Guidance for Industry

Size of Beads in Drug Products Labeled for Sprinkle

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

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Contains Nonbinding Recommendations

TABLE OF CONTENTS

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I. INTRODUCTION

This guidance provides applicants preparing or submitting new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics licensing applications (BLAs) the Center for Drug Evaluation and Research's current thinking on appropriate size ranges for beads[2] in drug products that are labeled to be administered via sprinkling (e.g., capsules or packets containing beads).

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

Certain drug products that contain beads within a capsule indicate in the labeling that the capsule can be broken and the internal beads can be sprinkled on soft foods and swallowed without chewing as an alternative administration technique. This is particularly common with drug products designed to have extended- or delayed-release characteristics (i.e., the beads are manufactured to release the drug product at different rates). To make certain that the intended product performance is achieved—whether from a capsule that has been broken or from a packet containing beads—it is important to have reasonable assurance that the patient will be able to swallow the beads (uncrushed) with the food with which the beads are mixed without stimulating the urge to chew. Additional assurances may be needed when the label also includes specific language concerning alternate administration via an enteral feeding tube.

[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] For the purposes of this guidance, the term *beads* will be used to describe the component particles in drug products labeled for sprinkle (i.e., beads, granules, pellets, sprinkles, particles, mini-tablets).

III. DISCUSSION

The recommendations in this guidance are based on literature on chewing and swallowing particle size and on Agency experience with NDAs and ANDAs submitted for these dosage forms. This guidance provides the following information related to drug products labeled for sprinkle: (1) appropriate maximum size for the beads, (2) special considerations for sprinkle drug products that include language in labeling concerning alternate administration via an enteral feeding tube, and (3) bioavailability or bioequivalence recommendations.

A. Maximum Bead Size for Drug Products Labeled for Sprinkle

To determine an appropriate maximum bead size, the Agency took two actions. First, the Agency reviewed studies of human mastication, which demonstrated that food is chewed to a median particle size range from 0.82 to 3.04 mm before swallowing.[3,4] Second, we examined currently approved drug products labeled for sprinkle that contain beads up to 2.4 mm and found no recognized safety risks or loss of efficacy associated with the bead size.

Based on this information, the Agency recommends a target bead size up to 2.5 mm with no more than 10 percent variation over this size, to a maximum size of 2.8 mm. The recommended bead size allowances consider the variability and differing manufacturing processes of beads (e.g., pellet versus mini-tablet manufacturing). If the proposed bead size is greater than that recommended in this guidance, the applicant should provide justification for the proposed bead size, including studies demonstrating that the bead can be swallowed without chewing using sprinkle administration in the intended population.

The Agency recognizes the specific importance of a maximum size limit for modified-release products, where unintentional chewing of beads may lead to pharmacokinetic differences, but also believes that maintaining a consistent maximum bead size for all drug products labeled for sprinkle is appropriate. Inadvertently chewing beads labeled for sprinkle may lead to noncompliance with taking medication because of taste, safety issues, and decreased drug product efficacy. The target and maximum bead size recommendations thus apply to all drug products that contain particles that are labeled for sprinkle administration, whether the product has immediate-, delayed-, or extended-release characteristics. Target and maximum bead size, including bead size distribution, can be determined through analytical sieving in accordance with USP <786>[5] or other appropriately validated methods.

The bead size distribution can be provided in the 3.2.P.3.3 (Description of Manufacturing Process and Process Controls) section or 3.2.P.5.1 (Specification) section, and the maximum bead size can be provided in the 3.2.P.1 (Description and Composition of the Drug Product) section or 3.2.P.3.4 (Control of Critical Steps and Intermediates) section of a common technical document (CTD) formatted application.

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[3] Jalabert-Malbos, M.L., Mishellany-Dutour, A., Woda, A., and Peyron, M.A., 2007, "Particle size distribution in the food bolus after mastication of natural foods," *Food Quality and Preference*, 18, 803-812.

[4] Peyron, M.A., Mishellany, A., and Woda, A., 2004, "Particle size distribution of food boluses after mastication of six natural foods," *Journal of Dental Research*, 83(7), 578-582.

[5] See USP <786> *Particle Size Distribution Estimation by Analytical Sieving.*

This recommendation applies only to NDAs, ANDAs, and BLAs for products that are not yet approved. Sponsors of currently approved NDAs, ANDAs, or BLAs for products that contain beads that do not meet the recommended limits in this guidance need not modify their product specifications, unless there is reason to believe that an individual product poses a particular risk to public health because of its bead size.

An ANDA that references a currently approved reference listed drug (RLD) that exceeds the recommended limits in this guidance may propose a target and maximum bead size equal to or less than that used in the currently approved RLD. If the proposed target and/or maximum bead size is greater than that used in the currently approved RLD, the applicant should provide justification for the proposed bead size, as described above. If the ANDA applicant has data regarding the RLD bead size variation, then those data should be provided to support the size(s) of the beads in the ANDA product. This information can be provided in the 3.2.P.2 (Pharmaceutical Development) section or 3.2.P.5.6 (Justification of Specification) section of a CTD formatted application.

B. Enteral Feeding Tube Administration

A small number of sprinkle drug products include language in the labeling that specifically provides for alternative administration via enteral feeding tubes to accommodate patients who cannot safely swallow or are unable to tolerate oral intake. Successful delivery of sprinkle drug products through an enteral feeding tube requires that all of the beads (uncrushed) be able to safely pass through the feeding tube and not cause tube occlusions.

Drug products that include this alternate administration method should demonstrate that the entire contents can be adequately administered. For example, in vitro in-use tests of the sprinkle drug product with feeding tubes indicated in the labeling can be used to support the product use with labeled routes of administration. Such a study or studies, as applicable, are recommended for NDAs and ANDAs, as bead size may vary or coating may differ between these products, resulting in varying ability to pass through a feeding tube. If there are questions about the design or analysis of such studies, the sponsors and/or applicants should contact the appropriate review division within the Office of New Drugs or the Office of Generic Drugs. There is no recommendation for these studies if the labeling does not specify enteral feeding tube administration. These studies can be provided in the 3.2.P.2 (Pharmaceutical Development) section or 3.2.P.5.6 (Justification of Specification) section of a CTD formatted application.

C. Bioavailability/Bioequivalence Recommendations

The acceptability of bead size and bead size differences from a bioavailability (BA) or bioequivalence (BE) perspective is directly evaluated in BA/BE studies.

In NDAs, in the case of capsules containing beads, for the labeling to indicate that the beads in the drug product can be sprinkled on soft foods, additional in vivo relative BA studies may be needed. This can be accomplished by administering beads that have been sprinkled on one of the soft foods (e.g., applesauce) that are listed in the labeling (test treatment) and comparing the sprinkled product's BA results to those of the product administered in the intact form (reference

treatment). Both products should be administered under fasting conditions.[6] In addition, the administration of beads when mixed with soft foods should be evaluated for the ability to take the product without chewing the beads. If there are questions about the design or analysis of such BA studies, the sponsors and/or applicants should contact the appropriate review division within the Office of New Drugs.

In ANDAs, when the labeling for the RLD for a modified-release drug product indicates that the product may be sprinkled on soft foods, a sprinkle study comparing the test and RLD products should be performed. Both treatments should be sprinkled on one of the soft foods that are listed in the labeling (e.g., applesauce). The BE data should be analyzed using average BE, and the 90-percent confidence interval criteria should be used to evaluate BE. Specific BE requirements for individual drug products can be found in the guidance for industry on *Bioequivalence Recommendations for Specific Drug Products*.[7]

In ANDAs, for immediate-release (IR) drug products labeled for sprinkle, it is generally not necessary to conduct a sprinkle BE study, as the expectation would be that the sprinkles would behave similarly for the test and RLD IR products.

If there are questions about the design or analysis of specific BE studies, the sponsors and/or applicants should contact the appropriate review division within the Office of Generic Drugs. The Agency may request additional BE studies under special circumstances if deemed appropriate.

[6] Information on BA studies of sprinkled drug products also can be found in the guidance for industry, *Food-Effect Bioavailability and Fed Bioequivalence Studies*, December 2002. CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[7] See www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm.