#279

Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered to be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting

Guidance for Industry

Submit comments on this guidance at any time. 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 FDA-2023-D-1275.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
June 2024

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Contains Nonbinding Recommendations

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Guidance for Industry

This guidance represents 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 describes an alternative approach for satisfying the requirements for the completion of the Bioequivalence technical section for generic Type A medicated articles (TAMAs) containing poorly soluble, locally acting, active pharmaceutical ingredients (APIs) that have little to no systemic absorption (and hence little to no systemic bioavailability), and for which blood level studies are not considered appropriate to demonstrate product bioequivalence. For the purpose of this guidance, poorly soluble refers to TAMAs containing APIs that do not meet the criteria of fully soluble as defined in Guidance for Industry (GFI) #171.[1] This guidance does not cover TAMAs containing poorly soluble APIs that are systemically absorbed and for which blood level bioequivalence studies are appropriate. For those TAMAs containing poorly soluble APIs that are systemically absorbed, sponsors should contact CVM to determine if the study attributes as described in GFI #35[2] are applicable.

This guidance is applicable to generic investigational new animal drug (JINAD) files and to abbreviated new animal drug applications (ANADAs). Although the recommendations in this guidance are discussed relative to generic new animal drug applications, the general principles described to demonstrate product bioequivalence may also be applicable to pioneer new animal drug applications (NADAs), investigational new animal drug (INAD) files, and supplemental ANADAs and NADAs.

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

[1] GFI #171, "Demonstrating Bioequivalence for Soluble Powder Oral Dosage Form Products, and Type A Medicated Articles Manufactured from Active Pharmaceutical Ingredients Considered to be Soluble in Aqueous Media," https://www.fda.gov/media/131173/download) (June 2023).

[2] GFI #35, "Bioequivalence Guidance," (https://www.fda.gov/media/70115/download) (November 2006).

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Section 512(c)(2)(A)(vi) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that generic new animal drug products be shown to be bioequivalent to the reference listed new animal drug (RLNAD), and section 512(n)(1)(E) of the FD&C Act requires that the sponsor provide information to show that the proposed product is bioequivalent to the RLNAD. Two products are considered to be bioequivalent when they are equal in the rate and extent to which the active pharmaceutical ingredient (API) becomes available at the site(s) of drug action (section 512(c)(2)(H)(i) of the FD&C Act). FDA's Center for Veterinary Medicine (CVM) has issued guidance on demonstrating bioequivalence through *in vivo* studies, and guidance on product types that may be eligible for a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaivers), including oral solutions and other solubilized forms, parenteral solutions, some topically applied dosage forms[3] and TAMAs with APIs that are considered to be water soluble.[4]

These guidance documents do not specifically address the unique challenges associated with demonstrating bioequivalence of TAMAs containing poorly soluble, locally acting APIs. As stated in GFI #35, the preferred hierarchy of bioequivalence studies (in descending order of sensitivity) is the blood level study, pharmacologic end-point study, and clinical end-point study. Because TAMAs containing poorly soluble, locally acting APIs are not amenable to demonstrating bioequivalence through *in vivo* blood level studies or pharmacologic end-point studies, a demonstration of bioequivalence would normally involve submission of clinical end-point bioequivalence study data for each indication, but this approach does not account for the unique characteristics of these products and typically would require multiple clinical end-point studies using hundreds of animals. While the use of multiple clinical end-point studies is still a valid scientific approach, CVM believes that the approach as described in this guidance document provides an alternative path to obtaining the required data for the demonstration of bioequivalence, while preserving the scientific foundations of such a determination. This alternate approach refines and reduces the use of animals in the pre-approval setting and addresses the obstacles associated with multiple clinical end-point studies, thereby reducing the number of clinical end-point studies needed to support bioequivalence of these products. In so doing, this approach can enhance the availability of generic drug products that have characteristics that do not align well with the recommendations in previously published guidance.

The approach to demonstrating bioequivalence as described in this guidance incorporates several established concepts that are described in bioequivalence guidance(s) for other dosage forms, using a combination of *in vitro* and *in vivo* data to support a determination of bioequivalence. The use of comparative physicochemical evaluations in concert with *in vitro* drug release are well-documented approaches to the demonstration of bioequivalence for a variety of human drug

[3] See footnote 2 on page 1.

[4] See footnote 1 on page 1.

products. While the application of this approach to TAMAs containing poorly soluble, locally acting APIs has not previously been described, the underlying principles are consistent with how CVM has approached the determination of bioequivalence in several other dosage forms. Consistent with previous guidance, an *in vivo* clinical end-point study remains an essential component of the evidence supporting a determination of bioequivalence for TAMAs containing poorly soluble, locally acting APIs.

Based on the Agency's experience using both *in vivo* and *in vitro* data to support a determination of bioequivalence, the alternate approach described herein should provide sufficient scientific evidence to demonstrate bioequivalence of TAMAs containing poorly soluble, locally acting APIs that have little to no systemic absorption.

III. Bioequivalence Approach for Poorly Soluble, Locally Acting Type A Medicated Articles

For TAMAs containing APIs that fail to meet the biowaiver criteria as defined in CVM's GFI #171, and for which *in vivo* blood level or pharmacologic end-point studies are not considered appropriate for demonstrating product bioequivalence, the rate-limiting factor influencing the equivalence of the proposed generic and reference products is their respective *in vivo* dissolution characteristics. Such a product's formulation and physicochemical characteristics are key determinants of *in vivo* dissolution performance. Based on an understanding of the critical factors influencing the rate and extent of API availability at the site of activity for these products, the determination of product bioequivalence can be based upon a combination of *in vitro* and *in vivo* bioequivalence assessments typically consisting of the following:

a. Qualitative (Q1), Quantitative (Q2), and Physicochemical (Q3) equivalence of the generic and RLNAD TAMA. In this context, equivalence is defined as the absence of any differences that would have an impact on the rate and extent that the API reaches its active site.

b. Equivalence of the *in vivo* performance of the generic and RLNAD TAMAs when used as indicated for one indication in each major species on the RLNAD product label.

c. Comparative *in vitro* dissolution testing of the generic and RLNAD TAMA formulations under varying conditions.

An assessment of bioequivalence will then be made by evaluating the data from the three determinations (a, b, and c) in its entirety. Therefore, if one determination (a, b, or c) in this approach fails to indicate sameness, then the product would be determined not to be bioequivalent. This approach leverages an understanding that the purpose of a clinical end-point bioequivalence study is not to repeat an effectiveness study to determine the dose-effect relationship of a particular drug, but rather it is to detect any formulation difference between the generic product and the RLNAD that may affect product bioavailability. As such, a separate clinical end-point study for multiple indications is unnecessary if the rate and extent of API availability at the site of action is not dependent on the indication and the products are sufficiently similar that any differences are not expected to impact the *in vivo* dissolution behavior. Thus, a determination of bioequivalence can be made based on the combined

acceptable *in vitro* dissolution and physicochemical comparisons, along with a successful clinical end-point bioequivalence assessment.

A. Data to Support a Determination of Bioequivalence

1. Q1, Q2, and Q3 Comparison to the RLNAD

Q1, Q2, and Q3 data from the generic TAMA should demonstrate equivalence to the RLNAD. CVM recommends testing multiple lots of the generic product (minimum of three) in parallel with multiple lots (minimum of five) of the RLNAD.

a. Q1 and Q2 (Qualitative and Quantitative Assessment)

Q1 and Q2 equivalence requires that the same API at the same concentration is used for the proposed generic and RLNAD products and that there are no differences in inactive ingredients that may significantly affect the bioavailability of the API(s). If there are known differences in the proposed formulation relative to that of the RLNAD, a justification should be provided as to why the proposed change will have no effect on the equivalence of the two products. If the API is biomass derived (i.e., where the drug substances may contain the active molecule(s), inactivated microorganisms used for production, other metabolites produced by the microorganisms used for production, and media components), the biomass characterization will be considered in the Q1 assessment.

b. Q3 (Physicochemical Assessment)

A meeting with CVM's Office of New Animal Drug Evaluation's (ONADE) Division of Manufacturing Technologies (HFV-140) should be requested to discuss the Q3 attribute characterizations needed to support a demonstration of product comparability. The physicochemical tests should reflect the critical quality attributes (CQAs) of the RLNAD, which are determined by formulation and manufacturing process. Testing should include all compendial tests, as well as impurity analysis and particle size distribution. If a United States Pharmacopeia (USP) monograph is not published for the RLNAD, then the attributes for evaluation should include assay and impurity analysis, along with a particle size distribution comparison of the generic and RLNAD products.

CVM considers the particle size distribution of the API to be a critical attribute impacting the bioequivalence of locally acting TAMAs but recognizes there is no practical way to measure the API particle size distribution when comparing the generic and RLNAD TAMAs. In lieu of directly comparing the API particle size distributions, the particle size distribution of the generic and RLNAD TAMAs should be assessed with the awareness that these data will include particle size information from both the API and excipients, making a meaningful comparison more difficult. The particle size distribution range of the generic TAMA should match or be within that of the RLNAD.

2. *In Vivo* Bioequivalence Studies

Sponsors should submit data demonstrating that their proposed product is bioequivalent to that of the RLNAD in an *in vivo* clinical bioequivalence study for one of the indications, for each major species on the RLNAD labeling. Typically, the indication being evaluated should have its site of action within the portion of the GI tract closest to the site of *in vivo* dissolution (i.e., where there are multiple indications, then sponsors should choose the one which is closest to the site where the majority of the *in vivo* dissolution is occurring). Sponsors proposing to demonstrate bioequivalence of an indication associated with a site not meeting this description, such as when local sites of action are situated throughout the gastrointestinal tract and the chosen indication's site of action is not the one closest to where the majority of the *in vivo* dissolution is occurring, should contact CVM to discuss the acceptability of the proposal prior to submission of a protocol or conducting an *in vivo* study. The *in vivo* clinical end point bioequivalence studies should be conducted using identical doses for the test and reference products, and the dose should be within the approved dose range for the RLNAD. CVM highly recommends the submission of a protocol prior to initiating pivotal studies. If one of the indications requires systemic drug absorption for activity, a blood level bioequivalence study will be necessary to demonstrate bioequivalence for that indication in lieu of, or in addition to, a clinical end-point study, even if another indication is associated solely with local drug concentrations. If a blood level study is needed, then a meeting should be arranged with CVM to determine the best path forward to demonstrate product bioequivalence.

3. Comparative *In Vitro* Dissolution Testing

The pivotal dissolution data should include at least three sets of dissolution curves, with each set using a different set of dissolution conditions (e.g., pH, paddle speed, buffer and/or surfactants). Prior to starting the pivotal studies, CVM recommends that sponsors submit preliminary data for five (5) dissolution conditions, using the RLNAD, so that CVM can concur upon the use of three of these conditions to support the pivotal generic-reference product comparison. For at least one of the pivotal dissolution conditions, the average percent dissolved for the RLNAD should be at least 85% and be demonstrably discriminatory (for example, the ability to detect changes in the rate and extent of API release due to modifications in product CQA's, or the ability to distinguish between marketed lots of the RLNAD).

a. Sample Considerations

- Across all *in vitro* test conditions, all proposed generic and RLNAD samples should contain the same amount (typically expressed as weight) of the TAMA.

- For any test condition, the volume of medium should be sufficient to ensure that the rate and extent of dissolution is determined by formulation rather than API solubility limitations. Sink conditions are desirable but may not be possible across all three test conditions. Optimally, the same volume of

medium will be used across all dissolution procedures. The amount (weight) of the TAMA sample used across all test conditions should be selected such that the *in vitro* dissolution is sensitive to potential formulation effects.

b. Generating Comparative Dissolution Data

The pivotal test should compare the *in vitro* dissolution profiles (12 vessels per lot) obtained from a minimum of five lots of the RLNAD and three lots of the proposed generic product.

- Typically, USP apparatus II (paddle) should be employed. If a sponsor determines that some other USP apparatus is preferable, the sponsor should provide their rationale for this decision to CVM.

- Typically, when the paddle is employed, rotational speeds should not exceed 100 RPM. Issues such as foaming, and fluid hydrodynamics should be considered when selecting a paddle speed.

- The temperature of the dissolution media should be consistent with that found in the digestive tract of the indicated species.[5]

- The pH range covered by the dissolution media should be consistent with that found across the digestive tract of the indicated species, as documented in GFI #171. If it is observed that the RLNAD degrades at a particular pH, the sponsor should provide data confirming this degradation. That information should be provided to CVM as justification for excluding that specific condition from the media used in the bioequivalence assessment.

- The buffers used in the media should be consistent with those documented in the USP Reagents and Reference Tables for Buffer Solutions.

- At least one condition should achieve ≥ 85% dissolution of the RLNAD formulation, and all conditions should achieve at least 60% dissolution.

- The use of surfactants should not exceed 2.0%. Justification for surfactant selection should be provided.

c. Dissolution Curves

- Dissolution methods should be discriminative. If dissolution is such that CVM questions the dissolution condition's ability to detect inter-product

[5] The use of a single set of *in vitro* conditions is generally considered appropriate for confirmation of product bioequivalence within a species. However, where there are multiple species involved there can be clinically relevant inter species differences that may impact the dissolution profile of the API and thereby affect the bioavailability of the API. Therefore, the dissolution conditions used to evaluate bioequivalence in one species may not be appropriate or acceptable for the evaluation of bioequivalence in animals of different species.

differences, then CVM will request more information to demonstrate the discriminative nature of the selected condition.

- The selection of dissolution timepoints should be such that it characterizes the beginning, middle, and terminal portions of the *in vitro* dissolution versus time profiles. It is acceptable for some modification in timepoint selection across the dissolution conditions if there are substantial differences in profile shape between the separate dissolution conditions. However, it is highly advised that if such modifications are needed, they be justified on the basis of the pilot study data generated with the RLNAD. These results should be discussed with CVM prior to initiating the pivotal dissolution study.

- Dissolution curves should show a gradual increase in percent dissolved over time (i.e., no less than 4 time points prior to reaching maximum dissolution). The first time point should be taken no later than 15 minutes after the initiation of testing. Product dissolution should proceed gradually over time. Samples should be taken to adequately define the entirety of the profile. For at least one of the conditions, the duration of the in vitro dissolution study should continue until at least 85% dissolution is achieved. For the other two conditions, no less than 60% dissolution should be achieved. If the methods are not adequate to achieve these criteria for % dissolved, modification of the *in vitro* dissolution method should be considered.

d. Criteria for Demonstrating Profile Comparability[6]

Dissolution comparisons will include both within and between lot comparisons and are expected to have a high variability between lots of the TAMAs. When the variability in the dissolution of the TAMA precludes the use of the f2 metric, the recommended method for generic versus RLNAD profile comparisons is the tolerance limit approach.[7] Alternatives to the use of this approach can be proposed by sponsors and will be considered on a case-by-case basis.

e. Data Acceptability

Because these TAMAs contain drugs that do not meet the solubility criteria described in CVM GFI #171, the resulting product dissolution is expected to proceed slowly (i.e., a test duration of greater than 4 hours prior to achieving 85% dissolved). Conditions that result in profiles that rapidly achieve a maximum

[6] In this context comparability means that there are no changes or differences that would alter the rate and extent at which the API interacts with its active site.

[7] Martinez MN and Zhao X. A Simple Approach for Comparing the *In-vitro* Dissolution Profiles of Highly Variable Drug Products: A Proposal. The AAPS Journal (2018) 20:78.

percent dissolved, that fail to adequately describe early, middle, and late phases of product *in vitro* behavior, or that fail to discriminate between batches that differ in the CQAs will affect CVM's final decision. What constitutes an appropriate demonstration of the discriminatory nature of the test is product specific and therefore should be discussed with CVM prior to proceeding with the pivotal *in vitro* dissolution study.

IV. Logistical Considerations

To maximize process efficiency for demonstrating the bioequivalence of TAMAs containing poorly soluble APIs (Figure 1), the sponsor should consider the following:

1. Meetings should be arranged with CVM early in the product development process to obtain recommendations on preliminary studies, data to be collected, and the most expeditious way to submit pilot and pivotal data for CVM review.

2. Protocols for all studies should be submitted for CVM concurrence prior to initiating pivotal studies.

3. To be considered bioequivalent to an RLNAD TAMA, all three components (Q1, Q2, and Q3 equivalence; *in vitro* dissolution comparisons; and *in vivo* bioequivalence assessment) should be evaluated by CVM and found to meet the criteria for declaring the proposed generic and reference product bioequivalent.

4. It is recommended that pivotal *in vivo* studies be initiated after the Q1, Q2, and Q3, and dissolution studies are completed.

V. Post-approval Changes

In addition to the typical chemistry, manufacturing, and controls (CMC) expectations for any post-approval change, the post-approval requirements for TAMAs with poorly soluble APIs may have additional considerations to address in order to demonstrate that bioequivalence has not been affected. These include but are not limited to:

A. Change to API Source

1. For a change in API supplier for a TAMA containing a poorly soluble API, a Q3 assessment of the drug product manufactured with the approved and proposed API source should be provided. At a minimum, testing should include assay (including potency, as applicable) and impurities testing, and should comply with all compendial requirements. In addition, a direct comparison of the particle size distributions of the API from the approved and proposed supplier(s) should be made. If particle size analysis is performed using sieving, at least five individual sieves within the range should be used; if a particle size analyzer is used, then D10, D50, and D90 should be reported. If the particle size distribution of the proposed API source changes relative to that of the approved API source, CVM may request additional data to support the approval if the nature of the change

leads to an uncertainty as to whether it has the potential to impact *in vivo* product performance.

2. For a new supplier of a biomass API, or a change in production microbial strain for an existing supplier, full characterization of the biomass API, including impurities, should be provided in addition to a comparison of particle size distributions of the proposed versus approved API.

B. Change in Manufacturing Process

For a change in the manufacturing process, a Q3 assessment of the TAMA manufactured before and after the change should be provided. If the process used to manufacture the TAMA changes such that it has the potential to impact *in vivo* product performance (as defined by changes identified in the Q3 assessment), CVM may request additional data to demonstrate that the change in manufacturing process does not impact the bioavailability of the API.

VI. Human Food Safety (HFS) Considerations

The submission of acceptable data to satisfy the requirements of a bioequivalence technical section does not imply that the drug product has satisfied the HFS technical section requirements for an (A)NADA. For drug product approval, all applicable legal requirements must be met, which includes addressing the tissue residue portion of the HFS technical section of the application. Sponsors should contact ONADE's Division of Human Food Safety (HFV-150) to discuss what, if any, additional information may be needed to satisfy the HFS requirements for an approval.

Figure 1. Decision tree for the applicable use of GFI #279