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DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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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[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance applies to orally administered drug products and provides recommendations to sponsors[2] who will use or recommend use of liquids[3] and/or soft foods as vehicles for drug administration in investigational new drug applications (INDs), new drug applications (NDAs), Biologics License Applications (BLAs), as applicable, and in supplements to these applications.[4] This guidance addresses the approaches recommended for suitability determination of vehicles intended for use with specific drug products by providing the following:

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

[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.

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

This guidance and the methods it describes do not replace existing guidance documents that address food-effect assessments on the drug product[5] or dosage form, or stability testing conducted to support a shelf-life determination.[6] For those drug products marketed with a vehicle for administration (i.e., the vehicle is co-packaged with the drug product), the recommendations regarding selection and methods provided in this guidance are applicable, but additional considerations and recommendations may also apply.

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

In general, FDA's guidance documents 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

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

In the absence of availability of a dosage form that is appropriate for the targeted patient population (e.g., pediatric, geriatric), small amounts of liquids and/or soft foods as described in the FDA-approved product labeling can be used as a suitable vehicle(s) for oral administration and immediate ingestion of the specific drug product. Generally, drug products mixed in small amounts of liquids (5 to 15 mL) or soft foods are used in pediatric and other patient populations who are unable to swallow solid oral dosage forms. Although sponsors are required to develop age-appropriate formulations as part of a pediatric drug development program[7] occasionally the development of age-appropriate dosage forms and formulations proves to be exceedingly complex. The use of a liquid such as infant formula or breast milk and/or soft food as a vehicle(s) may be the only option for delivering the drug substance to the targeted patient 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).

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

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

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

- During development (IND stage): to select a vehicle for administering the test drug product to populations who are unable to swallow solid oral dosage forms (e.g., children, older adult patients); and for some bioavailability (BA) studies conducted for formulation development and optimization.

- Prior to marketing application (NDA stage): to propose a vehicle(s) for use of the drug product for the original or additional condition of use (e.g., a new indication or new patient population).

- Postapproval or supplement submission: to propose changes to the drug product or its labeling that necessitate reassessment of compatibility and suitability of the approved vehicle.

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

III. GENERAL CONSIDERATIONS AND RECOMMENDATIONS

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

[8] Refer to the following: http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130996.htm and http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm063814.htm.

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

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

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

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

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

[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.

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

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

B. Impact of Vehicle on the Drug Product

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

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

C. Patient Adherence and Acceptance: Palatability and Swallowability[13]

Adherence is defined as the degree of constancy and accuracy with which a patient takes a drug product as instructed by his or her healthcare provider, and is a key factor in successful 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.

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

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

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

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

D. Drug Product and Vehicle

1. Preparation and Handling Procedures

In the selection of the vehicle, consideration should be given to the complexity of the preparation, homogeneity of the mixture, and handling procedures as these can result in decreased accuracy in dose delivery. Mixing drug products (intact or manipulated) with liquids 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 Opinion in Colloid & Interface Science, 18:349-359.

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

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

2. Dose and Dosing Volume

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

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

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

[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/adminstration device) and labeling.

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

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.*

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

- Recommended type(s) of soft food or liquid vehicle(s);
- Detailed vehicle use information, such as the volume and temperature range of the qualified vehicle(s) that are approved for use;
- Recommended critical manipulations, such as emptying capsule contents or crushing a tablet for ease of administration;
- For repeated or multiple use dosing, information concerning the conditions to support preparation of the drug product-vehicle mixture and instructions for its storage between uses;
- Information on compatibility of the recommended vehicle(s) with feeding tube characteristics;
- Information on liquids and soft foods found to be unacceptable, and the rationale for avoiding their use as vehicles.

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

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

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

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

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

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

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

A. Analytical Method

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

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

B. Assessment of the Drug Substance in the "Mixture"

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

1. Sample Handling

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

[21] See guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics.*
[22] See ICH guidance for industry *Q2R1Validation 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*.

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

2. Integrity, Potency, Stability, and Homogeneity

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

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

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

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

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

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

3. Dissolution/Drug Release Testing

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

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

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

[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.

4. Dosage Form Specific Considerations

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

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

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

V. LOCATION OF DATA IN SUBMISSIONS

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

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

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

APPENDIX A

Commonly Used Soft Foods and Liquids With Their Approximate pH Range

	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

Reference, unless otherwise noted,
https://www.clemson.edu/extension/hgic/food/pdf/hgic3030.pdf.

a: Clin. Ther. 2008, 30 (7), 1300-1308.
b: National Secondary Drinking Water Regulations (http://www.water-research.net/index.php/standards/secondary-standards).
c: Grapefruit juice is not recommended for using as a vehicle (www.health.harvard.edu/fhg/updates/update0206d.shtml). Its inclusion here is for reference purposes only.
d: Honey is not recommended for children under age of 12 (Spika JS, N Shaffer, N Hargrett-Bean, S Collin, KL MacDonald, PA Blake, 1989, Risk Factors for Infant Botulism in the United States, Am J Dis Child, 143(7):828-832, and https://www.cdc.gov/dotw/botulism/index.html).
e: http://elitepublishing.net/ph_foods.html.

APPENDIX B

Examples of Labeling Language

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

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

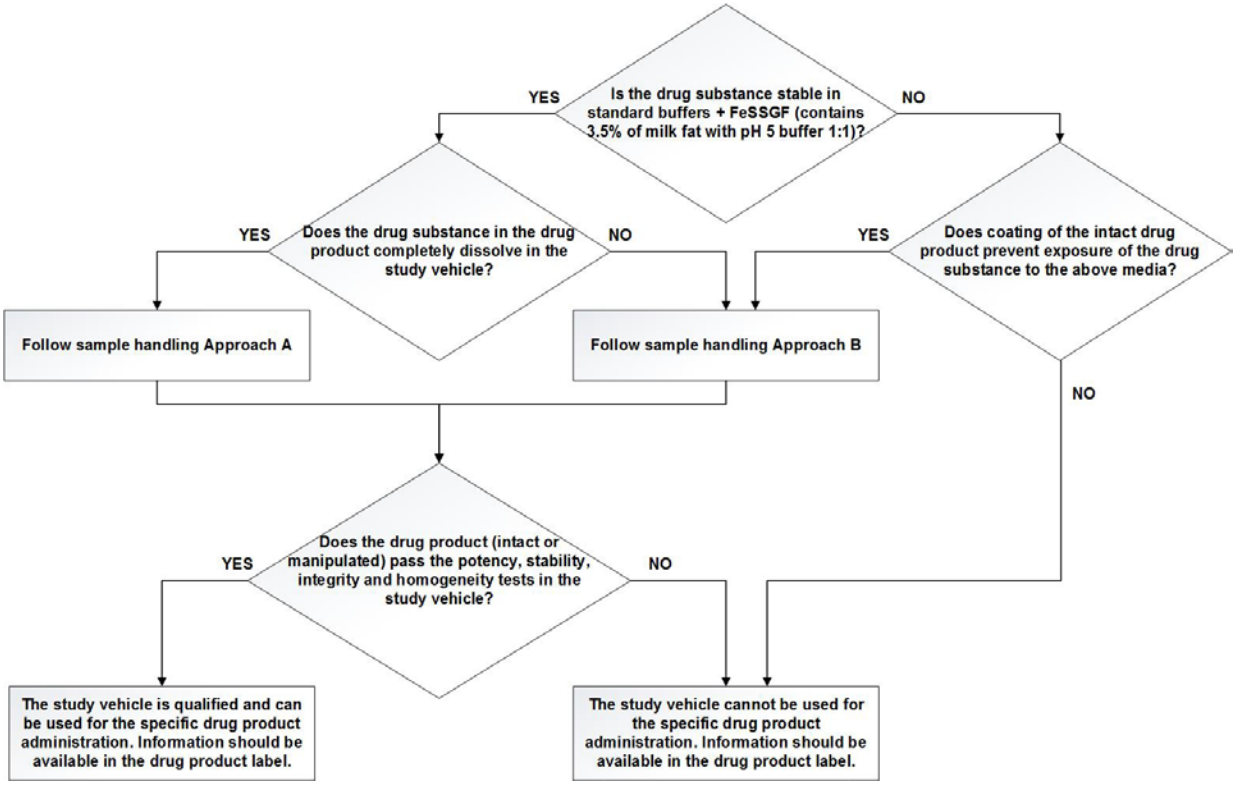
- *Drug Y packet contents can be administered 1) dissolved in 1 teaspoonful (5 mL) of cold or room temperature milk or breast milk, or 2) mixed with a teaspoonful (5 mL) of cold or room temperature applesauce or banana puree. Puddings or formula containing soybean flour, and vegetable purees should not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

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

APPENDIX C

Sample Handling and Qualification Decision Tree

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



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

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

Depending on the type of sample (diluted soft food or liquid), sample preparation 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.

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

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

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.