Guidance for Industry

Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Generics

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I. INTRODUCTION

Tablets and capsules are widely manufactured and prescribed and may provide a number of advantages over other dosage forms, including ease of storage, portability, ease of administration, and accuracy in dosing.

While generic formulations of these drug products are required to be both pharmaceutically and therapeutically equivalent to a reference listed drug (RLD),[2] we are concerned that differences in physical characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors. We believe these patient safety concerns are important, and we are recommending that generic drug manufacturers consider physical attributes when they develop quality target product profiles (QTPPs) for their generic product candidates.

The recommendations in this guidance apply to abbreviated new drug applications (ANDAs) and their supplements for additional strengths that are submitted to the Office of Generic Drugs (OGD).

This guidance does not apply to approved ANDAs (generic drugs) already on the market.[3] However, if the Agency determines that an approved product should be modified because the size or shape of a product poses a risk to public health, we will notify the holder of the ANDA.

[1] This guidance has been prepared by the Office of Generic Drugs in the Office of Pharmaceutical Science in CDER.

[2] *Reference listed drug* means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. See 21 CFR 314.3(b). FDA publishes the identification of RLDs in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (i.e., Orange Book).

[3] If the manufacturer of a RLD makes a postapproval change to the size or shape of a previously approved tablet or capsule, the generic versions generally will not need to be modified. However, the Agency could ask for modifications to the product if there are safety reasons.

This guidance does not discuss other oral dosage forms (e.g., chewable tablets, oral tablets for suspension/solution, orally disintegrating tablets, sublingual tablets, troches, gums).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Differences in Size and Shape of Tablets and Capsules between a Reference Listed Drug and a Drug Product Subject to an Abbreviated New Drug Application

1. Size

Difficulty swallowing tablets and capsules can be a problem for many individuals and can lead to a variety of adverse events and patient noncompliance with treatment regimens. It is estimated that over 16 million people in the United States have some difficulty swallowing, also known as dysphagia.[4,5] For these individuals, swallowing a tablet or a capsule can be particularly challenging. A survey of adults on difficulties swallowing tablets and capsules suggests that this problem goes well beyond the patient population with clinically recognized dysphagia and may affect as many as 40 percent of Americans. Of those who experience difficulty swallowing medication, less than a quarter discuss the problem with a health care professional, 8 percent admit to skipping a dose of prescribed medication, and 4 percent have discontinued therapy because the tablets and/or capsules were difficult to swallow.[6] Individuals who find it difficult to swallow tablets and capsules frequently blame the size.[7,8]

Size and shape of tablets and capsules affect the transit of the product through the pharynx and esophagus and may directly affect a patient's ability to swallow a particular drug product. Larger tablets and capsules have been shown to prolong esophageal transit time. This can lead to disintegration of the product in the esophagus and/or cause injury to the esophagus, resulting in pain and localized esophagitis and the potential for serious sequelae including ulceration,

[4] Agency for Health Care Policy and Research, March 1999, Diagnosis and Treatment of Swallowing Disorders (Dysphagia) in Acute-Care Stroke Patients. Summary, Evidence Report/Technology Assessment: Number 8.
[5] Robbins J et al., August 21, 2001, July/August 2002, Dysphagia Research in the 21st Century and Beyond: Proceedings From Dysphagia Experts Meeting, Journal of Rehabilitation Research and Development, 39 No. 4, 543-548.
[6] Harris Interactive Inc. for Schwarz Pharma, 2003, Pill-Swallowing Problems in America: A National Survey of Adults. 1–39.
[7] See footnote 4.
[8] Bhosle M, Benner J, DeKoven M, Shelton J., 2009, Difficult to Swallow: Patient Preferences for Alternative Valproate Pharmaceutical Formulations. Patient Prefer Adherence 3, 161-171.

stricture, and perforation.[9,10] Other adverse events such as pain, gagging, choking, and aspiration are related to swallowing difficulties in the oropharyngeal phase of swallowing and increasingly occur at larger tablet and capsule sizes.[11,12]

Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties at tablet sizes greater than approximately 8 mm in diameter.[13,14,15] The size of the tablet or capsule influences esophageal transit, irrespective of patient factors and administration techniques (i.e., use of fluids, patient position). Smaller tablets generally have been shown to have significantly faster transit times in these studies. Channer and Virjee specifically compared the transit time of 8 mm diameter round tablets to 11 mm diameter round tablets and 14 mm x 9 mm oval tablets and found the transit times for the 8mm round tablet to be significantly shorter than for 11 mm round and 14 mm oval tablets ($p<.02$ and $p<.04$, respectively).[16] In addition, significantly more patients were aware of the larger round tablets (>8 mm) sticking in the esophagus compared with the 8 mm round tablets.[17] Although there has been less research quantifying the effects of size difference on the oropharyngeal phase of swallowing, increasing tablet or capsule size is believed to correlate with increasing difficulty with oropharyngeal transfer.

2. Shape

For any given size, certain shapes may be easier to swallow than others. In vitro studies suggest that flat tablets have greater adherence to the esophagus than capsule-shaped tablets.[18] Studies in humans have also suggested that oval tablets may be easier to swallow and have faster esophageal transit times than round tablets of the same weight.[19,20] Patient compliance with medication regimens may be influenced by the size and shape of a tablet or capsule.

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[9] Drug and Therapeutics Bulletin, 1981; Tablets and Capsules that Stick in the Oesophagus, 19(9), 33-34.
[10] Channer, K, Virjee, JP. 1986, The Effect of Size and Shape of Tablets on their Esophageal Transit. Journal of Clinical Pharmacology, 26, 141-146.
[11] Kelly J, D'Cruz G, Wright D, 2010, Patients with Dysphagia: Experiences of Taking Medication. Journal of Advanced Nursing 66(1), 82-91.
[12] Jackson LD, Little J, Kung E, Williams EM, Siemiatkowska K, Plowman S, 2008, Safe Medication Swallowing in Dysphagia; A Collaborative improvement Project. Healthcare Quarterly 11, 110-116.
[13] See footnote 10.
[14] Wamberg T., Jorgensen, F., Hasselbalch, H., Hey, H., 1983, The Prejudgement of the Esophageal Transfer of Tablets and Capsules. Archiv der Pharmazie Chemistry in Life Sciences, Ed. 11, 24-31.
[13] Brotherman, DP,. Bayraktaroglu, T.O., Garofalo, R.J., 2004, Comparison of Ease of Swallowing of Dietary Supplement Products for Age-Related Eye Disease. Journal of American Pharmacists Association, 44, 587-593.
[16] See footnote 10.
[17] Ibid.
[18] Marvola M., Rajaniemi M., Marttila E., Vahervuo K., Sothmann A., 1983, Effect of Dosage Form and Formulation Factors on the Adherence of Drugs to the Esophagus. Journal of Pharmaceutical Sciences 72(9), 1034-1036.
[19] See footnote 10.
[20] Hey H., Jorgensen F., Sorensen K., Hasselbelch H., Wamberg T., 1982, Esophageal Transit of Six Commonly used Tablets and Capsules. British Medical Journal 285, 1717-1719.

3. Patient Factors

A variety of other factors may affect a patient's ability to swallow a tablet or a capsule. For example, age could be a factor. Children and adolescents, as well as the elderly, are more likely to have difficulty swallowing tablets or capsules. Body position, fluid intake, and the presence of certain medical conditions (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease) may also affect a patient's ability to swallow tablets and capsules.

The Agency recognizes that a variety of factors may affect the ability of a patient to swallow a tablet or capsule. Although not all patient factors can be addressed through pharmaceutical design and manufacture, the physical characteristics of a product can be. These characteristics influence the ability of certain patients to swallow the product, particularly in vulnerable populations. We believe that tablets and capsules can be effectively developed and manufactured to minimize swallowing difficulties, which can encourage and improve patient compliance with medication regimens. FDA recommends that applicants design and develop generic drugs with this in mind.

B. Other Physical Attribute Considerations

The presence and composition of a coating can also potentially affect the ease of swallowing tablets or capsules. The lack of a film coating can increase the risk of tablet arrest compared with a coated tablet of the same size and shape. Coating also can affect other factors that contribute to patient acceptance, such as palatability and smell.

The weight of the tablet or capsule also may affect transit time, with heavier tablets or capsules having faster transit times compared to similarly-sized, lighter tablets or capsules. Surface area, disintegration time, and propensity for swelling when swallowed are additional parameters that can influence esophageal transit time and have the potential to affect the performance of the drug product for its intended use. These physical attributes should also be considered when developing a QTPP for generic drug products intended to be swallowed intact.

III. RECOMMENDATIONS

The recommendations in this guidance are based on published literature regarding patient experiences swallowing tablets and capsules and Agency experience with NDAs and ANDAs submitted for oral tablets and capsules.

A. Size

For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the Agency recommends that generic oral tablets and capsules intended to be swallowed intact should be of a similar size to their corresponding RLD. The Agency recommends limiting size differences between therapeutically equivalent tablets as follows:

- If the RLD is less than or equal to 17 mm in its largest dimension,[21] the generic product should be no more than 20 percent larger than the RLD in any single dimension (the resulting dimension not to exceed 17 mm) and no more than 40 percent larger than the RLD in volume.[22]

- If the RLD is greater than 17 mm in its largest dimension, the generic product should be no larger than the RLD in any single dimension or in volume.

- We recommend that the largest dimension of a tablet or capsule should not exceed 22 mm and that capsules should not exceed a standard 00 size.[23]

Additional flexibility may be given for products that are 8 mm or smaller in their largest dimension, but efforts should be made to develop tablets and capsules that are of a similar size and shape to the RLD.

Under the standard capsule size convention (see Attachment), the allowances described above will generally allow an increase of one capsule size, when the RLD capsule is of size 3 or smaller. When the RLD capsule is of size 2 or larger, an increase of one capsule size should only be considered when adequate justification can be provided for the size increase. These recommendations would allow an increase of one capsule size when the capsule size is less than capsule size 00 (refer to the Attachment).

The Agency recognizes that two drug products may have different recommended upper size limits, but size should be considered as part of a single product risk/benefit profile. When establishing therapeutic equivalence, the applicant should compare their generic product only to the RLD.

B. Shape

In addition to the size recommendations described above, we recommend manufacturing tablets and capsules that have a similar shape or have a shape that has been found to be easier to swallow compared with the shape of the RLD. Evaluating and comparing the largest cross sectional areas of the RLD and generic product is one strategy to quantify changes in shape.[24] Tablets and capsules that have a larger cross sectional area (e.g., tablets that are rounder) would generally be more difficult to swallow than tablets or capsules of the same volume but with smaller cross sectional areas.

If a tablet or capsule intended to be swallowed intact differs from the criteria recommended in this guidance document, then the applicant should contact OGD before establishing the QTPP.

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[21] The largest dimension refers to the length of oval or capsule shaped tablets or the diameter of round tablets.

[22] For the purposes of this guidance, volume refers to the volume occupied by the tablet or capsule.

[23] An internationally accepted numbering system for capsule sizes is used in approved U.S. drug products. A table of typical size specifications under this system is provided in the Attachment.

[24] For the purposes of this guidance, the largest cross sectional area is defined by the largest cross sectional area of the tablet that lies in a plane perpendicular to the longest axis of the tablet. If the shape of tablet is unconventional (e.g., pentagon, triangle, diamond, heart, etc.), then the largest cross sectional area will be defined as the area of the smallest circle, oval, or ellipse that would completely enclose this largest cross sectional shape.

There are a variety of techniques that may be used to determine the volume measurements of a tablet or capsule, including use of pycnometers, or calculations based on physical measurements of the tablet or die used to produce the tablet. For the purpose of this guidance, spatial imaging and/or the use of computer models is recommended, because they are accurate and applicable to a variety of shapes, although other appropriately validated methods may be used if properly justified.

The size of a tablet or capsule should be provided in the common technical document (CTD) format,[25] section 3.2.P.1, *Description and Composition of the Drug Product* of the ANDA. Any studies and/or related information should be provided in the CTD section, 5.3.1.2, *Comparative Bioavailability and Bioequivalence Study Reports.* The Agency may request samples for evaluation of the physical attributes of a tablet or capsule.

C. Other Physical Attributes

Other physical attributes of tablets and capsules should be considered in the context of their effect on ease of swallowing. For example, tablet coating, weight, surface area, disintegration time, and propensity for swelling should be considered when developing a QTPP for generic tablets.

Description of these physical characteristics should be provided in the CTD section 3.2.P.1, *Description and Composition of the Drug Product* of the ANDA. Any studies to support sizes outside the recommendation provided in this guidance should be provided in the CTD section 3.2.P.2, *Pharmaceutical Development* or CTD section 3.2.P.5.6, *Justification of Specifications.*

D. Biowaivers

A biowaiver (i.e., the waiver of in vivo bioequivalence data) for additional strengths of a solid oral dosage form is generally granted if it meets one of the criteria set forth in the regulations,[26] one of which is proportional similarity between strengths in active and inactive ingredients. Compositional proportionality may be particularly relevant when considering tablet size and tablet formulation for other strengths (both lower and higher) of the same dosage form to be considered for a waiver of the in vivo bioequivalence study requirement. Although compositional proportionality may exist when all active and inactive ingredients are in the same proportion between different strengths, other methods of achieving compositional proportionality may be more amenable to maintaining appropriate tablet sizes for generic products when compared with the RLD. A detailed description of how the Agency defines proportional similarity can be found in the *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*.[27]

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[25] See ICH guidance for industry *M4Q: The CTD — Quality*. It is available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under International Conference on Harmonisation – Quality.

[26] See 21 CFR 320.22(d).

[27] This guidance is available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Biopharmaceutics.

FDA recommends that applicants consider Agency published guidance, product specific guidance,[28] and relevant regulations[29] on the waiver process when designing and formulating other strengths of the same dosage form that will be studied with bioequivalence studies. For specific questions related to biowaivers, you should contact the appropriate review division within OGD.

[28] This guidance is available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Bioequivalence Recommendations for Specific Products.

[29] See 21 CFR 320.22.

Attachment

Standard sizes of two-piece capsules (Domestic Supplier)

Size	Volume (ml)	Locked length (mm)	External diameter (mm)
5	**0.13**	**11.1**	**4.91**
4	**0.21**	**14.3**	**5.31**
3	**0.3**	**15.9**	**5.82**
2	**0.37**	**18**	**6.35**
1	**0.5**	**19.4**	**6.91**
0	**0.68**	**21.7**	**7.65**
0E	**0.7**	**23.1**	**7.65**
00	**0.95**	**23.3**	**8.53**
000	**1.37**	**26.14**	**9.91**
13	**3.2**	**30**	**15.3**
12	**5**	**40.5**	**15.3**
12el	**7.5**	**57**	**15.5**
11	**10**	**47.5**	**20.9**
10	**18**	**64**	**23.4**
7	**24**	**78**	**23.4**
Su07	**28**	**88.5**	**23.4**