Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs

Guidance for Industry

DRAFT GUIDANCE

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

October 2022
Generic Drugs

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Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (Agency or FDA) on this topic.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 is intended to assist applicants who are submitting abbreviated new drug applications (ANDAs) for liquid-based and/or other semisolid products applied to the skin, including integumentary and mucosal (e.g., vaginal) membranes, which are hereinafter called *topical products*.[2] Because of the complex route of delivery associated with these products, which are typically locally acting, and the potential complexity of certain formulations, topical products (other than topical solutions) are classified as complex products.[3]

This guidance provides recommendations for physicochemical and structural (collectively, *Q3*) characterizations that can be used (1) to identify the dosage form of a proposed generic (test) topical product and (2) to describe properties of the drug product that may be critical to its performance (to support a demonstration of bioequivalence (BE)[4]). When comparing the Q3 attributes of two topical products (e.g., to support a demonstration of BE), we generally advise that applicants conduct a comparative Q3 characterization of their proposed generic product against the reference standard, which ordinarily is the reference listed drug (RLD).[5] This

[1] This guidance has been prepared by the Office of Generic Drugs in collaboration with the Office of Pharmaceutical Quality, both in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Topical products in ANDAs within the scope of this guidance include ointments, creams, lotions, emulsions, pastes, shampoos, gels, suspensions, solutions, sprays, aerosols, foams, and other semisolid and/or liquid-based dosage forms dispensed with a structured arrangement of matter (which may include more than one phase state). This guidance does not address products other than the topical products mentioned in this footnote, although the scientific principles discussed herein may be relevant in other contexts and drug products.

[3] A *complex product*, as defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023 – 2027 (GDUFA III Commitment Letter) (available at https://www.fda.gov/media/153631/download), includes, among others, products with complex formulations (e.g., colloids) and complex routes of delivery (e.g., locally acting drugs such as dermatological products).

[4] *Bioequivalence* is defined in § 314.3(b).

[5] A *reference listed drug* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)). A *reference standard*, which is selected by FDA, is the specific drug product that the ANDA applicant must use in conducting any in vivo bioequivalence testing required to support

guidance does not address Q3 characterization of topical products for purposes of product quality control. Basic Q3 characterization of a topical product can be used to describe its dosage form (e.g., an emulsion). See section III of this guidance for more information on (1) a characterization of appearance and texture, (2) a characterization of phase states, and (3) a characterization of the structural organization of matter. These three types of characterizations typically constitute a basic Q3 characterization of a topical product.

Comprehensive Q3 characterization of a topical product can be used to compile a detailed profile of Q3 attributes that specifically describes the nature of that product and identifies a collection of attributes that describe the arrangement of matter (e.g., the polymorphic form(s) of the active ingredient(s) and/or the pH of the drug product) that may modulate the systemic or local availability of the active ingredient(s) from the product. See section III of this guidance for more information on the 10 types of characterizations that typically constitute a comprehensive Q3 characterization of a topical product.

Comprehensive Q3 characterization of a reference standard for a topical product provides a detailed profile of Q3 attributes that is quintessentially characteristic of that reference standard; it establishes a reference for the arrangement of matter in that drug product. Because Q3 characterization describes essential attributes of a drug product that may be critical to its performance, differences in Q3 attributes between a test topical product and reference standard can indicate a risk that the differences may potentially impact the respective bioavailability[6] (BA) and/or BE of the two products. Conversely, a demonstration that there are no significant differences in Q3 attributes between a test topical product and reference standard substantially mitigates the risk of potential failure modes for BE that may otherwise arise from any significant differences in Q3 attributes.

It is beyond the scope of this guidance to discuss specific reference standards for topical products or to enumerate the specific tests and comparative product characterizations that are recommended for each such product. FDA recommends that applicants consult this guidance in conjunction with any relevant product-specific guidances (PSGs)[7] and in conjunction with any other relevant guidances for industry[8] when considering the design and conduct of Q3 characterization tests that may be appropriate to support a demonstration that a proposed generic

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approval of its ANDA (see § 314.3(b)). We recommend that the reference standard also be used for in vitro testing. There may be circumstances (e.g., when the RLD is no longer marketed) in which the reference standard is a drug product other than the RLD. For more information on RLD and reference standard products, see the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] *Bioavailability* is defined in § 314.3(b).

[7] Generic drug product-specific guidances are available at the Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[8] Other relevant guidances include the draft guidances for industry *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs* (October 2022) and *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs* (October 2022). When final, these guidances will represent FDA's current thinking on these topics.

topical product and its reference standard are of the same dosage form[9] and are bioequivalent. FDA also recommends that applicants routinely refer to FDA's guidance web pages because additional guidances may become available that could assist in the development of a generic topical product.

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

This guidance has been developed as part of FDA's Drug Competition Action Plan,[10] which, in coordination with the Generic Drug User Fee Amendments (GDUFA)[11] program and other FDA activities, is intended to increase competition in the marketplace for prescription drugs, facilitate the entry of high-quality and affordable generic drugs, and improve public health.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) generally requires an ANDA to contain, among other things, information to show that the proposed generic drug product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD.[12] Thus, an ANDA will not be approved if the test product's dosage form differs from that of the RLD (and no suitability petition under section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93 was approved) and/or if information submitted in the ANDA is insufficient to show that the test product is bioequivalent to the RLD.[13] Generally, a generic drug

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[9] The proposed generic topical product generally must have the same dosage form as its RLD. See section 505(j)(2)(A)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(2)(A)(iii)), § 314.94(a)(6) (21 CFR 314.94(a)(6)), and § 314.127(a)(4) (21 CFR 314.127(a)(4)) (requiring ANDAs to contain information to show that the dosage form of the drug product is the same as that of the RLD absent an approved suitability petition); see also section 505(j)(2)(C) of the FD&C Act (permitting an ANDA applicant to submit a suitability petition requesting certain changes from the RLD, including a change in dosage form). In cases in which the reference standard is a drug product other than the RLD, we generally anticipate that a demonstration using Q3 characterizations that the proposed generic topical product has the same dosage form as its reference standard will be sufficient to demonstrate that the proposed generic topical product has the same dosage form as its RLD. However, there may be circumstances in which the proposed generic topical product may need to make an additional showing to demonstrate that its dosage form is the same as the RLD.

[10] See FDA Drug Competition Action Plan (implemented in 2017 and designed to, among other things, further encourage robust and timely market competition for generic drugs), available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan.

[11] In this guidance, *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012, Title III, Food and Drug Administration Safety and Innovation Act (Public Law 112-144), the Generic Drug User Fee Amendments of 2017, Title III, FDA Reauthorization Act of 2017 (Public Law 115-52), and the Generic Drug User Fee Amendments of 2022, Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).

[12] See section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94.

[13] See section 505(j)(2)(A)(iii) and (iv) of the FD&C Act; see also § 314.127(a)(4) and (a)(6).

product intended for topical use "shall contain the same inactive ingredients as [its RLD] . . . [h]owever, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[14]

Additionally, for a drug product that is a solution for application to the skin (i.e., a topical solution), in vivo BE may be self-evident and a requirement of in vivo data for a product may be waived.[15] The scientific principle is that if there is no difference in any aspect of the test product's formulation compared to the RLD's formulation that may significantly affect systemic or local availability, then BE between the test product and RLD is considered self-evident. This scientific principle applies to topical solutions as well as semisolid dosage forms. However, the Q3 attributes of semisolid dosage forms are generally more complex, compared to solutions. Therefore, a comprehensive characterization of relevant Q3 attributes in semisolid dosage forms is recommended to determine whether or not differences may exist in their physicochemical or structural attributes.

This guidance describes the concepts of sameness, similarity, or difference in Q3 attributes of topical products and describes specific product characterizations that can be used to demonstrate the sameness, similarity, or difference in Q3 attributes between test topical products and reference standards for topical products. These concepts (and relevant product characterizations) can apply to a drug product that is a solution for application to the skin (e.g., characterization of physicochemical properties like pH), and are particularly useful when comparing test topical products and reference standards for topical semisolid products.

As noted above, there are two primary purposes for which Q3 characterization may be useful for topical products:

1. To identify the dosage form.

   The nomenclature used to describe the dosage form of topical products (e.g., solutions, suspensions, gels, lotions, creams, shampoos, ointments, pastes, etc.) is not precisely defined by a systematic classification of the compositional, physicochemical, or structural attributes of the drug product. Consequently, for topical products, it may not be possible to infer the Q3 attributes of a particular dosage form based upon the dosage form nomenclature. For example, a product designated as a cream may be comprised of a classic oil-in-water emulsion microstructure, or it may be an aqueous dispersion of different components. An ointment may be comprised of different types of components with different types of Q3 attributes; as examples, an ointment may have an oleaginous hydrocarbon base as a single phase with particles of suspended active ingredient(s), or it may be a water-in-oil emulsion, or it may be comprised of a polyethylene glycol base. In addition, although lotions are typically considered to be more fluid than creams, this may not always be true, and some creams may contain a substantially greater percent composition of water and volatiles than some lotions. Also, although creams and lotions

[14] § 314.94(a)(9)(v).

[15] § 320.22(b)(3) (21 CFR 320.22(b)(3)).

are typically considered to be emulsions, structural features like globules or droplets may not always be evident, and conversely, some gels may be emulsion dosage forms.

For topical products submitted in ANDAs, a comparison of basic Q3 characterizations (explained in section III of this guidance) for both the test topical product and reference standard is recommended as a reliable approach to demonstrate that a test topical product and its reference standard are the same dosage form.[16]

2. To describe properties of the drug product that may be critical to its performance, which can support a demonstration of BE.

   Physicochemical attributes of a drug product, such as pH, or structural attributes, such as globule size, may have the potential to impact product performance, and these physicochemical or structural characteristics may be sensitive to the formulation design and manufacturing processes. Thus, comprehensive Q3 characterization establishes a detailed profile of measurements for Q3 attributes that may be critical to product performance under relevant conditions (e.g., at different temperatures, at different shear rates/stresses, at different times during metamorphosis, and/or after being dispensed from a container closure system).

   These Q3 attributes (discussed further in section III of this guidance) may confer important functionality to topical products. For example, the functional properties of a petrolatum-based ointment may include a relatively high occlusivity, high apparent viscosity, and long residence time at the site of administration. By contrast, the functional properties of an alcohol-based gel may include a relatively low occlusivity, low viscosity, and relatively rapid evaporation with characteristically rapid changes in the thermodynamic activity of the active ingredient(s) and in the rate of active ingredient delivery into the skin.

   Additionally, differences in Q3 attributes between a test topical product and its reference standard may alter BA and/or increase the risk of failure modes for BE. In the context of this guidance, failure modes are considered to be the mechanisms by which problems might arise with the BE (or expected therapeutic performance) of a drug product as a result of a difference in one or more attributes of a test topical product compared to its reference standard, which could result in undesirable consequences for a patient. For example, differences in Q3 attributes can affect the solubility or stability of the active ingredient(s) in the formulation, the number and types of phase states, the diffusion and partitioning of active and inactive ingredients within the formulation and/or into the skin, the metamorphosis of the formulation on the skin, and/or the thermodynamic activity profile of the active ingredient(s), all of which may influence BA and BE. Thus, a comparison of comprehensive Q3 characterizations of the test topical product and reference standard for a topical product may be submitted in an ANDA to support an assessment of whether there are differences in Q3 attributes between the test topical product and its reference standard that may affect BE.

[16] See footnote 9.

In summary, there are two primary purposes for which it is meaningful to compare the Q3 attributes of test topical products and reference standards for topical products. Basic Q3 characterization (explained in section III of this guidance) can describe the dosage form; thus, a comparison of basic Q3 characterizations can be used to demonstrate that the test topical product and its reference standard are the same dosage form.[17] Comprehensive Q3 characterization provides a detailed profile of relevant Q3 attributes that is quintessentially characteristic of the reference standard; thus, a comparison of comprehensive Q3 characterizations can be used to support a demonstration of BE when the detailed profile of Q3 attributes for the test topical product matches the detailed profile of Q3 attributes for the reference standard (discussed further in section IV of this guidance).

III. RECOMMENDATIONS FOR Q3 CHARACTERIZATION

Basic Q3 characterization of a topical product, which can be used to describe its dosage form (e.g., an emulsion), typically includes (1) a characterization of appearance and texture, (2) a characterization of phase states, and (3) a characterization of the structural organization of matter.

Comprehensive Q3 characterization establishes a detailed profile of Q3 attributes that may be critical to product performance under relevant conditions (e.g., at different temperatures, at different shear rates/stresses, at different times during metamorphosis, and/or after being dispensed from a container closure system). The Q3 attributes of the dispensed product may be important to characterize and compare between different packaging configurations for a test topical product (e.g., tube versus pump).

The particular Q3 attributes that should be assessed for a specific proposed generic topical product to obtain a comprehensive Q3 characterization will depend on the nature and complexity of its reference standard. The following list provides general recommendations on the characterizations that may be used (as feasible) to create a detailed profile of relevant Q3 attributes for a comprehensive Q3 characterization.

1. ***Characterization of appearance and texture***: includes as complete as possible a description of the look, feel, and smell of the dispensed product. Observations should characterize the color, clarity/opaqueness, texture, odor, and other product attributes (e.g., *free from particulate matter* or *free from particles of the active ingredien*t). For example, a specific cream may be described as *a white to off-white, smooth, opaque, soft-to-the-touch cream containing uniformly dispersed drug substance with an alcohol smell that is free from phase separation and foreign particulate matter*. As another example, a specific ointment may be described as *a yellowish, opaque, viscous semisolid ointment containing uniformly dispersed drug substance with a greasy texture and without an unpleasant*

[17] See footnote 9.

odor, lumps, or foreign particulate matter. As yet another example, a specific gel may be described as *a translucent, white, hydroalcoholic, flowable gel with an alcohol odor and no clumping or particulate matter*.

2. ***Characterization of phase states***: includes representative high resolution micrographs (microscopy images) at multiple magnifications, with detailed sample preparation information. High resolution micrographs of the drug product at different magnifications that illustrate the absence of undissolved particulate matter may support a determination that any active ingredient is dissolved in the dosage form. Similarly, high resolution micrographs of the drug product at different magnifications, which illustrate the absence of any visible microstructures, may support a determination that the drug product is a single-phase dosage form. In this manner, single-phase products, multiple-phase products (e.g., emulsions), and products with suspended active ingredient(s) (or an absence of particulate matter) can be differentiated.

3. ***Characterization of structural organization of matter***: includes an assessment of particle-size distribution and crystal habit, and/or emulsion globule-size distribution (as relevant, for multiple phase products). Full profiles of the particle- and globule-size distributions should be submitted for all relevant samples. In addition, for emulsions, the type of emulsion (e.g., oil-in-water or water-in-oil) should be assessed for the test topical product and reference standard using appropriate techniques (e.g., use of a water-soluble dye followed by microscopic evaluation, or dilution followed by assessment with a voltmeter).

4. ***Characterization of polymorphic form(s) of the active ingredient(s)***: includes in situ characterization within the drug product (for products with suspended active ingredient(s)). An absence of evidence for the existence of polymorphs does not constitute evidence that polymorphs do not exist. Therefore, a characterization of the polymorphic form(s) of the active ingredient in the test topical product and reference standard is typically recommended when the active ingredient (or unidentified particulate matter) is suspended in the drug product. The control of any polymorphic forms of the active ingredient in the test topical product should be justified in an ANDA, based upon the considerations outlined in Decision Tree #4 within the International Council for Harmonisation (ICH) guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000).

5. ***Characterization of rheological behavior***: includes the following characterizations using a rheometer appropriate for monitoring the (non-Newtonian) flow behavior of liquid and semisolid dosage forms (more sophisticated rheological characterizations may be appropriate in some circumstances):

    a. When feasible, complete flow curves (plotted as both shear stress versus shear rate and viscosity versus shear rate) should consist of multiple data points across the range of attainable shear rates, typically until low- or high-shear plateaus are identified; at a minimum, the apparent viscosity at low-, medium-, and high-shear rates should be characterized.

    b. Yield stress values should be reported if the material tested exhibits plastic flow behavior.

c. The linear viscoelastic response (storage and loss moduli versus frequency) should be measured and reported, if relevant.

6. ***Characterization of water activity and/or drying rate***: includes an assessment of evaporation rate and is recommended for certain drug products with volatile ingredients (including water). For example, it may be informative to evaluate the water activity for a topical product that is an emulsion containing less than 50% weight/weight (w/w) of water, because differences in manufacturing processes may impact the interactions between the multiple phases in the formulation. Similarly, it may be informative to measure the drying rate for an alcohol-based gel that is expected to evaporate rapidly following topical application. However, neither water activity nor drying rate may be relevant for a petrolatum-based ointment.

7. ***Characterization of pH and buffering***: includes a measurement of the pH of the product formulation, for drug products with an aqueous content, as well as a description of any buffer system, when relevant.

8. ***Characterization of oleaginous components***: includes using the tests listed in the relevant United States Pharmacopeia (USP) monograph for petrolatum, for petrolatum-based ointments containing approximately 70% (w/w) or greater oleaginous content; quantitative results should be reported for each test (not only a pass/fail result). For example, the average observed melting temperature (drop point) should be recorded when using the procedure described in USP <741> (Class III), and the pH of the pooled washings from the alkalinity test should be measured with a calibrated pH meter. A characterization of the relative proportions of different hydrocarbons in the topical product is recommended when characterizing or comparing oleaginous formulations (e.g., petrolatum-based ointments).

9. ***Characterization of specific gravity***: includes an assessment of the density of the product, which may be influenced by entrapped air, and should characterize the mass of drug product in a given volume.

10. ***Characterization of metamorphosis-related changes***: includes an assessment of the influence of dispensing the drug product from different packaging configurations (e.g., a tube versus a pump) on the Q3 attributes of the dispensed dose. A characterization of batches of different ages, ideally age-matched as closely as possible for the test and reference batches, is recommended to provide information on the metamorphosis of a formulation during its shelf life (e.g., involving a change in apparent viscosity, globule-size distribution, or particle-size distribution). If any Q3 attribute of a test topical product batch is outside the range characterized for that attribute among the batches of the reference standard (i.e., beyond the variability of the reference standard), the difference(s) in the Q3 attribute between the test topical product and reference standard may cause a difference in therapeutic performance.

The relevant comparative Q3 characterizations and any associated information described above should be submitted in the ANDA within the pharmaceutical development section of the electronic Common Technical Document (section 3.2.P.2). Information about the factors (e.g., related to the manufacturing process) that influence the Q3 attributes of the test topical product should also be included within section 3.2.P.2. The relevant comparative Q3 characterizations

should be performed with a minimum of three batches of the test topical product and with three batches (as available) of the reference standard.

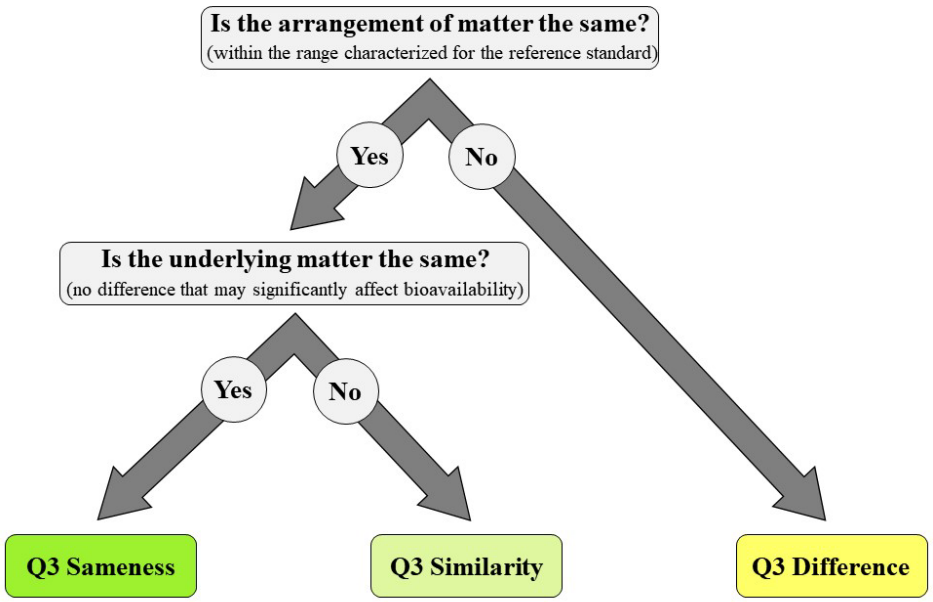
IV. Q3 COMPARABILITY AND IMPLICATIONS FOR BIOEQUIVALENCE

A detailed profile of relevant Q3 attributes describes the arrangement of matter in a particular product formulation. That underlying matter may include hydrogen ions (which can be characterized by a pH measurement), polymers (whose structural organization and interactions bestow a formulation with characteristic rheological properties), solvents (whose physicochemical and structural interactions with other matter bestow a formulation with a characteristic solvent activity and evaporation profile), or other types of matter.

The Q3 characterization of a product formulation describes the arrangement of matter in that specific (individual) formulation. Because a Q3 characterization of a product formulation only describes the arrangement of matter in that specific (individual) formulation, a Q3 characterization does not inherently involve a comparison. Therefore, when comparing the Q3 attributes of two product formulations, separate concepts are needed to describe how the detailed profiles of Q3 attributes compare—i.e., the concepts of sameness, similarity, and difference.

Comparative Q3 characterizations of a test topical product and its reference standard may reveal that the detailed profiles of relevant Q3 attributes for the two topical products are the same, similar, or different. This section describes the concepts of *Q3 sameness*, *Q3 similarity*, and *Q3 difference* (with a simplified illustration in Figure 1) and discusses the potential relevance of each to supporting a demonstration of BE in an ANDA for a topical product.

Figure 1: A Simplified Illustration of Q3 Sameness, Q3 Similarity, and Q3 Difference



A. Q3 Sameness

A test topical product that meets the following criteria would generally be considered as *Q3 the same* as its reference standard:

a. Each relevant Q3 attribute of the test topical product, characterized in multiple batches, is:
   i. demonstrated by the applicant to be within the range characterized for that Q3 attribute of the reference standard for the topical product, potentially characterized in multiple batches, or
   ii. determined by the Agency to be within the acceptable variability for the reference standard for the topical product[18]; and

b. There is no difference[19] in the components or composition of the test topical product and reference standard for the topical product that may significantly affect systemic or local availability.

A demonstration of Q3 sameness between a test topical product and its reference standard substantially mitigates the risk of potential failure modes for BE. Consequently, a test topical product that is a solution for application to the skin and is Q3 the same as its reference standard would generally satisfy the criteria for a waiver of evidence of in vivo BA or BE outlined in § 320.22(b)(3).[20] For a test topical semisolid product that is shown to be Q3 the same as its reference standard, only limited additional (in vitro, in silico, and/or in vivo) evidence may generally be recommended to support a demonstration of BE.[21] In general, for a test topical semisolid product that would satisfy the criteria for Q3 sameness (defined above), a demonstration of BE may include the comparative Q3 characterizations of the test topical product and reference standard for a topical product (per the recommendations in section III of

[18] FDA may supply acceptance criteria for Q3 attributes in a PSG. See footnote 7.

[19] Certain differences in the components or composition of the test topical product and reference standard for a topical product may not preclude a demonstration of Q3 sameness where the differences would not be expected to significantly affect systemic or local availability. Examples of such differences could include a test topical product that (1) contains a quantitative difference in the amount of a pH-adjusting agent (that is used to adjust the pH of the test product to be the same as that of the reference standard), (2) uses the same quantitative amounts (or quantitative ranges) of each of the same subcomponents of a preblended ingredient used in the reference standard, or (3) uses a different grade of the same inactive ingredient that is considered to have the same identity as the inactive ingredient used in the reference standard.

[20] We note that § 320.22(b)(3) requires a comparison between the formulation of the test topical product and the RLD. Although ordinarily the reference standard is the RLD, in certain circumstances the reference standard is a drug product other than the RLD. See footnote 5. We additionally note that the inactive ingredients in a generic topical product need not match those in the RLD so long as the applicant "identifies and characterizes [any] differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." 21 CFR 314.94(a)(9)(v). In certain circumstances—i.e., where the reference standard is a drug product other than the RLD, and where the reference standard has different inactive ingredients than the RLD—it is possible that a showing of Q3 sameness between the test product and the reference standard would not necessarily satisfy the criteria for a waiver under § 320.22(b)(3).

[21] Specific recommendations for demonstrating BE for any particular test topical product compared to its reference standard are beyond the intended scope of this guidance.

this guidance), as well as a demonstration of an equivalent rate of release for the active ingredient from the test topical product and reference standard for a topical product, based upon an acceptable in vitro release test (IVRT). In addition, for products that are emulsions, FDA typically recommends that applicants demonstrate there is no significant difference in the rate and extent of BA for the active ingredient based upon an acceptable in vitro permeation test (IVPT), as relevant to the site and mechanism of action. The draft guidances for industry *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs* (October 2022), and *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs* (October 2022) provide additional information relating to the IVRT and IVPT studies that can support a demonstration of BE (when final, these guidances will represent FDA's current thinking on these topics).

B. Q3 Similarity

A test topical product that meets the following criteria would generally be considered as *Q3 similar* to its reference standard:

a. Each relevant Q3 attribute of the test topical product, characterized in multiple batches, is:
   i. demonstrated by the applicant to be within the range characterized for that Q3 attribute of the reference standard for the topical product, potentially characterized in multiple batches, or
   ii. determined by the Agency to be within the acceptable variability for the reference standard for the topical product[22]; and

b. There is a difference in the components or composition of the test topical product and reference standard for the topical product that may significantly affect systemic or local availability.

A demonstration of Q3 similarity between a test topical product and its reference standard substantially mitigates the risk of many potential failure modes for BE, but not those arising from the specific difference(s) in the components or composition of the test topical product and its reference standard. Consequently, a test topical product that is a solution for application to the skin and is Q3 similar to its reference standard would generally not satisfy the criteria for a waiver of evidence of in vivo BA or BE outlined in § 320.22(b)(3). For a test topical semisolid product that would satisfy the criteria for Q3 similarity (defined above), demonstrating BE may include all the evidence recommended for a test topical semisolid product that is shown to be Q3 the same as its reference standard, as well as evidence to mitigate the risk of specific failure modes for BE associated with the difference(s) in the components or composition of the test topical product and its reference standard.

For such products, the following should be considered: (1) what failure modes for BE might arise from the specific difference(s) in the components or composition between the test topical product and reference standard, and (2) what evidence could mitigate the risk of those specific failure

[22] See footnote 18.

modes for BE. For example, if a test topical product that would satisfy the criteria for Q3 similarity contains only inactive ingredients in proposed amounts that would not exceed the amounts of the same inactive ingredients in FDA-approved drug products (see information in FDA's Inactive Ingredient Database[23]) for a similar context of use, this would mitigate the risk of some potential failure modes for BE.

C. Q3 Difference

A test topical product in an ANDA that meets the following criteria would generally be considered as *Q3 different* from its reference standard:

a. One or more relevant Q3 attributes of the test topical product, characterized in multiple batches, is:
   i. not demonstrated by the applicant to be within the range characterized for that Q3 attribute of the reference standard for the topical product, potentially characterized in multiple batches, and
   ii. not determined by the Agency to be within the acceptable variability for the reference standard for the topical product; and

b. There may or may not be a difference in the components or composition of the test topical product and reference standard for the topical product that may significantly affect systemic or local availability.

Because there are myriad reasons why a test topical product may be shown to be Q3 different from its reference standard, it is beyond the scope of this guidance to make recommendations about what additional evidence may be recommended to support a demonstration of BE in such situations.

V. COMMUNICATIONS WITH THE AGENCY

If a prospective ANDA applicant is developing a topical product and has questions about a BE approach (potentially based upon Q3 characterization), the prospective applicant may submit a controlled correspondence[24] to FDA, or if the topical product is a complex product (i.e., not a topical solution), may request a pre-ANDA meeting with FDA.[25] A controlled correspondence is appropriate if the prospective applicant has a specific and targeted inquiry about the generic drug

[23] See, e.g., the draft guidance for industry *Using the Inactive Ingredient Database* (July 2019). When final, this guidance will represent FDA's current thinking on this topic. The Inactive Ingredient Database is available at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

[24] See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020) for information on the types of inquiries accepted as controlled correspondence and on how to submit controlled correspondence to the Office of Generic Drugs.

[25] A pre-ANDA meeting may be granted for topical solutions that would not qualify for a waiver under § 320.22(b)(3), when resources permit and when a meeting would add value to the ANDA development program. See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (November 2020) for information on the enhanced pathway for discussions between FDA and a prospective applicant preparing to submit an ANDA for a complex product as defined in that guidance.

development process. For example, a controlled correspondence is particularly useful when a prospective applicant seeks feedback from the Agency about whether a proposed formulation (or up to three formulations) would be suitable for a specific BE approach recommended in a PSG.

A pre-ANDA meeting is mainly intended to assist complex generic drug development. A pre-ANDA meeting is appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter that would fall outside the scope of controlled correspondence for a complex product. A pre-ANDA meeting is particularly useful when a prospective applicant seeks feedback from the Agency about whether a proposed formulation (or up to three formulations) would be suitable for a specific BE approach proposed by the prospective applicant as an alternative to a recommended BE approach in the PSG for that drug product, or in instances where there is no PSG available for the specific complex product. Prospective applicants intending to submit an ANDA for a topical product that relies upon a Q3-characterization-based BE approach, for which relevant recommendations have not been published in a PSG, are encouraged to request a pre-ANDA meeting with FDA to discuss their proposed BE approach.

FDA recommends that applicants perform, at minimum, basic Q3 characterization (explained in section III of this guidance) of the reference standard before submitting a controlled correspondence or pre-ANDA meeting request. In addition, product characterizations relevant to the nature, complexity, and identification of potential failure modes for BE[26] associated with the test topical product will help to facilitate communication and/or discussion between the applicant and FDA. Although FDA does not communicate information to prospective applicants about whether a proposed test topical product is Q3 the same as (or similar to) the reference standard, the Agency does intend to communicate whether specific proposed formulations may be suitable ones with which to demonstrate BE using a specific approach proposed by the prospective applicant or recommended by FDA in a PSG.

[26] See the ICH guidance for industry *Q9 Quality Risk Management* (June 2006).