Identifying High Drug Load Solid Oral Products with Swallowing-Related Adverse Events for In Vitro Swallowability Testing

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Introduction

Difficulty swallowing solid oral dosage forms can negatively impact patient compliance and cause safety concerns. Results from a survey showed up to 4% participants discontinued treatments and 7% rejected taking pills that were hard to swallow.[1]

During generic drug development, swallowability of the test product compared to the reference listed drug (RLD) is an important safety consideration, especially for products containing high amounts of active pharmaceutical ingredient (API). These high drug load (HDL) products may present formulation challenges to generic drug developers to reduce product size to be consistent with the recommendations in the FDA Guidance for Industry "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules".[2] For the purpose of this analysis, HDL products were defined as those containing at least 1 g of API, although the total product weight can be higher.

Because currently available methods to assess swallowability (i.e., direct observation and videoendoscopy) involve human subjects,[3] there is a general need to develop reliable in vitro systems for the assessment of swallowability to limit potential safety risk from swallowability testing in human subjects. The purpose of this analysis was to identify HDL drug candidates with varying availability of swallowing-related adverse events (SrAEs), size, and shape among the RLDs and their corresponding generic drugs to serve as potential controls for validating in vitro swallowability methods in development.

Materials and Methods

A list of all approved active new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for oral tablets and capsules containing at least 1 g of API was compiled from FDA databases (as of December 2021). The information regarding these products' single largest dimension (in mm) and shape was then collected. Applications for products with alternative methods of administration (e.g., allowing to dissolve) recommended in the product labeling were excluded.

For each application that met the above criteria, clinical study reports in the development program and post-marketing reports were reviewed to collect SrAEs utilizing specific search terms as listed in Table 1. A subset of NDA products with high numbers of SrAEs were then analyzed to compare the size, shape, and availability of SrAEs to their corresponding ANDA products.

Search terms	Exclusion criteria
❑ Swallow/swallowing/swallowed ❑ Dysphagia ❑ Choke/choking/choked ❑ Split/cut/break ❑ Big/large/size ❑ Stuck ❑ Throat/(o)esophagus/(o)esophageal	❑ Pre-existing dysphagia ❑ Concurrent conditions causing swallowing difficulties

Table 1. Search terms utilized to collect SrAEs

Results

- Out of 240 approved oral tablet or capsule products containing at least 1 g of API, 31 NDA products (28 tablets, 3 capsules; 24 APIs) and 115 ANDA products (98 tablets, 17 capsules; 15 APIs) met our criteria for further analysis.
- Thirty out of 31 NDA products (96.8%) and 107 out of 115 ANDA products (93.0%) had single largest dimension larger than the 17 mm referenced in the Size and Shape Guidance.[2]
- Most NDA (85.7%) and ANDA (68.4%) tablet products were oval.
- Twenty-eight out of 31 NDA products (90.3%) and 30 out of 115 ANDA products (26.1%, 15 corresponding NDAs) had SrAE(s) reported during drug development and/or post-marketing.
- Due to the limited number of capsule products with HDL, the remainder of the results will focus on tablet products with HDL.

Results (cont.)

- Among 28 NDA tablet products with HDL, 24 products (85.7%) had at least one SrAE (Figure 1). Among 98 ANDA tablet products with HDL, 28 products (28.6%) had at least one SrAE (Figure 2).

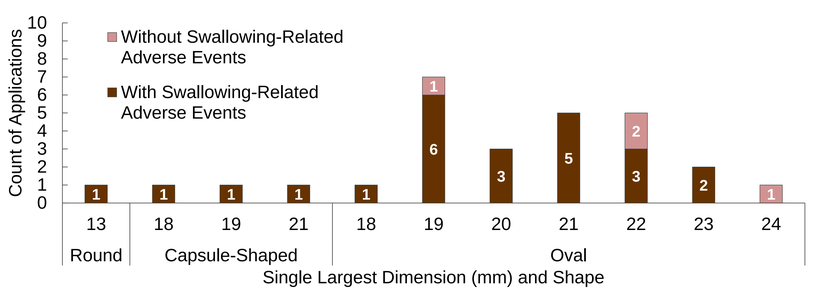

Figure 1. Availability of SrAEs by size and shape among NDA tablet products with HDL (N=28)

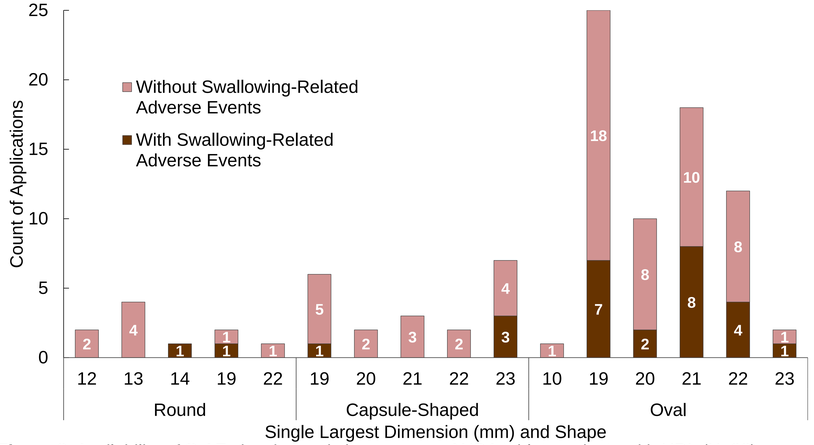

Figure 2. Availability of SrAEs by size and shape among ANDA tablet products with HDL (N=98)

- Fourteen out of 28 NDA products (50%) and 2 out of 98 ANDA products (2.04%) reported more than 10 SrAEs.

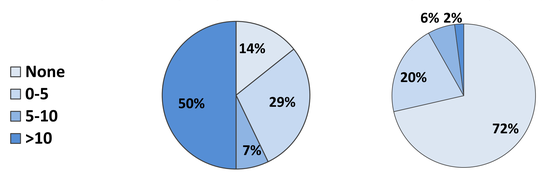

Figure 3. Number of SrAEs reported among NDA (N=28, left) and ANDA (N=98, right) tablet products with HDL

- Of the 14 NDA tablet products with more than 10 SrAEs each, three products A, B, and C, had multiple approved active ANDAs with varying availability of SrAEs reported and different largest dimensions and shapes from NDAs (Table 2).

NDA Product	Dosage Form	NDA Largest Dimension (mm)	NDA Shape	Percent of ANDAs with SrAE(s) and with > 10 SrAEs	ANDA Largest Dimension (mm)	ANDA Tablet Shape
A	Tablet	19	Oval	18.75%; 6.25%	19-23	Oval
B	Tablet	20	Oval	28.57%; 0%	13-21	Round, oval
C	Tablet	23	Oval	33.33%; 0%	19-23	Oval, capsule-shaped

Table 2. Profile of three NDA products with more than 10 SrAEs and their ANDA products

Summary of Findings & Discussions

- Based on our analysis, most drug products (>90%) with HDL (>1 g API) were relatively large in size (> 17 mm). Most tablet products were oval, which might be attributed to their shorter esophageal transit time compared to round tablets of the same weight.[1]
- The results of this analysis showed that most NDA products containing at least 1 g of API had SrAEs reported, but a relatively lower percentage of ANDA products had SrAEs reported. However, this finding might be attributed to the following factors of NDA programs and/or products: larger sample sizes, longer duration of clinical studies, different study population, multiple ANDA products per NDA product, and longer duration of availability on the market.

Conclusions

- The current analysis identified three NDA products (A, B, and C) and their corresponding ANDAs with varying availability of SrAEs, size, and shape, that could potentially serve as controls when developing and validating in vitro swallowability test methods.
- Further analyses on dispensing and sales data among NDA and ANDA products and other product characteristics (e.g., weight, volume, and coating) are warranted to identify more generalizable products for in vitro swallowability method validation.

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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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