Guidance for Industry

Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Guidance for Industry[1]
Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

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I. INTRODUCTION

This guidance provides recommendations to sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding what criteria should be met to facilitate the evaluation and labeling of tablets that have been scored. (A scoring feature facilitates the practice of tablet splitting.[2]) Specifically, this guidance recommends:

- Guidelines to follow, data to provide, and criteria to meet and detail in an application to approve a scored tablet.
- Nomenclature and labeling for approved scored tablets.

This guidance does not address specific finished-product release testing, where additional requirements may be appropriate for scored tablets.

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

The Agency has previously considered tablet scoring as an issue when determining whether a generic drug product is the same as the reference listed drug (RLD).[3] One characteristic of a tablet dosage form is that it may be manufactured with a score or scores. This characteristic is

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] A score is a debossed line that runs across the planar surface of the tablet, while tablet splitting is the practice of breaking or cutting a higher-strength tablet into smaller portions.
[3] See the Manual of Policies and Procedures on *Scoring Configuration of Generic Drug Products* (5223.2), November 1, 1995.

useful because the score can be used to facilitate the splitting of the tablet into fractions when less than a full tablet is desired for a dose. Although there are no standards or regulatory requirements that specifically address scoring of tablets, the Agency recognizes the need for consistent scoring between a generic product and its RLD.

Consistent scoring ensures that the patient is able to adjust the dose, by splitting the tablet, in the same manner as the RLD. This enables the patient to switch between products made by different manufacturers without encountering problems related to the dose. In addition, consistent scoring ensures that neither the generic product nor the RLD has an advantage in the marketplace because one is scored and one is not.

CDER's Drug Safety Oversight Board considered the practice of tablet splitting at its October 2009 and November 2010 meetings.[4] During those meetings, they discussed how insurance companies and doctors are increasingly recommending that patients split tablets, either to adjust the patients' dose or as a cost-saving measure.[5] Because of this, the Agency conducted internal research on tablet splitting and concluded that in some cases, there are possible safety issues, especially when tablets are not scored or evaluated for splitting. The Agency's concerns with splitting a tablet included variations in the tablet content, weight, disintegration, or dissolution, which can affect how much drug is present in a split tablet and available for absorption. In addition, there may be stability issues with splitting tablets.[6,7]

Tablet splitting also is addressed in pharmacopeial standards. The European Pharmacopeia (EP) currently applies accuracy of subdivision standards for scored tablets—and has at various times also included standards for content uniformity, weight variation, and loss of mass—while the United States Pharmacopeia published a Stimuli article in 2009 proposing criteria for loss of mass and accuracy of subdivision for split tablets.[8]

III. DISCUSSION

As an outgrowth of these discussions and developments, we are providing recommendations for application content regarding the scientific basis for functional scores on solid oral dosage form products to ensure the quality of both NDA and ANDA scored tablet products. To accomplish

[4] Public summaries of the Drug Safety Oversight Board meetings are available at www.fda.gov/AboutFDA/CentersOffices/CDER/ucm082136.htm.

[5] It should be noted that FDA considers tablet splitting to be manufacturing under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Therefore, establishments that engage in tablet splitting must register with FDA and comply with the Agency's current good manufacturing practice (CGMP) regulations in 21 CFR parts 210 and 211. Furthermore, unless the tablet splitting is conducted pursuant to the drug product's approved labeling, the resultant split drugs are considered new drugs under the FD&C Act and, therefore, require an approved new drug application before they may be introduced into interstate commerce. However, we intend to exercise enforcement discretion and generally would not object to tablet splitting if it is performed by a pharmacist pursuant to a valid prescription for an individually identified patient.

[6] Na Zhao et al., 30 November 2010, 401(1-2), "Tablet Splitting: Product quality assessment of metoprolol succinate extended release tablets," *International Journal of Pharmaceutics.*

[7] Rakhi Shah et. al., 26 August 2010, "Tablet Splitting of a Narrow Therapeutic Index Drug: A Case with Levothyroxine Sodium," *AAPS PharmSciTech*.

[8] Geoff Green et al., November-December 2009, 35(6), "Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets," *Pharmacopeial Forum*.

this, we have developed consistent and meaningful criteria by which scored tablets can be evaluated and labeled by (1) providing a harmonized approach to chemistry, manufacturing, and controls (CMC) reviews of scored tablets; (2) ensuring consistency in nomenclature (e.g., score versus bisect) and labeling; and (3) providing information through product labeling or other means to healthcare providers.

A. Guidelines and Criteria

Below are guidelines and criteria by which a scored tablet's characteristics will be evaluated as part of the review process:

1. The dosage amount meant to be achieved after splitting the tablet should not be below the minimum therapeutic dose indicated on the approved labeling.

2. The scored dosage form should be safe to handle and not pose risk of unintended drug exposure (e.g., teratogenic, chemotherapeutic, hormones).

3. Modified release products for which the control of drug release can be compromised by tablet splitting (e.g., tablets controlled by an osmotic pump system or an exterior film coat) should not have a scoring feature.

4. The split tablet, when stored in standard high-density polyethylene pharmacy bottles and caps (no seal), should meet established stability requirements for a period of 90 days at 25º C, plus or minus 2º C/60 percent Relative Humidity (RH), plus or minus 5 percent RH.

5. The split tablet portions should meet the same finished-product testing requirements as for a whole-tablet product with equivalent strength. A risk assessment should be provided to justify the tests and criteria for product with the proposed functional score. The resulting data should be provided to the Agency for evaluation. The assessment should be undertaken on both tablets that are split nonmechanically (by hand) and tablets that are split mechanically (with a tablet splitter). Any recommended dissolution test data must be generated on a minimum of 12 individual split tablet portions.

   Below are the typical criteria, by dosage form, that should be assessed during Pharmaceutical Development (3.2.P.2.) of NDAs and ANDAs and during primary/exhibit stability batches and scale-up. As indicated above, a risk assessment should be performed to justify criteria for each product.

   a. Immediate Release Solid Oral Dosage Forms

   - USP <905> Uniformity of Dosage Units - Testing for Weight Variation is permitted for split tablet portions intended to contain 25 mg or more of a drug substance that comprises 25 percent or more (by weight) of the split tablet portion. Otherwise, the test for Content Uniformity should be used.

- Tablet splitability at both ends of the proposed hardness range should be demonstrated by:

    1. Ensuring a loss of mass of less than 3.0 percent.

    2. Confirming that the split tablet portions meet the USP Friability requirement.

- Dissolution data on split tablet portions should meet finished-product release requirements.

b. Modified Release Solid Oral Dosage Forms (Using Matrix Technology)

- All above criteria under section III.A.5.a should be met.

- Dissolution should be demonstrated at both ends of the hardness range.

- Dissolution on whole versus split tablet portions should meet the similarity factor (f2) criteria.[9]

c. Modified Release Solid Oral Dosage Forms (Using Compressed Film Coated Components)

- All above criteria under sections III.A.5.a and III.A.5.b should be met.

- Dissolution profile on pre-compressed beads versus post-compressed whole and split tablet portions should meet similarity factor (f2) criteria to ascertain the integrity of beads during compression.

6. The scored tablet should be tested using the indicated patient population to ensure patients can split the tablet correctly, as labeled.

[9] See the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

7. Scoring configuration of generic drug products should be the same as the RLD.[10]

   - Where the scoring configuration is protected by patent, contact the Office of Generic Drugs for guidance.

   - For scoring configurations proposed for abbreviated applications that were accepted through the suitability petition process, contact the Office of Generic Drugs for guidance.

8. New study data on tablet splitability should be provided during the postapproval period for any product changes at Level 2 and Level 3 as defined in the Agency's Scale-up and Post-Approval Changes (SUPAC) guidances.[11]

B. Nomenclature and Product Labeling

New products that meet the above-referenced criteria can be labeled as having a *functional score.* Such labeling should appear in all of the following sections of the prescribing information[12]:

- "Dosage Forms and Strength" section of the Highlights.
- "Dosage Forms and Strength" section of the Full Prescribing Information.
- "How Supplied" section of the Full Prescribing Information.

This information should also be included in the patient package insert or medication guide. New products that do not meet the criteria, and therefore are not approved by FDA, should not have a scoring feature or any reference to scoring (including language such as bisected, etc.) in the labeling.

For currently marketed products, manufacturers have the option to perform such an assessment and provide data for evaluation to the drug product application. Product labeling should be updated to state that it has a functional score. In this way, the use of the term *functional score* in the labeling can communicate to healthcare providers that the product has been evaluated against the established criteria.

[10] See the Manual of Policies and Procedures on *Scoring Configuration of Generic Drug Products* (5223.2), November 1, 1995, for information on what should happen if a change is made to the RLD.
[11] Go to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm for a listing of all SUPAC guidances.
[12] See 21 CFR 201.57(a)(8) and 201.57(c)(4)(ii).