Swallowability of Solid Oral Drug Products in Regulatory Submissions: Patient-Specific Features, Product Physical Attributes, and Clinical Swallowability Study Designs

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Background

- **Solid oral dosage forms (SODFs) are**
  - tablets, capsules, or similar drug products intended for oral use[1]
  - most common dosage forms in the market[2]
- **Swallowability is**
  - defined by U.S. Food and Drug Administration (FDA) as the "patient being able to take the drug without gagging or choking"[3]
  - a critical attribute of SODFs to ensure patient compliance and safety[4]
  - affected by factors in Fig. 1[5-9]
- **Assessing swallowability is an ongoing issue for drug developers and regulatory agencies** for reasons such as:
  - ensuring suitable formulations for pediatric patients[10-11]
  - maintaining generic drug quality by ensuring physical similarity to reference drug products[12]
  - selecting promising test formulations for further development

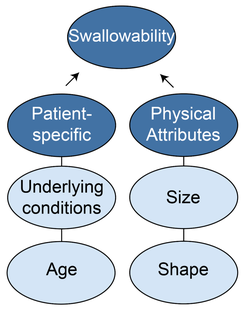


Fig. 1 Swallowability of SODFs is influenced by both patient-specific factors and physical attributes of the SODF.[5-9] Examples are included in the diagram.

Problems and Objectives

The problems:

1) Features of SODFs that may predict swallowability issues arising during the regulatory process are uncertain.
2) No standard methods for assessing swallowability of SODFs are available.

The objectives:

1) To identify any commonalities in patient-specific features or physical attributes of SODFs with swallowability issues in regulatory submissions.
2) To determine common practices in approaches taken to assess swallowability in regulatory submissions.

Methods

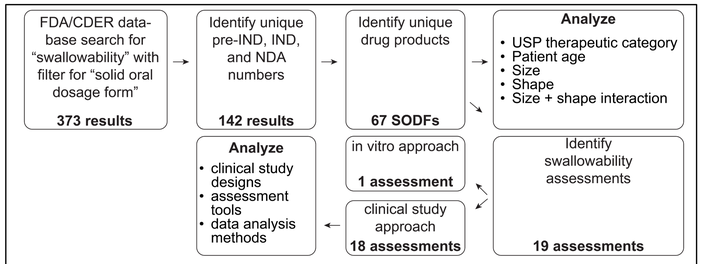


Fig. 2: Schematic of methodology to identify SODFs where the topic of swallowability was raised in regulatory communications and to identify swallowability assessments. (CDER- Center for Drug Evaluation and Research, IND- Investigational New Drug Application, NDA- New Drug Application, USP- U.S. Pharmacopeia)

- An internal database with documents dating back to January 1, 2014, was searched to identify drug products where swallowability issues were raised in their regulatory communications as described in Fig. 2.
- The search yielded a variety of documents (i.e., internal meeting minutes, communications between the Agency and industry, study plans, and study reports) that were individually reviewed.
- Information from the documents and the regulatory submission package(s) were analyzed as described in Fig. 2.

Results

Patient-specific Features

Underlying conditions

Table 1: U.S. Pharmacopeia (USP) therapeutic categories of 67 SODFs with swallowability issues in regulatory submissions. "Other" combines USP categories with only one SODF.

USP Therapeutic Category	Tally (n=67)	USP Therapeutic Category	Tally (n=67)
Blood Glucose Regulators	15 (22%)	Antipsychotics	3 (4%)
Antivirals	14 (21%)	Central Nervous System	3 (4%)
Analgesics	5 (7%)	Immunological	2 (3%)
Gastrointestinal Agents	5 (7%)	Genetic, Enzyme, or Protein Disorder	2 (3%)
Inflammatory Bowel Disease	5 (7%)	Cardiovascular	2 (3%)
Respiratory Tract/Pulmonary	3 (4%)	Other	8 (12%)

- Most SODFs were blood glucose regulators (22%).
- None were indicated for patients experiencing diseases complicated by dysphagia.

Age

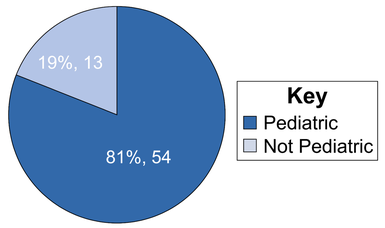


Fig. 3: Swallowability issues in regulatory submissions can be divided based on whether they were related to pediatric suitability concerns (n=67).

- Swallowability in pediatric patients was an issue for 81% of SODFs.

Product Physical Attributes

Size

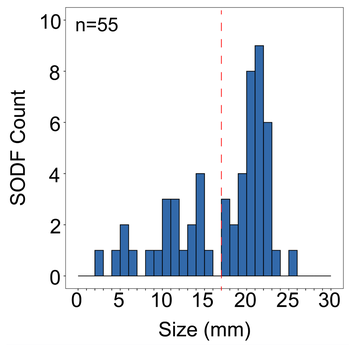


Fig. 4: Histogram showing the frequency of the sizes of SODFs where the topic of swallowability was raised. The size of an SODF is the length of the single largest dimension. The red dashed line indicates a cutoff of 17 mm. SODFs greater than or equal to 17 mm in length were considered large.[12] Size data were available for 55 of 67 SODFs.

- The majority of SODFs (62%) were large in size (≥ 17 mm based on FDA guidance).[12]

Shape

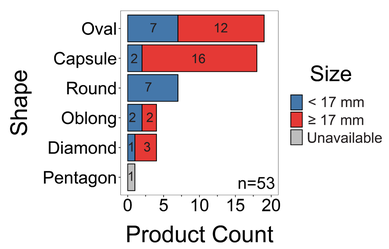


Fig. 5: Frequency of the shapes of the SODFs where the topic of swallowability was raised broken down by size. Data were available for 53 of 67 SODFs.

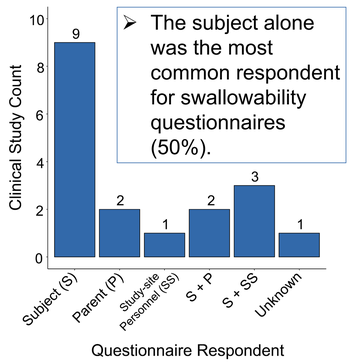
- SODFs were most commonly oval or capsule in shape (70%).
- Most large SODFs (≥17 mm in size)[12] were oval or capsule in shape (85%).
- No large SODFs were round in shape.

Clinical Swallowability Study Designs

Table 2: Comparison of clinical swallowability study designs for SODFs where swallowability issues were raised in regulatory submissions with common practices identified.

Study Component		Tally (n=18)	Common Practice?
Target population	Adult healthy volunteer	2 (11%)	Enrolling pediatric patients
	Adult patients	1 (6%)	
	Pediatric healthy volunteer	2 (11%)	
	Pediatric patients	13 (72%)	
Endpoint assessing swallowability	Primary	4 (22%)	Not primary endpoint
	Secondary	6 (33%)	
	Exploratory	3 (17%)	
	Uncategorized	2 (11%)	
	Not a stated endpoint	3 (17%)	
SODF swallowed	Active drug product	8 (44%)	Unclear
	Matching placebo only	6 (33%)	
	Both	4 (22%)	
SODF administrations	Single	10 (56%)	Unclear
	Multiple	8 (44%)	
Swallowability assessment tool administrations	Single	9 (50%)	Unclear
	Multiple	9 (50%)	
Assessment tool	Questionnaire	18 (100%)	Use questionnaire

- Clinical swallowability study designs exhibited trends and inconsistencies.



- The subject alone was the most common respondent for swallowability questionnaires (50%).

Fig. 6: Frequency of the respondents for questionnaires in clinical swallowability studies (n=18)

Table 3: Top 3 questions on questionnaires by respondent.

	Question	Subject	Parent	Study-site
1	**Swallowability**	14	3	2
2	**Palatability**	8	2	n/a
3	**Acceptability**	6	n/a	n/a

Results continued

Clinical Swallowability Study Designs Continued

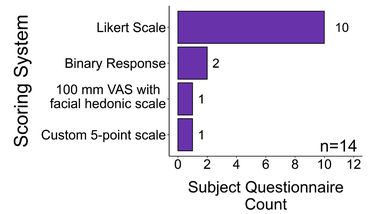


Fig. 7: Frequency of the scoring systems used by subjects to respond to the top question about swallowability on questionnaires (n=14). (VAS- Visual Analog Scale)

- Subjects used Likert scales to score their swallowing experience.

Table 4: Data analysis approach for questionnaires with common practices identified.

Approach		Tally (n=18)	Common Practice?
Dichoto-mization	Yes	11 (61%)	Dichotomize data
	No	4 (22%)	
	Unknown	3 (17%)	
Statistics	Descriptive	12 (67%)	Use descriptive statistics
	Advanced	2 (11%)	
	Unknown	4 (22%)	

- Questionnaire responses were often dichotomized (61%) for analysis.
- Basic descriptive statistics (e.g., frequency of responses, averages, etc.) were used to analyze the data (67%).

Conclusions

1) Primary features leading to swallowability issues for SODFs in regulatory submissions include
   - patient-specific features like pediatric suitability
   - physical attributes of large size and oval or capsule shape
2) Common practices were identified for clinical swallowability study components with trends; however, common practices could not be identified for those study components with no clear trend.

Discussion

1) The identification of features leading to swallowability issues in regulatory submissions can
   - inform drug developers to avoid swallowability issues
   - allow FDA to more efficiently review SODFs with similar features
2) The significant and substantial variations in clinical swallowability study design may affect the swallowability measurement obtained because of
   - sample size
   - questionnaire design
   - learning effect in swallowing
   - quality of a placebo
   - reliability of a respondent
   - properties of a response scale
   - data analysis approach

Altogether, there remains a need for developing standardized designs, validated assessment tools, and quality assurance for clinical swallowability assessments.

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