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A Brief Review of FDA-Approved New Drug Applications Labeled with Sprinkle Administration

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PURPOSE

Capsules and tablets are the most common dosage forms. However, pediatric and geriatric populations may have difficulty swallowing the whole solid medication [1-2]. Novel solid oral dosage forms, such as mini-tablets, chewable tablets, and sprinklable capsule formulations, are promising ways to help patients with difficulty swallowing tablets or capsules [3-4]. Sprinkle formulations are drugs that contain powders, granules, or pellets that can be easily mixed with various food vehicles prior to administration (**Figure 1**). If a drug product is approved for sprinkle administration, labeling generally includes the following: the recommended types of food vehicles, detailed vehicle use information, preparation of drug product-food vehicle mixture, and instructions for storage.

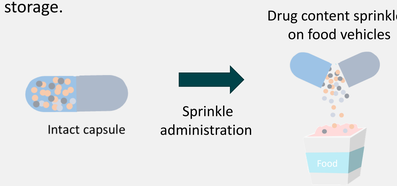

Figure 1. Schematic of general sprinkle administration method

OBJECTIVE

Currently, there are very few databases or reports that summarize sprinkle products' labeling information. The objective of the current study was to use U.S. Food and Drug Administration (FDA) public datasets to summarize FDA-approved new drug application (NDA) drug products with sprinkle administration labeling and critical information about drug substance properties, dosage forms, and sprinkle labeling information (e.g., food vehicles, drug product-food contact time).

METHODS

FDA-approved drug products (modified release and immediate release drug products) and labeling information were collected from openFDA (https://open.fda.gov/), an Application Programming Interface that makes publicly available FDA data about drugs accessible [5].

openFDA provides easily access public datasets, including drug (e.g., drug product labeling and recall enforcement report); device (e.g., classification, registrations, and listings); and food (e.g., adverse events). Since openFDA launched, there have been more than 436 million Application Programming Interface requests.

OpenFDA received approximately 45% Application Programming Interface requests for product labeling, followed by NDC directory (33%), adverse event reports (19%), Drugs@FDA (2%), and enforcement reports (1%) (**Figure 2**). The collected data from structured product labeling, drugs@FDA and NDC directory were further processed, analyzed, and visualized by Power BI (Microsoft), a business intelligence platform that provides real-time interactive analytics. Data were also categorized into "drug substance," "drug product," and "sprinkle labeling." for analysis. The openFDA drug product labeling Application Programming Interface provides data from 2009 (when labeling was posted in the Structured Product Labeling format) to present.

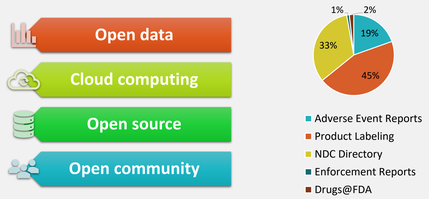

Figure 2. Overview of openFDA and Application Programming Interface requests from drug product labeling dataset (over 8.2 million requests from June 22, 2022, to July 22, 2022)

RESULTS

1. Sprinkle labeling

Currently, the sprinkle labeling is recommended to include essential information of recommended food vehicles, such as vehicles use information, preparation of the drug-vehicle mixture, and storage [6]. Information related to sprinkle administration is suggested to be discussed in the DOSAGE AND ADMINISTRATION section with a cross-reference to the CLINICAL PHARMACOLOGY section for additional details, if available [6]. The product labeling query searches for sprinkle information in different labeling sections showed that DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY are the most common sections for sprinkle-related information (**Figure 3**).

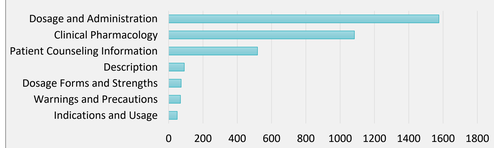

Figure 3. Labeling records matched for sprinkle information (Data source: api.fda.gov/drug/label.json)

2. A review of FDA-approved NDAs with sprinkle labeling

Filters were applied to the searchable fields (e.g., application_number: NDAs; product_type: human prescription drug; route: oral; and dosage_and_administration: sprinkle information) to extract the dataset (**Figure 4**). The analysis of the collected data showed that there are 60 human prescription drug products (NDAs) approved for sprinkle administration as of July 2022 (**Figure 5**).

results.dosage_form	results.spl_id	results.product_type	results.rou	results.market
PELLET	612d2f4-19e4-4aae-89ce-bef7bfc5cb3e	HUMAN PRESCRIPTION DRUG	ORAL	*20190828*
GRANULE, DELAYED RELEASE	c7cde07a-d242-4f4d-930c-86c0f54934af	HUMAN PRESCRIPTION DRUG	ORAL	*20120601*
CAPSULE, EXTENDED RELEASE	7b03dfec-6250-40b8-96b6-67e47a9377a1	HUMAN PRESCRIPTION DRUG	ORAL	*20050531*
TABLET, DELAYED RELEASE	f9ca9c7d-e726-4439-bafa-df0139c11b3d	HUMAN PRESCRIPTION DRUG	ORAL	*20160526*
CAPSULE, EXTENDED RELEASE	8c4180f5-acfa-486f-a7ed-f5712f0682f7	HUMAN PRESCRIPTION DRUG	ORAL	*20020605*
CAPSULE, EXTENDED RELEASE	3b27a1e2-8571-4d48-94cd-199a33329794	HUMAN PRESCRIPTION DRUG	ORAL	*20140820*
CAPSULE, EXTENDED RELEASE	69bbb7a7-deed-4c83-83ed-26b0c50beb1a	HUMAN PRESCRIPTION DRUG	ORAL	*20171109*
CAPSULE, EXTENDED RELEASE	4e2c781f-cc8a-4b97-b0d9-3dd657289708	HUMAN PRESCRIPTION DRUG	ORAL	*20071002*
CAPSULE, EXTENDED RELEASE	1ed0b4b7-fcd4-441d-a2ee-6ac7d82ed2da	HUMAN PRESCRIPTION DRUG	ORAL	*20140411*
GRANULE	adba34db-8d7e-418b-9e16-31deae47c4ab	HUMAN PRESCRIPTION DRUG	ORAL	*20170518*
CAPSULE	008fb44d-7296-4e3c-a9ad-a6e55b2033a8	HUMAN PRESCRIPTION DRUG	ORAL	*20141210*
CAPSULE, EXTENDED RELEASE	30d2428b-5fc0-4533-9490-e8283e28caf6	HUMAN PRESCRIPTION DRUG	ORAL	*20030812*
CAPSULE	86073687-f88c-4448-9abe-7b9775baeb68	HUMAN PRESCRIPTION DRUG	ORAL	*20190504*
CAPSULE, EXTENDED RELEASE	f112c189-5a07-46a6-b27a-34f5f6da9a47	HUMAN PRESCRIPTION DRUG	ORAL	*20110602*

Figure 4. Sprinkle dataset in Power BI interface

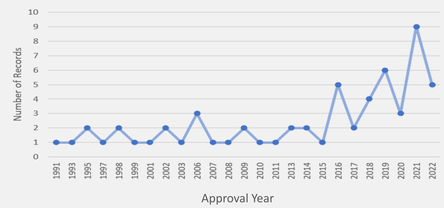

Figure 5. The trend of approved-NDAs with sprinkle labeling (Data source: api.fda.gov/drug/drugsfda.json)

2.1 Drug substances and pharmacological classes

Table 1 lists top 5 drug substances approved for sprinkle administration. Among them, the top one drug substance approved for sprinkle administration is methylphenidate hydrocholoride, a central nervous system stimulant indicated for the treatment of children with attention deficit hyperactivity disorder (ADHD), with five NDAs (METADATE CD, RITALIN LA, APTENSIO XR, JORNAY PM, and ADHANSIA XR). An estimated 6.1 million US children have been diagnosed with ADHD, including 388,000 children aged 2–5 years [7]. Of these children, about 18% were treated with medication. To help pediatric patients who can't swallow the whole medication, oral dosage forms (e.g., capsules or tablets) can be opened up or crushed and sprinkled onto various food vehicles.

2.2 Drug products: dosage forms

Powders, granules, pellets, capsules (e.g., extended-release, delayed-release), and tablets have been approved for sprinkle administration (**Figure 6**).

Table 1. Top 5 drug substances approved for sprinkle administration

Drug rank	Drug substance	Pharmacologic class	Number of approvals
1	Methylphenidate hydrochloride	Central nervous system stimulant	5
2	Cysteamine bitartrate	Cystine depleting agent	2
3	Carbamazepine	Mood stabilizer	2
4	Esomeprazole magnesium	Proton pump inhibitor	2
5	Topiramate	Decreased central nervous system disorganized electrical activity	2

Capsules can be opened and sprinkled on food vehicles. Tablets (e.g., DORYX MPC; Doxycycline) containing delayed-release pellets may also be administered by carefully breaking up the tablet and sprinkling the pellets on food vehicles. Powder products (e.g., FOSRENOL; Lanthanum carbonate) can also be sprinkled on a small quantity of soft foods and consumed immediately.

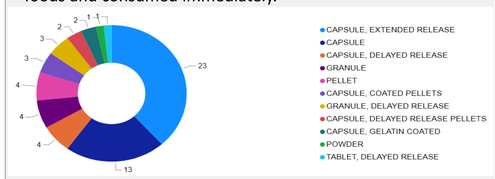

Figure 6. Dosage forms approved for sprinkle administration (Data source: api.fda.gov/drug/ndc.json)

2.3 Food vehicles

2.3.1 Food vehicle types

Food vehicles, such as applesauce, yogurt, fruit juice (apple juice, orange juice, etc.), pudding, jelly/jam, ice cream, syrup, mashed potato, puree, cheese, oatmeal, butter, baby food/infant formula, and nutritional supplements have been mentioned in the sprinkle administration labeling. It is worth noting that applesauce (49%) is the most commonly used food vehicles for sprinkle administration, followed by yogurt (11%) and pudding (10%).

2.3.2 Food-drug mixture contact time

The majority (68%) of the drug products, after being sprinkled on food vehicles, are recommended to be consumed right away. Some drug-food mixtures, if stored properly, can be used after a few hours. For example, the mixture of ALTACE (Ramipril) and soft foods can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration. CELEBREX (Celecoxib)-applesauce mixture can be kept refrigerated for up to 6 hours under refrigerated conditions (2°C to 8°C). For food-drug contact time, a two-hour stability test is recommended by current FDA guidance to ensure physical and chemical stability of the drug product-vehicle mixture if it is intended to be used immediately or within 2 hours [6].

CONCLUSIONS

A review of the essential sprinkle-related information collected from openFDA for FDA-approved NDAs with sprinkle labeling can help researchers better understand the characteristics of drug products with soft food labeling.

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