
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)**

**May 2012
CMC
Rev. 1**

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*Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov*

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TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. BACKGROUND.....	1
III. DISCUSSION.....	2
A. Maximum Bead Size for Drug Products Labeled for Sprinkle.....	2
B. Enteral Feeding Tube Administration	3
C. Bioavailability/Bioequivalence Recommendations	3



1 **Guidance for Industry¹**
2 **Size of Beads in Drug Products Labeled for Sprinkle**
3

4
5 This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It
6 does not create or confer any rights for or on any person and does not operate to bind FDA or the public.
7 You can use an alternative approach if the approach satisfies the requirements of the applicable statutes
8 and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for
9 implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate
10 number listed on the title page of this guidance.
11

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14 **I. INTRODUCTION**
15

16 This guidance provides applicants preparing or submitting new drug applications (NDAs),
17 abbreviated new drug applications (ANDAs), and biologics licensing applications (BLAs) the
18 Center for Drug Evaluation and Research's current thinking on appropriate size ranges for beads²
19 in drug products that are labeled to be administered via sprinkling (e.g., capsules or packets
20 containing beads).
21

22 FDA's guidance documents, including this guidance, do not establish legally enforceable
23 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
24 be viewed only as recommendations, unless specific regulatory or statutory requirements are
25 cited. The use of the word *should* in Agency guidances means that something is suggested or
26 recommended, but not required.
27

28 **II. BACKGROUND**
29

30 Certain drug products that contain beads within a capsule indicate in the labeling that the capsule
31 can be broken and the internal beads can be sprinkled on soft foods and swallowed without
32 chewing as an alternative administration technique. This is particularly common with drug
33 products designed to have extended- or delayed-release characteristics (i.e., the beads are
34 manufactured to release the drug product at different rates). To make certain that the intended
35 product performance is achieved—whether from a capsule that has been broken or from a packet
36 containing beads—it is important to have reasonable assurance that the patient will be able to
37 swallow the beads (uncrushed) with the food with which the beads are mixed without stimulating
38 the urge to chew. Additional assurances may be needed when the label also includes specific
39 language concerning alternate administration via an enteral feeding tube.
40
41

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).

Contains Nonbinding Recommendations

42 **III. DISCUSSION**

43
44 The recommendations in this guidance are based on literature on chewing and swallowing
45 particle size and on Agency experience with NDAs and ANDAs submitted for these dosage
46 forms. This guidance provides the following information related to drug products labeled for
47 sprinkle: (1) appropriate maximum size for the beads, (2) special considerations for sprinkle
48 drug products that include language in labeling concerning alternate administration via an enteral
49 feeding tube, and (3) bioavailability or bioequivalence recommendations.

50 51 **A. Maximum Bead Size for Drug Products Labeled for Sprinkle**

52
53 To determine an appropriate maximum bead size, the Agency took two actions. First, the
54 Agency reviewed studies of human mastication, which demonstrated that food is chewed to a
55 median particle size range from 0.82 to 3.04 mm before swallowing.^{3,4} Second, we examined
56 currently approved drug products labeled for sprinkle that contain beads up to 2.4 mm and found
57 no recognized safety risks or loss of efficacy associated with the bead size.

58
59 Based on this information, the Agency recommends a target bead size up to 2.5 mm with no
60 more than 10 percent variation over this size, to a maximum size of 2.8 mm. The recommended
61 bead size allowances consider the variability and differing manufacturing processes of beads
62 (e.g., pellet versus mini-tablet manufacturing). If the proposed bead size is greater than that
63 recommended in this guidance, the applicant should provide justification for the proposed bead
64 size, including studies demonstrating that the bead can be swallowed without chewing using
65 sprinkle administration in the intended population.

66
67 The Agency recognizes the specific importance of a maximum size limit for modified-release
68 products, where unintentional chewing of beads may lead to pharmacokinetic differences, but
69 also believes that maintaining a consistent maximum bead size for all drug products labeled for
70 sprinkle is appropriate. Inadvertently chewing beads labeled for sprinkle may lead to
71 noncompliance with taking medication because of taste, safety issues, and decreased drug
72 product efficacy. The target and maximum bead size recommendations thus apply to all drug
73 products that contain particles that are labeled for sprinkle administration, whether the product
74 has immediate-, delayed-, or extended-release characteristics. Target and maximum bead size,
75 including bead size distribution, can be determined through analytical sieving in accordance with
76 USP <786>⁵ or other appropriately validated methods.

77
78 The bead size distribution can be provided in the 3.2.P.3.3 (Description of Manufacturing
79 Process and Process Controls) section or 3.2.P.5.1 (Specification) section, and the maximum
80 bead size can be provided in the 3.2.P.1 (Description and Composition of the Drug Product)
81 section or 3.2.P.3.4 (Control of Critical Steps and Intermediates) section of a [common technical
82 document \(CTD\) formatted application](#).

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*.

Contains Nonbinding Recommendations

83 This recommendation applies only to NDAs, ANDAs, and BLAs for products that are not yet
84 approved. Sponsors of currently approved NDAs, ANDAs, or BLAs for products that contain
85 beads that do not meet the recommended limits in this guidance need not modify their product
86 specifications, unless there is reason to believe that an individual product poses a particular risk
87 to public health because of its bead size.
88

89 An ANDA that references a currently approved reference listed drug (RLD) that exceeds the
90 recommended limits in this guidance may propose a target and maximum bead size equal to or
91 less than that used in the currently approved RLD. If the proposed target and/or maximum bead
92 size is greater than that used in the currently approved RLD, the applicant should provide
93 justification for the proposed bead size, as described above. If the ANDA applicant has data
94 regarding the RLD bead size variation, then those data should be provided to support the size(s)
95 of the beads in the ANDA product. This information can be provided in the 3.2.P.2
96 (Pharmaceutical Development) section or 3.2.P.5.6 (Justification of Specification) section of a
97 CTD formatted application.
98

B. Enteral Feeding Tube Administration

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100
101 A small number of sprinkle drug products include language in the labeling that specifically
102 provides for alternative administration via enteral feeding tubes to accommodate patients who
103 cannot safely swallow or are unable to tolerate oral intake. Successful delivery of sprinkle drug
104 products through an enteral feeding tube requires that all of the beads (uncrushed) be able to
105 safely pass through the feeding tube and not cause tube occlusions.
106

107 Drug products that include this alternate administration method should demonstrate that the
108 entire contents can be adequately administered. For example, in vitro in-use tests of the sprinkle
109 drug product with feeding tubes indicated in the labeling can be used to support the product use
110 with labeled routes of administration. Such a study or studies, as applicable, are recommended
111 for NDAs and ANDAs, as bead size may vary or coating may differ between these products,
112 resulting in varying ability to pass through a feeding tube. If there are questions about the design
113 or analysis of such studies, the sponsors and/or applicants should contact the appropriate review
114 division within the Office of New Drugs or the Office of Generic Drugs. There is no
115 recommendation for these studies if the labeling does not specify enteral feeding tube
116 administration. These studies can be provided in the 3.2.P.2 (Pharmaceutical Development)
117 section or 3.2.P.5.6 (Justification of Specification) section of a CTD formatted application.
118

C. Bioavailability/Bioequivalence Recommendations

119
120
121 The acceptability of bead size and bead size differences from a bioavailability (BA) or
122 bioequivalence (BE) perspective is directly evaluated in BA/BE studies.
123

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

Contains Nonbinding Recommendations

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

134
135 In ANDAs, when the labeling for the RLD for a modified-release drug product indicates that the
136 product may be sprinkled on soft foods, a sprinkle study comparing the test and RLD products
137 should be performed. Both treatments should be sprinkled on one of the soft foods that are listed
138 in the labeling (e.g., applesauce). The BE data should be analyzed using average BE, and the 90-
139 percent confidence interval criteria should be used to evaluate BE. Specific BE requirements for
140 individual drug products can be found in the guidance for industry on *Bioequivalence*
141 *Recommendations for Specific Drug Products*.⁷

142
143 In ANDAs, for immediate-release (IR) drug products labeled for sprinkle, it is generally not
144 necessary to conduct a sprinkle BE study, as the expectation would be that the sprinkles would
145 behave similarly for the test and RLD IR products.

146
147 If there are questions about the design or analysis of specific BE studies, the sponsors and/or
148 applicants should contact the appropriate review division within the Office of Generic Drugs.
149 The Agency may request additional BE studies under special circumstances if deemed
150 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.