic applicant referencing the same RLD is recommended to conduct an *in vivo* fasting sprinkle BE study to demonstrate that their generic product is bioequivalent to RLD when sprinkled on one of the soft foods or liquids mentioned in RLD labeling, normally applesauce. For ANDAs, recommendations for *in vivo* BE studies involving administration with liquids or soft foods are communicated to applicants through the respective PSG.

The only limitation of our study is that we did not have information on the PSG development status for the three NDAs with no published PSGs since all the data utilized in the study were extracted from the public domain.

CONCLUSION

In this analysis, we found that almost all MR RLD products approved for sprinkle administration have recommendations for sprinkle BE study in their current PSGs. These findings suggest that prospective applicants who plan to develop MR generic products should (1) explore the FDA public web page for the availability of the product-specific BE recommendations for the proposed products and (2) understand the recommended study design and follow the recommended study procedure. Using the recommendations in the PSGs, applicants can submit more complete ANDAs

that will clearly demonstrate that their generic product has no significant differences from the RLD product in all labeled routes of administration. The current PSGs should make ANDA assessments more efficient by providing more clarity to industry on study design and how to conduct *in vivo* BE studies including those involving sprinkle administration. FDA publishes new and revised PSGs describing the Agency's current recommendations on demonstrating BE. For awareness of the agency's current recommendations to demonstrate BE, applicants should monitor the regular release of new and revised PSGs in the Federal Register and on FDA Web site.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Seager H. Drug-delivery products and the zydis fast-dissolving dosage form. *J Pharm Pharmacol.* 1998;50:375-82. doi:10.1111/j.2042-7158.1998.tb06876.x
2. Suzuki, H., Onishi H, Takahashi Y, *et al*. Development of oral acetaminophen chewable tablets with inhibited bitter taste. *Int J Pharm.* 2003;251:123-132. doi:10.1016/S0378-5173(02)00595-1
3. Lee HS, Lee JJ, Kim MG, *et al*. Sprinkle formulations-A review of commercially available products. *Asian J Pharm Sci*. 2020;15:292-310. doi:10.1016/j.ajps.2019.05.003
4. Richey, RH, Hughes C, Craig J, *et al*. A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice. *Int J Pharm*. 2017;518:155-166. doi:10.1016/j.ijpharm.2016.12.032
5. Thomson SA, Tuleu C, Wong IC, *et al*. Minitablets: New modality to deliver medicines to preschool-aged children. *Pediatrics*. 2009;123:e235-8.
6. Cloyd JC, Tuleu C, Wong IC, *et al*. Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference. *J Pediatr.* 1992;20:634-638. doi:10.1016/s0022-3476(05)82496-5
7. CDER. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. Silver Spring: CDER; 2002. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/food-effect-bioavailability-and-fed-bioequivalence-studies [Last accessed on 2022 Nov 04].
8. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an Abbreviated New Drug Application; 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug [Last accessed on 2022 Oct 13].
9. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments; 2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-liquids-andor-soft-foods-vehicles-drug-administration-general-considerations-selection-and-vitro [Last accessed on 2022 Sep 09].
10. Pavloff N, Hauser TA, Williams C, *et al*. The effect of food and liquid pH on the integrity of enteric-coated beads from cysteamine bitartrate delayed-release capsules. *Drug Des Devel Ther.* 2018;12:2795-2804. doi:10.2147/DDDT.S174928
11. Wells, KA, Losin, WG. *In vitro* stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. *Clin Ther.* 2008;30:1300-1308. doi:10.1016/S0149-2918(08)80054-9
12. FDA Product-Specific Guidances for Generic Drug Development. Available from: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidancesgeneric-drug-development [Last accessed on 2022 Oct 18].
13. FDALabel Database. Available from: https://fdalabel.fda.gov/fdalabel/ui/search [Last accessed on 2022 Sep 08].

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