
Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Mamta Gautam-Basak, 301-796-0712.

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

**July 2018
Pharmaceutical Quality/CMC**

Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**July 2018
Pharmaceutical Quality/CMC**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	GENERAL CONSIDERATIONS AND RECOMMENDATIONS.....	3
	A. Selection of Liquids and Soft Foods: Compatibility and Suitability	4
	B. Impact of Vehicle on the Drug Product	5
	C. Patient Adherence and Acceptance: Palatability and Swallowability	5
	D. Drug Product and Vehicle.....	6
	1. <i>Preparation and Handling Procedures</i>	<i>6</i>
	2. <i>Dose and Dosing Volume.....</i>	<i>7</i>
	E. Drug Product and Vehicle Mixtures for Repeated Use or Multiple Users	7
	F. Special Case: Administration of Drug Product and Vehicle Mixtures via Feeding Tubes	8
	G. Information from In Vivo and In Vitro Studies.....	8
	H. Recommendations for Labeling.....	8
IV.	IN VITRO METHODS RECOMMENDED FOR ASSESSING IMPACT OF A VEHICLE ON PRODUCT QUALITY ATTRIBUTES.....	10
	A. Analytical Method.....	10
	B. Assessment of the Drug Substance in the “Mixture”.....	10
	1. <i>Sample Handling.....</i>	<i>10</i>
	2. <i>Integrity, Potency, Stability, and Homogeneity</i>	<i>11</i>
	3. <i>Dissolution/Drug Release Testing</i>	<i>12</i>
	4. <i>Dosage Form Specific Considerations</i>	<i>13</i>
V.	LOCATION OF DATA IN SUBMISSIONS	13
APPENDIX A	14	
	Commonly Used Soft Foods and Liquids With Their Approximate pH Range.....	14
APPENDIX B	15	
	Examples of Labeling Language.....	15
APPENDIX C	16	
	Sample Handling and Qualification Decision Tree.....	16

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Use of Liquids and/or Soft Foods as Vehicles for Drug**
2 **Administration: General Considerations for Selection and In Vitro**
3 **Methods for Product Quality Assessments**
4 **Guidance for Industry¹**
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

13
14
15 **I. INTRODUCTION**
16

17 This guidance applies to orally administered drug products and provides recommendations to
18 sponsors² who will use or recommend use of liquids³ and/or soft foods as vehicles for drug
19 administration in investigational new drug applications (INDs), new drug applications (NDAs),
20 Biologics License Applications (BLAs), as applicable, and in supplements to these applications.⁴
21 This guidance addresses the approaches recommended for suitability determination of vehicles
22 intended for use with specific drug products by providing the following:
23

- 24 • Considerations for selection of liquids and/or soft foods as vehicles.
25
26 • Standardized in vitro methodology and data recommendations for drug product quality
27 assessments to qualify vehicle(s) for drug product administration.
28

¹ This guidance has been prepared by a multidisciplinary team including offices within the Center for Drug Evaluation and Research and the Office of Pediatric Therapeutics in the Office of the Commissioner at the Food and Drug Administration.

² For the purposes of this guidance, the term “sponsor” includes “applicant” and “application holder.”

³ Liquid, other than water.

⁴ This guidance does not address use of vehicles for the purpose of demonstrating bioequivalence in generic drug products. For abbreviated new drug applications (ANDAs), recommendations for in vivo bioequivalence studies involving administration with liquids or soft foods will continue to be communicated in the respective product-specific Agency guidance. With respect to ANDAs and the recommendations contained in this guidance, we note that immediate-release solid oral dosage forms generally are considered to be products for which formulation differences between generic products and their reference listed drug (RLD) would not impact administration with vehicles. The vehicle studies on the RLD would establish the compatibility of the active ingredient with the recommended vehicles, and need not be repeated in an ANDA unless there is a risk that the formulation of the ANDA product would have a different impact on dosing with vehicles. When needed, the in vitro approaches in this guidance could be used to confirm that the formulation of a generic product is compatible with the vehicles of administration in the RLD label. If FDA determined that in vivo data are needed to support use of a vehicle for a generic product, the Agency would describe such data in its recommended product-specific bioequivalence studies.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 29 • Recommendations to communicate acceptable (qualified) vehicles in drug product
30 labeling. If certain foods are found unacceptable, they should also be included in the
31 labeling.
32

33 This guidance and the methods it describes do not replace existing guidance documents that
34 address food-effect assessments on the drug product⁵ or dosage form, or stability testing
35 conducted to support a shelf-life determination.⁶ For those drug products marketed with a
36 vehicle for administration (i.e., the vehicle is co-packaged with the drug product), the
37 recommendations regarding selection and methods provided in this guidance are applicable,
38 but additional considerations and recommendations may also apply.
39

40 If a different approach than those recommended in this guidance is used, sponsors are
41 encouraged to discuss the proposed approach with the appropriate FDA quality assessment staff
42 before conducting the studies.
43

44 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
45 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
46 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
47 the word *should* in Agency guidances means that something is suggested or recommended, but
48 not required.
49

50 51 **II. BACKGROUND**

52
53 There are many commercial drug product dosage forms such as granules, pellets, powders, or
54 tablets for which the drug product labeling includes instructions for the optional use of soft foods
55 or liquids as vehicles for their administration.
56

57 In the absence of availability of a dosage form that is appropriate for the targeted patient
58 population (e.g., pediatric, geriatric), small amounts of liquids and/or soft foods as described in
59 the FDA-approved product labeling can be used as a suitable vehicle(s) for oral administration
60 and immediate ingestion of the specific drug product. Generally, drug products mixed in small
61 amounts of liquids (5 to 15 mL) or soft foods are used in pediatric and other patient populations
62 who are unable to swallow solid oral dosage forms. Although sponsors are required to develop
63 age-appropriate formulations as part of a pediatric drug development program⁷ occasionally the
64 development of age-appropriate dosage forms and formulations proves to be exceedingly
65 complex. The use of a liquid such as infant formula or breast milk and/or soft food as a
66 vehicle(s) may be the only option for delivering the drug substance to the targeted patient
67 population. Liquids and/or soft foods that are shown not to alter performance of the drug

⁵ See guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* and guidance for industry *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations*.

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ See ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

⁷ See section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Contains Nonbinding Recommendations

Draft — Not for Implementation

68 product, and are deemed compatible and suitable for use in the targeted patient populations, are
69 considered suitable for use as vehicles with the specific drug product. The drug product-vehicle
70 mixture is not considered a new dosage form of the existing drug.

71
72 To ensure consistency in drug product quality when administered with a vehicle, it is important
73 to standardize the methodology supporting vehicle selection, and the supportive data to designate
74 vehicle suitability. Standardization of the preparation and use instructions for the drug product-
75 vehicle mixture is also important, as ambiguity in instructions or incomplete information can
76 lead to unintended outcomes, including dosing errors and/or misuse of the drug product.

77
78 The methodology described in this guidance is intended to improve consistency in these areas
79 and applies to potential use of vehicles during different stages of drug development, including
80 lifecycle management as follows:

- 81
- 82 • During development (IND stage): to select a vehicle for administering the test drug
83 product to populations who are unable to swallow solid oral dosage forms (e.g., children,
84 older adult patients); and for some bioavailability (BA) studies conducted for
85 formulation development and optimization.
 - 86
 - 87 • Prior to marketing application (NDA stage): to propose a vehicle(s) for use of the drug
88 product for the original or additional condition of use (e.g., a new indication or new
89 patient population).
 - 90
 - 91 • Postapproval or supplement submission: to propose changes to the drug product or its
92 labeling that necessitate reassessment of compatibility and suitability of the approved
93 vehicle.
- 94

95 Considerations and in vitro methods described in this guidance are also applicable for selecting
96 vehicles out of necessity in unusual circumstances, such as when considering counterterrorism
97 measures.⁸ In such cases, when the benefits outweigh risks and alternate dosage forms are
98 unavailable, liquids and/or soft foods may be used as vehicles for specific drug products.

99

100

101 III. GENERAL CONSIDERATIONS AND RECOMMENDATIONS

102

103 Only those liquids and/or soft foods demonstrated to have no appreciable effect on drug product
104 performance should be proposed as vehicles. The potential impact of a vehicle on drug product
105 performance is determined by assessment of drug product quality attributes, including potency
106 (assay), in vitro dissolution/release, and other pertinent attributes when the drug product is used
107 with the proposed vehicle(s). In section IV, standardized in vitro methods for evaluating
108 compatibility of the proposed liquid and/or soft food are described.

109

⁸ Refer to the following:

<http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130996.htm> and
<http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm063814.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

110 In the subsequent sections of this document, an “intact” drug product refers to solid oral dosage
111 forms such as granules, pellets, powders, as well as certain specific modified release drug
112 products such as coated mini-tablets or beads that are labeled to be administered via sprinkling
113 (e.g., capsules or packets containing beads).⁹ When a drug product requires handling to make it
114 suitable for administration in a vehicle, such as crushing a tablet, emptying capsule contents,
115 making serial dilutions, or mixing syrup into a vehicle, the resultant product is referred to as a
116 “manipulated” drug product in this document. If critical manipulations are needed, such as
117 emptying capsule contents or crushing a tablet to mix with the vehicle for ease of administration,
118 the impact of the manipulations should be studied. The preparation and use instructions provided
119 in labeling should give clear instructions that can be followed by the patient, caregiver, or
120 healthcare professional in a homecare setting or a healthcare facility.¹⁰

121
122 The following are key considerations and recommendations for selection and use of vehicles for
123 drug product administration and are intended to ensure that any liquid or soft food proposed as a
124 vehicle does not compromise drug product performance.

A. Selection of Liquids and Soft Foods: Compatibility and Suitability

125
126
127 Using liquids and soft foods as vehicles for drug administration can prove to be challenging
128 because many factors such as seasonal, regional and climate conditions can influence the
129 composition of natural food substances. Liquids and soft foods that have relatively small
130 fluctuations in their composition and characteristics (such as sugar content, acidity, viscosity)
131 may be better candidates for screening as potentially compatible liquids and/or soft foods with
132 drug products for further testing. Liquids and/or soft foods should be screened with consideration
133 of the following characteristics: 1) the drug substance, 2) the drug product, 3) the properties of
134 the proposed vehicle, such as its acidity/alkalinity and binding/chelating characteristics, and 4)
135 the target population. For liquid dosage forms, composition of the drug product (including use of
136 stabilizing, emulsifying, and suspending agents) should be considered when selecting possible
137 vehicles to mix with the drug product. If possible, sponsors should identify more than one
138 compatible vehicle to provide options for patients with allergy or intolerance to a single vehicle.

139
140 For compatibility assessments, the pH value of proposed liquids and soft foods should be
141 considered before further testing for their compatibility with the intact or manipulated drug
142 product, including products with coatings. For example, for drug products with an intact enteric
143 protective coating suitable for an acidic environment with pH values up to pH 5, the proposed
144 vehicle should not have a pH value higher than 5, as exposing the coating to higher pH values
145 will disrupt and remove the coating from the drug product.^{11,12} See Appendix A for commonly
146 used soft foods and liquids with their approximate pH ranges.

147
148

⁹ See guidance for industry *Size of Beads in Drug Products Labeled for Sprinkle*.

¹⁰ See guidance for industry *The Content and Format for Pediatric Use Supplements*.

¹¹ Wells KA and Losin WG, 2008, In Vitro Stability, Potency, and Dissolution of Duloxetine Enteric-Coated Pellets After Exposure to Applesauce, Apple Juice, and Chocolate Pudding, *Clin Ther*, 30(7):1300-1308.

¹² Jurecki ER, Cunningham A, Mahoney JJ, Tingley D, Chung S, James N, Cohen-Pfeffer JL, 2014, Sapropterin Dihydrochloride Mixed with Common Foods and Beverages, *Top Clin Nutr*, 29 (4), 325-331.

Contains Nonbinding Recommendations

Draft — Not for Implementation

149 It is important that a comprehensive suitability determination is performed to evaluate potential
150 use of the proposed vehicle in the targeted patient population. Suitability determinations should
151 include a composite assessment of multiple factors, such as the patient’s medical condition;
152 perceptions of the product-vehicle mixture such as flavor, texture, and mouthfeel; and age-
153 related responses to physical characteristics of the mixture. For example, perception of mouthfeel
154 of the intact or manipulated drug product in the vehicle mixture will vary with the targeted
155 patient population. Graininess of the drug product and vehicle mixture can trigger chewing in
156 young patients.

157
158 If a certain liquid or soft food is considered unsuitable for the targeted patient population, even if
159 the proposed vehicle(s) and the intact or manipulated drug product are chemically compatible,
160 the indicated soft food or liquid may not be considered an acceptable vehicle for use. For
161 example, adding a drug product to applesauce or another soft food is inappropriate if the targeted
162 patient population is infants who are not yet eating solid food. Such data, when available, for
163 liquids and soft foods evaluated and found to be unacceptable should also be submitted,
164 including the rationale for avoiding their use as vehicles.

B. Impact of Vehicle on the Drug Product

165
166
167
168 A direct assessment of the impact of the proposed vehicle on the intact or manipulated drug
169 product should be conducted to determine the compatibility of the proposed vehicle with the
170 drug product. Specifically, a liquid or soft food is considered suitable for use as a vehicle for
171 drug product administration when it has no appreciable effect on drug product stability or
172 performance. The resulting drug product-vehicle mixture should exhibit no change in potency (as
173 determined by assay) over the proposed use time period and no significant change in drug release
174 characteristics. See section IV for recommended methods.

175
176 Once combined, the drug product and vehicle mixture should be ingested immediately (or as
177 directed in the labeling) to avoid dosing errors or inadvertent dosing, and inadvertent
178 contamination of the drug product-vehicle mixture. When the labeling calls for immediate use of
179 the mixture, such use should be adequately supported by product quality assessments that are
180 carried out at pre-determined times over two hours after preparation of the mixture. The two-
181 hour assessment period is considered to provide the necessary time window to ensure physical
182 and chemical stability of the drug product-vehicle mixture. Microbiological testing is not needed
183 for the drug product-vehicle mixture if it is intended to be used within two hours because the risk
184 of microbial proliferation to harmful levels is minimal. See section IV for recommended test
185 methods.

C. Patient Adherence and Acceptance: Palatability and Swallowability¹³

186
187
188
189 Adherence is defined as the degree of constancy and accuracy with which a patient takes a drug
190 product as instructed by his or her healthcare provider, and is a key factor in successful
191 therapeutic intervention. Factors that impact adherence include: 1) patient acceptance of the

¹³ Thompson CA, Lombardi DP, Sjostedt P, Squires LA, 2013, Industry Survey on Current Practices in the Assessment of Palatability and Swallowability in the Development of Pediatric Oral Dosage Forms, Therapeutic Innovation and Regulatory Science 47(5):542-549.

Contains Nonbinding Recommendations

Draft — Not for Implementation

192 drug product; 2) the willingness of the patient to use a drug product as intended; and 3) the
193 ability of the caregiver to administer the drug product as intended.

194
195 Acceptance of the drug product is determined in part by palatability and swallowability that
196 would determine the patient adherence. Palatability is defined as the quality of a drug product
197 that makes it pleasant or acceptable in terms of taste, after-taste, smell, and texture and is a
198 critical factor in determining patient acceptance of oral dosage forms. Swallowability may be
199 defined as the patient being able to take the drug without gagging or choking. Taste sensation
200 develops early in life and evolves with age. In general, the goal should be to develop drug
201 formulations with a neutral taste that would be acceptable to the majority of patients. Although
202 taste-masking technology is advancing rapidly, for those drug products where taste-masking is
203 not possible, alternate approaches such as mixing with appropriate liquids and/or soft foods to
204 mask taste can be employed to improve palatability of a finished dosage form. In cases where the
205 drug substance dissolves in the vehicle, the drug product and vehicle mixture should be
206 adequately taste-masked, if necessary for palatability.

207
208 Palatability of a drug product mixed with a vehicle can be influenced by factors including, but
209 not limited to, concomitant disease, condition or medication and targeted patient population (e.g.,
210 pediatric or geriatric). Disease states can also influence a patient's sensory perceptions and affect
211 the patient's ability to swallow certain dosage forms. In addition, cultural aspects such as diet
212 and societal influences can impact a patient's preference for certain liquids or soft foods as
213 vehicles. Therefore, the palatability and swallowability of the drug product mixed with the
214 vehicle should be determined in the intended population of use.

215
216 Methods for quantitative assessments of palatability and swallowability for drug products are
217 advancing and continue to evolve.^{14,15} Sponsors should discuss their planned approach to assess
218 palatability and swallowability of their drug product with the appropriate review division. The
219 assessments should consider relevant patient characteristics (such as age, disease or medical
220 condition, concomitant medications, etc.), characteristics of the vehicle mixture(s) (such as taste,
221 flavor, texture, and mouthfeel), and the ability of patients in the targeted population to swallow
222 the drug product-vehicle mixture.

223

D. Drug Product and Vehicle

224

1. Preparation and Handling Procedures

225

226
227
228 In the selection of the vehicle, consideration should be given to the complexity of the
229 preparation, homogeneity of the mixture, and handling procedures as these can result in
230 decreased accuracy in dose delivery. Mixing drug products (intact or manipulated) with liquids
231 or soft foods may allow masking of an unpleasant taste, after-taste, smell and/or texture, or may

¹⁴ Squires LA, Lombardi DP, Sjostedt P, Thompson CA, 2013, A Systematic Literature Review on the Assessment of Palatability and Swallowability in the Development of Oral Dosage Forms for Pediatric Patients, *Therapeutic Innovation and Regulatory Science*, 47(5):533-541.

¹⁵ Stokes JR, Boehm MW, Baier SK, 2013, Oral Processing, texture and mouthfeel: From rheology to tribology and beyond, *Curr Opin in Colloid & Interface Science*, 18:349-359.

Contains Nonbinding Recommendations

Draft — Not for Implementation

232 aid to facilitate swallowing of solid oral dosage forms. For ease of administration and to ensure
233 dosing accuracy, as appropriate, an oral syringe or measuring spoon should be included with the
234 drug product along with clear use instructions.¹⁶

235
236 Carrying out dilutions accurately in a homecare setting can be difficult. To enable accurate
237 dosing, tablet splitting of non-scored tablets or dilutions should be avoided, unless stated in the
238 label. Even with functionally scored tablets, there are limitations in accurately dividing a tablet
239 into dose strengths beyond that provided by the scoring.¹⁷ For example, we recommend against
240 dividing nonfunctionally scored tablets into smaller doses (such as one-fourth of a tablet),
241 because it can result in crumbling of the tablet and inaccuracy of the recommended dose. For
242 unscored tablets the manufacture/availability of multiple strengths of the drug product is highly
243 encouraged.

244 245 2. *Dose and Dosing Volume*

246
247 The suggested volume of the vehicle for mixing with solid oral dosage forms should take into
248 consideration the age, size, and average consumption of the vehicle by the targeted patient
249 population. For example, children younger than two years old may not be able or willing to
250 ingest large volumes of liquids or soft foods at one time, whereas this volume may be acceptable
251 for an older child or adult. To ensure administration of the full dose of the drug and to facilitate
252 swallowing, the smallest volume of vehicle(s) sufficient to provide acceptable taste-masking,
253 roughly 5 to 15 mL, should be used to prepare the drug product and vehicle mixture. In addition,
254 homogeneous (i.e., uniform) mixing of the drug product in a smaller volume of vehicle is
255 generally easier and will facilitate complete administration of the dose. If the homogeneous
256 mixing of the intact or manipulated drug product with a small volume of the vehicle is difficult
257 and requires a large volume (e.g., more than 15 mL) of the vehicle for dosing, exploring alternate
258 vehicles should be considered to avoid incomplete dosing if all of the drug product and vehicle
259 mixture cannot be readily ingested.

260 261 **E. Drug Product and Vehicle Mixtures for Repeated Use or Multiple Users**

262
263 Generally, use of vehicles for drug administration refers to single use of the preparation where
264 the drug product, once mixed with the liquid or soft food, is consumed immediately by a single
265 patient. Under certain circumstances, use of the drug product-vehicle mixture preparation for
266 multiple doses (e.g., one or more patients) can be considered acceptable (i.e., in a healthcare
267 facility or in another setting where qualified professionals are responsible for preparing the drug
268 product-vehicle mixtures and dosing the patients). Adequate characterization of the drug product
269 and vehicle mixture (including adequate in-use stability data and microbiological assessments),
270 and instructions for preparing the drug product-vehicle mixture, should be included in the
271 submission to support such multiple dose labeling statements.

272
273

¹⁶ We recommend that ANDAs for which the RLD contains these materials submit data and information in the application to demonstrate the proposed generic product contains equivalent materials (e.g., dosing/administration device) and labeling.

¹⁷ See guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

F. Special Case: Administration of Drug Product and Vehicle Mixtures via Feeding Tubes

In cases where the drug product labeling describes feeding tube administration, orally administered drug products can be given through a feeding tube (oral or enteral) to pediatric or adult patients who are unable to ingest solid or liquid dosage forms.¹⁸ In addition to the recommended assessments in this guidance, the feasibility and risk of administration of the drug product-vehicle mixture through a feeding tube should be addressed. For example, if the product may be administered by feeding tube, then an assessment demonstrating delivery of full volume of the mixture with no loss of drug product or potency is necessary, and should include the volume of solution to be used to rinse the feeding tube to ensure complete administration of the mixture. Similarly, factors that can result in the risk of drug aspiration or blockage of the tube should be evaluated.

G. Information from In Vivo and In Vitro Studies

If the sponsor anticipates use of liquid or soft foods as vehicles for drug administration during drug development and/or after market approval, data from in vivo and in vitro studies should be submitted. Studies to support the compatibility and suitability of the selected vehicle(s), the supporting methodology, and timing of such studies should be discussed with the appropriate review division early in drug development (such as during pre-IND, end-of-phase 2 (EOP2) meetings), or postapproval, as applicable.

If a liquid or soft food is ultimately recommended as a vehicle(s) for drug administration, patient dosing information should be included in the labeling. For example, this includes the studied vehicle(s), volume of the vehicle(s), frequency of dosing, along with the pharmacokinetic information, if available, which should be included in the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section of labeling. For complete information, see section H: Recommendations for Labeling.

Under special circumstances the Agency may request additional studies and in vivo bioavailability data if deemed appropriate (e.g., if there is reason to believe there may be interactions requiring further assessment).

The in vitro methods described in this document are for selection and qualification of vehicles; they do not replace in vivo food-effect studies.¹⁹

H. Recommendations for Labeling

If a liquid or soft food is qualified as a vehicle(s) and recommended for the administration of a drug for the target indicated population (or sub-population), such information should be summarized in labeling. The labeling should include sufficient information to ensure that the

¹⁸ Williams NT, 2008, Medication administration through enteral feeding tubes, *Am J Health-Syst Pharm*, 65:2347-2357.

¹⁹ See guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* and guidance for industry *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

316 healthcare provider, patient, and/or caregiver has the essential information to use the
317 recommended vehicle(s) to administer the drug safely and effectively and to avoid substitutions
318 that are unacceptable. Labeling should include, as applicable:

- 319
- 320 • Recommended type(s) of soft food or liquid vehicle(s);
- 321
- 322 • Detailed vehicle use information, such as the volume and temperature range of the
- 323 qualified vehicle(s) that are approved for use;
- 324
- 325 • Recommended critical manipulations, such as emptying capsule contents or crushing a
- 326 tablet for ease of administration;
- 327
- 328 • For repeated or multiple use dosing, information concerning the conditions to support
- 329 preparation of the drug product-vehicle mixture and instructions for its storage between
- 330 uses;
- 331
- 332 • Information on compatibility of the recommended vehicle(s) with feeding tube
- 333 characteristics;
- 334
- 335 • Information on liquids and soft foods found to be unacceptable, and the rationale for
- 336 avoiding their use as vehicles.
- 337

338 A succinct summary of the compatibility and suitability study and data that supports the use of
339 liquid or soft food vehicles in the target population as well as relevant data concerning
340 unacceptable vehicles should be discussed in the Pharmacokinetics subsection of the CLINICAL
341 PHARMACOLOGY section.²⁰

342

343 The DOSAGE AND ADMINISTRATION section should include directions for administering
344 the drug using the recommended liquid or soft food vehicle.²² This section should also include
345 information on the target indicated patient population for delivering the drug using a liquid or
346 soft food vehicle (e.g., pediatric patients, older adults who have difficulty swallowing solid oral
347 dosage forms) as well as the preparation, administration, and storage of the mixed drug product-
348 vehicle. The Instructions for Use should contain detailed patient-appropriate directions for the
349 preparation, administration, and storage of the mixed drug product-vehicle by a patient or
350 caregiver, if applicable.

351

352 A cross-reference to the CLINICAL PHARMACOLOGY section for additional details
353 concerning the liquid or soft food vehicles should be included. See Appendix B for examples for
354 the preparation, administration, and storage of the mixed drug product-vehicle in the DOSAGE
355 AND ADMINISTRATION section.

356
357
358

²⁰ See guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

359 **IV. IN VITRO METHODS RECOMMENDED FOR ASSESSING IMPACT OF A** 360 **VEHICLE ON PRODUCT QUALITY ATTRIBUTES**

361
362 The following approaches are recommended to determine whether a proposed vehicle is
363 compatible and suitable for use with the drug product. Also, see Appendix C (Sample Handling
364 and Qualification Decision Tree) and section IV.B.
365

366 The product quality data generated from the following studies, as applicable for the dosage form,
367 should be included in a report to support qualification of each proposed vehicle and to support
368 that the drug product quality is maintained when the drug product is mixed with the qualified
369 vehicles.
370

371 **A. Analytical Method**

372
373 A validated analytical method should be used to quantify the amount of drug substance in the
374 vehicle mixture for the assessments described in section B below. The drug substance may or
375 may not be exposed to the vehicle depending on the dosage form and sample preparation. If the
376 dosage form remains intact in the vehicle, changes in assay (potency) and drug product
377 performance/integrity are not expected, but the absence of such changes should be verified.
378

379 The analytical method for assay of drug substance in the proposed vehicle should be developed
380 and validated in accordance with the principles outlined in guidances.^{21,22,23,24} The source of
381 analytical interferences, if observed, between ingredients in liquids or soft foods with the drug
382 substance and the excipients in the dosage forms should be determined.
383

384 **B. Assessment of the Drug Substance in the “Mixture”**

385
386 A series of assessments should be performed to qualify the proposed vehicle for a specific drug
387 product as outlined in the Sample Handling and Qualification decision tree in Appendix C.
388 The following describes the sequence of the assessments in the decision tree:
389

390 *1. Sample Handling*

391
392 A basic screen should be carried out to determine stability of the drug substance in standard GI
393 buffer media and in Fed State Simulated Gastric Fluid (FeSSGF), which is buffer media
394 containing milk. Sample handling processes, depending on the stability of the drug substance in
395 the screening media, or the ability of a drug product coating to prevent exposure to a drug
396 substance that is unstable in the screening media, are described in the decision tree in Appendix
397 C.
398

²¹ See guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics*.

²² See ICH guidance for industry *Q2R1 Validation of Analytical Procedures: Text and Methodology*.

²³ See ICH guidance for industry *Q2A Text on Validation of Analytical Procedures*.

²⁴ See ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

399 For sample preparation approach B, described in Appendix C, the intact drug product or
400 particulate material containing the drug substance should be separated from the mixture, and
401 integrity and dissolution tests should be performed on the solid particles.

402

403 2. Integrity, Potency, Stability, and Homogeneity

404

405 **Integrity:** A qualified vehicle should be shown to maintain the drug substance quality attributes.
406 If the drug product has a coating and is used intact, the qualified vehicle should have no impact
407 on the coating and as a result, on the integrity of the drug substance within the drug product. In
408 the cases where a coated tablet is to be crushed before mixing and the integrity of the coated
409 tablet is intentionally compromised, or where the drug product dissolves in the vehicle, exposing
410 the drug substance, the potential for the proposed vehicle to impact the integrity of the drug
411 substance (e.g., changes in polymorphic form, loss of bead integrity) should be evaluated.

412

413 **Potency (assay):** Potency assessment should determine the amount of the drug substance in the
414 drug product-vehicle mixture to support the recommended labeled use time. The testing should
415 be carried out after mixing or dissolving and again two hours after incubating the drug product
416 with the vehicle to support immediate use. If the proposed labeling will include manipulation of
417 the drug product prior to mixing with the vehicle (e.g., emptying capsule contents or crushing a
418 tablet), this should be done prior to the potency assessment. Samples should be collected at
419 predefined time points and assayed for determination of potency. The test should demonstrate a
420 lack of significant change in assay from the original value (where a significant change is defined
421 as no more than five percent of the original value).²⁵

422

423 When providing mass balance (total recovery) calculations for products where the sample
424 contains particulate material (sample preparation approach B), the amount of drug substance
425 extracted from particulate or intact drug product (such as coated beads, pellets) and the amount
426 of drug substance dissolved/released into the drug product and vehicle mixture should be
427 determined. The recovery data should be consistent with the labeled claim.

428

429 **Stability:** Stability assessment of the drug product-vehicle mixture should be provided to
430 support labeling instructions for its preparation and labeled use time. To qualify a vehicle for
431 immediate drug administration, a two hour stability assessment (USP controlled room
432 temperature: 20° C-25° C)²⁶ should be conducted in a manner consistent with immediate use of
433 the mixture as described in the labeling. Additionally, stability assessment under refrigerated
434 conditions (USP controlled cold temperature: 2° C-8° C) may be needed.

435

436 If potency testing of the drug product and the vehicle mixture suggests possible interactions (e.g.,
437 a significant loss in the amount of the drug substance is observed), the stability assessment
438 should include testing for degradation products to verify drug substance and drug product
439 integrity, as applicable. Stability-indicating methods should be used to determine the presence of
440 an impurity (in amounts exceeding the accepted threshold) or formation of new degradants as a
441 result of a potential interaction between the multiple components of the drug product and vehicle
442 mixture.

²⁵ See ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

²⁶ See USP 40-NF 35, General Chapter <659> PACKAGING AND STORAGE REQUIREMENTS.

Contains Nonbinding Recommendations

Draft — Not for Implementation

443
444 **Homogeneity (dose uniformity):** The proposed vehicle(s) should also be suitable for
445 preparation of homogeneous mixtures. The drug product should be thoroughly mixed with the
446 liquid or soft food to ensure a homogeneous mixture. Even though the drug product and vehicle
447 mixture is prepared for immediate use, it is possible that the patient may not ingest all of the
448 mixture immediately. In such cases, the more homogeneous the mixture is, the more reliable the
449 estimate of the ingested dose. To evaluate the homogeneity of the mixture, the drug product and
450 vehicle mixture should be divided into equal portions (n=3 to 6) and tested.

451
452 **3. Dissolution/Drug Release Testing**

453
454 Composition of soft foods or liquids such as added thickeners, sweetening agents, and other
455 ingredients can alter release and delivery of drug substance from the drug product.²⁷ In cases
456 where the drug substance is not immediately dissolved in the liquid or soft food, dissolution/
457 release testing of drug substance from the dosage form mixed with the proposed vehicle should
458 be carried out according to established methods.²⁸ Dissolution testing should be conducted in
459 media typically used for testing solid oral dosage forms and USP Apparatus I or Apparatus II can
460 be used. The following dissolution media are generally recommended: (1) 0.1 N HCl or
461 simulated gastric fluid USP without enzymes; (2) USP buffer at pH 4.5; (3) USP buffer at pH 6.8
462 or simulated intestinal fluid USP with or without enzymes; and (4) FFESSGF.^{29,30} The sample
463 preparation process should enable assessment of drug dissolution/release patterns for the drug
464 product-vehicle mixture in a manner consistent with drug dissolution/release characteristics and
465 claims for the drug product.

466
467 Typically, 12 individual units of the dosage form are used for dissolution testing of a drug
468 product. This information should be included in the vehicle qualification report or cross-
469 referenced to the drug product information in the submission. For dissolution/release testing of
470 drug substance from the drug product-vehicle mixture, data from six units mixed into the
471 proposed vehicle should be collected at each pre-determined sampling time. A comparison of the
472 dissolution profile for the original product with the drug product mixed with the proposed
473 vehicle should meet the similarity factor (f₂) acceptance criteria.³¹

474
475 Depending on the targeted patient population, dosage form, and drug substance characteristics,
476 additional in vitro testing may be appropriate to understand the effect of the proposed vehicle(s)
477 on the in vivo dissolution of the drug product.

478
479

²⁷ Manrique, YJ, Lee, DJ, Islam, F, Nissen, LM, Cichero, Stokes, JR, Steadman, KJ, 2014, Crushed Tablets: Does the Administration of Food Vehicles and Thickened Fluids to Aid Medication Swallowing Alter Drug Release? *J Pharm Sci* 17(2):207-219.

²⁸ See guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.

²⁹ Klein, S, 2010, The use of Biorelevant media to forecast in vivo performance of a drug, *AAPSJ*, p 397-406.

³⁰ Marques, MRC, Loebenberg, R, and Almukainzi, M, 2011, Simulated Biological Fluids with Possible Application in Dissolution Testing, *Dissolution technologies*, p 15-28.

³¹ *Ibid*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

480 4. *Dosage Form Specific Considerations*

481
482 **For liquid drug products** such as syrups, emulsions, or similar dosage forms, it may be possible
483 to mix the drug product homogenously with the vehicle. In vitro methods for product quality and
484 performance assessments should follow sample preparation and handling, see Appendix C,
485 Approach A of the Decision Tree.

486
487 Dosage form characteristics and composition of the drug product should be considered to ensure
488 that sample preparation and handling approaches are consistent with the intended in vivo
489 performance of the drug product.

490
491 Certain use conditions, such as emergency use, and/or use in a professional healthcare setting,
492 may necessitate other testing approaches that are not discussed in this guidance. We recommend
493 that sponsors consult with the appropriate review division for cases that require unique
494 considerations.

495 496 497 **V. LOCATION OF DATA IN SUBMISSIONS**

498
499 The information supporting selection and qualification of the vehicle to be mixed with the drug
500 should be provided as a separate report in the 3.2.P.2 (Pharmaceutical development) section of a
501 common technical document (CTD)³²-formatted application.

502
503 In the proposed labeling portion of a submission, information related to the drug product-vehicle
504 mixture including important preparation and administration instructions should be included in
505 the DOSAGE AND ADMINISTRATION section, and any relevant pharmacokinetic
506 information, if available, should be included in the Pharmacokinetics subsection of the
507 CLINICAL PHARMACOLOGY section of labeling.

508

³² See ICH guidance for industry *M4Q(R1) Technical Requirements for Registration of Pharmaceuticals for Human Use*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

509 **APPENDIX A**

510

511 **Commonly Used Soft Foods and Liquids With Their Approximate pH Range**

512

	pH range
Apples (puree)	3.34 – 3.90
Apple juice	3.35 – 4.00
Applesauce	3.10 – 3.60
Baby food, unstrained	5.95 – 6.05
Bananas (puree)	4.5 – 5.2
Buttermilk	4.41 – 4.83
Carrots (puree)	5.88 – 6.40
Chocolate pudding ^(a)	5.5 – 6.0
Coconut milk	6.1 – 7.0
Cranberry juice	2.30 – 2.52
Drinking water ^(b)	6.5 – 8.5
Fruit jellies	3.0 – 3.5
Fruit jam	3.5 – 4.5
Grapefruit juice ^(c)	2.90 – 3.25
Honey ^(d)	3.70 – 4.20
Infant formula	5.7 – 6.0
Maple syrup ^(e)	4.6 – 5.15
Milk	6.4 – 6.8
Orange juice	3.30 – 4.19
Orange marmalade	3.00 – 3.33
Peanut butter	6.28
Pineapple juice	3.30 – 3.60
Rice pudding ^(a)	4 – 5
Soybean milk	7
Strawberries	3.00 – 3.90
Strawberry jam	3.00 – 3.40
Yogurt	4.4 – 5.0

513

514 Reference, unless otherwise noted,

515 <https://www.clemson.edu/extension/hgic/food/pdf/hgic3030.pdf>.

516

517 a: Clin. Ther. 2008, 30 (7), 1300-1308.

518 b: National Secondary Drinking Water Regulations ([http://www.water-research.net/index.php/standards/secondary-](http://www.water-research.net/index.php/standards/secondary-standards)

519 [standards](http://www.water-research.net/index.php/standards/secondary-standards)).

520 c: Grapefruit juice is not recommended for using as a vehicle

521 (www.health.harvard.edu/fhg/updates/update0206d.shtml). Its inclusion here is for reference purposes only.

522 d: Honey is not recommended for children under age of 12 (Spika JS, N Shaffer, N Hargrett-Bean, S Collin, KL

523 MacDonald, PA Blake, 1989, Risk Factors for Infant Botulism in the United States, Am J Dis Child, 143(7):828-

524 832, and <https://www.cdc.gov/dotw/botulism/index.html>).

525 e: http://elitepublishing.net/ph_foods.html.

526

527

Contains Nonbinding Recommendations

Draft — Not for Implementation

528 APPENDIX B

529

530 Examples of Labeling Language

531

532 The following examples illustrate labeling text for the DOSAGE AND ADMINISTRATION
533 section for drug products (as is or in a manipulated form) that can be mixed with liquids or soft
534 foods. The labeling should include specific use information, such as the volume and temperature
535 of the qualified vehicle(s) approved for use.

536

537 • *Drug X capsules should be swallowed intact with a glass of water. For patients with*
538 *swallowing difficulties, Drug X capsules can be opened and the contents sprinkled onto*
539 *a teaspoon (5 mL) or tablespoon (15 mL) of soft food and ingested immediately. Use*
540 *only foods that do not require chewing, such as apricot, banana, or sweet potato baby*
541 *food; applesauce; and instant pudding. Contact of the capsule contents with foods such*
542 *as milk, custard, ice cream, and many other dairy products can dissolve the protective*
543 *(or enteric) coating and destroy the drug substance.*

544

545 • *Drug Y packet contents can be administered 1) dissolved in 1 teaspoonful (5 mL) of*
546 *cold or room temperature milk or breast milk, or 2) mixed with a teaspoonful (5 mL)*
547 *of cold or room temperature applesauce or banana puree. Puddings or formula*
548 *containing soybean flour, and vegetable purees should not be used because the fiber in*
549 *these foods can bind the drug substance. Liquids or other foods can be ingested*
550 *subsequent to the administration of Drug Y packet contents.*

551

552 • *Once Drug Y packet is opened, the full dose (with or without mixing with milk, breast*
553 *milk, or the apple and banana puree) must be administered immediately. If all of the*
554 *mixture is not ingested, discard any unused portion. Any unused contents of Drug Y*
555 *packet must not be stored for future use.*

556

Contains Nonbinding Recommendations

Draft — Not for Implementation

557 APPENDIX C

558

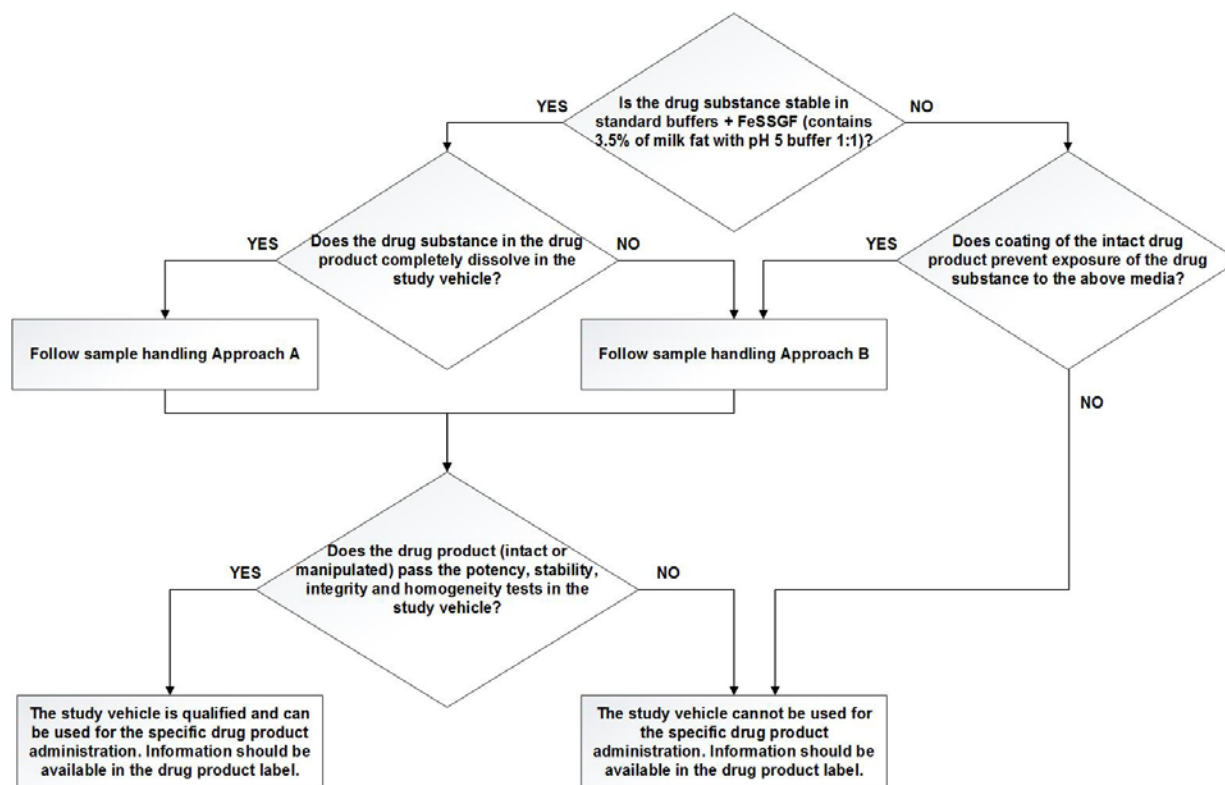
559 Sample Handling and Qualification Decision Tree

560

561 Approaches for sample preparation and handling are described to support drug product quality
562 assessments to determine whether the selected soft food or liquid qualifies for use as a vehicle.

563

564



565

566

567 * Drug product labeling should describe the qualified vehicle and any studied vehicles that cannot be used.

568

569 Sample handling Approach A (drug substance is completely dissolved and particulate 570 material, if any, is not the drug substance):

571

572 Depending on the type of sample (diluted soft food or liquid), sample preparation may involve a
573 simple filtration step followed by chromatographic separation and analysis of the drug substance;
574 in some cases, an additional extraction step from the soft food or liquid may be required before
575 sample analysis.

576

577 Sample handling Approach B (sample contains particulate material and some of the drug 578 can be in the particulate material):

579

580 a) Once the sample is taken from the media (soft food or liquid), the particulate matter is
581 washed and separated for further analysis.

582

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 583
584
585
586
587
588
589
590
591
592
593
594
595
- b) The wash and the remaining soft food or liquid is combined and processed for assaying for the drug substance.
 - c) The particulate matter (such as pellets) retrieved from the vehicle and washed as in Approach A above should be tested according to the dissolution method to determine release characteristics, as well as the amount of remaining drug substance in the particulate material.
 - d) Depending on the type of sample (diluted soft food or liquid), sample preparation in Approach B above may involve a simple filtration step followed by chromatographic separation and analysis of the drug substance; in some cases an additional extraction step from the soft food or liquid may be required before sample analysis.