# #171

# Draft Revised Guidance for Industry

## Waivers from the Requirement to Demonstrate Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles

***This guidance document is being distributed for comment purposes only.***

*This draft revised Guidance #171 is intended to provide clarification of the scientific basis for concepts and recommendations conveyed in the original guidance. In addition, the table containing estimated gastric volumes for each of the various animal species has been revised. However, applicants may propose an alternative gastric volume value for a particular species when using the dosage adjusted approach. No new concepts have been introduced in this draft revised guidance and its scope has not been modified.*

Submit comments on this draft revised guidance by the date provided in the *Federal Register* notice announcing the availability of the draft revised guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2004-D-0045 (formerly 2004D-0283).

For questions regarding this document, contact Charli M. Long, Center for Veterinary Medicine (HFV-170), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-402-0850, email: charli.long-medrano@fda.hhs.gov.

Additional copies of this draft revised guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Veterinary Medicine**
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# Draft Revised Guidance for Industry

# Waivers from the Requirement to Demonstrate Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles

*This draft guidance, when finalized, represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 office responsible for this guidance as listed on the title page.*

## I. PURPOSE

This draft revised guidance document describes how the Center for Veterinary Medicine (CVM) intends to evaluate requests for waiving the requirement for submitting data demonstrating the bioequivalence of animal drugs in soluble powder oral dosage form products and Type A medicated articles. It expands upon CVM's Bioequivalence Guidance,[1] particularly the section on Criteria for Waiver of *In Vivo* Bioequivalence Study.

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

The recommendations in this draft revised guidance are premised on the assumption that a sponsor will be bridging between identical dosage forms (e.g., Type A medicated article for use in complete feed to Type A medicated article for use in complete feed; soluble powder for use in drinking solution to soluble powder for use in drinking solution). Therefore, it is not appropriate to use the recommendations in this guidance to compare the solubility of two drug products where the active pharmaceutical ingredient (API) will be administered in differing manners (e.g., drinking water versus complete feed, complete feed for administration throughout the day versus top dress). CVM encourages sponsors to contact the Center to discuss that type of comparison.

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.

[1] CVM Guidance for Industry #35, "Bioequivalence Guidance," November 8, 2006 (see page 7).

## II. BACKGROUND

In general, an ANADA must include information to show that the proposed generic new animal drug and reference listed new animal drug (RLNAD) are bioequivalent.[2] This requirement is patterned very closely on the human generic drug provision.[3]

The Center for Drug Evaluation and Research's (CDER) regulations implementing the bioequivalence requirement are at 21 CFR part 320. In most cases, there must be an *in vivo* demonstration of no significant differences in the rate and extent of drug availability associated with the proposed generic and reference drug products when administered at the same molar dose under similar conditions.[4] In certain circumstances, however, the demonstration of bioequivalence does not need to be established on the basis of *in vivo* studies.[5] For several categories of human drug products, including oral solutions, bioequivalence is considered self-evident under specified conditions. In other circumstances, a large body of research on human intestinal physiology has been used to support a determination of product bioequivalence of solid oral dosage forms based upon the use of *in vitro* approaches.[6] In this regard, the human Biopharmaceutics Classification System (BCS) criteria have been applied to support the use of an *in vitro* approach to document product bioequivalence for highly soluble, highly permeable, rapidly dissolving, and orally administered drug products.[7] However, because the BCS criteria have been established without considering the physiology of the gastrointestinal tract of veterinary species, these criteria cannot be applied to support the use of an *in vitro* approach to document product bioequivalence for highly soluble, highly permeable, rapidly dissolving, and orally administered veterinary drug products.

CVM has issued guidance on *in vivo* bioequivalence studies, which includes a list of some of the product categories, including oral solutions and other solubilized forms that may be eligible for an *in vivo* bioequivalence waiver. That guidance states, "in general, the generic product being considered for a waiver contains the same active and inactive ingredients in the same dosage form and concentration and has the same pH and physicochemical characteristics as an approved pioneer product."[8] This draft revised guidance provides additional information and recommendations regarding bioequivalence waivers for soluble powder oral dosage form products intended for use in animal drinking water and Type A medicated articles intended for use in animal feed.

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[2] Section 512(n)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).
[3] Section 505(j)(2)(A)(iv) of the FD&C Act.
[4] 21 CFR 320.1(e) and 320.21(b). CDER's guidance on how to meet the bioequivalence requirements set forth in 21 CFR part 320 is contained in CDER Draft Guidance for Industry, "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations," March 2014 (see page 3).
[5] 21 CFR 320.21(b), (f), and 320.22.
[6] 21 CFR 320.22(b)(3). CDER Draft Guidance for Industry, "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations," March 2014 (see page 10-12).
[7] Additional information about these waivers and the biopharmaceutics classification system CDER uses are in CDER Draft Guidance for Industry, "Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," May 2015 (see pages 3-9).
[8] CVM Guidance for Industry #35, "Bioequivalence Guidance," November 8, 2006 (see page 7).

## III. **DISCUSSION**

This draft revised guidance describes how CVM intends to evaluate requests to waive the requirements for conducting a bioequivalence study, hereafter referred to in this guidance as "biowaivers," for certain categories of animal drug products.

### A. Biowaivers for soluble powder oral dosage form products.

CVM believes it is appropriate to grant biowaivers for oral dosage forms known as "soluble powders" that meet the solubility requirements discussed in this guidance. Such products are intended for administration to animals via the drinking water that is provided on an *ad libitum* basis under most husbandry systems.

The conceptual basis for granting biowaivers for "soluble powders" is that once an API is in solution before administration, the drug product's formulation will usually not influence the bioavailability of the active ingredient. This is because, from a mechanistic perspective, the rate-limiting step in systemic API absorption will be: a) the rate of gastric transit, or b) the permeability of the API across the gastrointestinal (GI) mucosal membranes. Both of these variables are formulation-independent, relying solely on the API and the characteristics of the GI tract of that animal species. Similarly, if an API acts locally within the GI tract (i.e., not systemically absorbed), the local exposure to the dissolved API in the proposed and reference drug product formulations will be equivalent if the API is already in solution because the rate-limiting step is the API movement down the GI tract and its lateral diffusion across the viscous intestinal contents. The only exceptions of which CVM is aware are when the formulation of the drug product contains substances other than the API that could cause a direct pharmacologic effect (e.g., altered GI transit time, membrane permeability, or drug metabolism), or when there is inactivation of the API by, for example, a chelating agent.

Therefore, in making biowaiver decisions for soluble powders, CVM intends to evaluate: 1) solubility data provided by the sponsor to ensure that, before administration, the drug product will go into solution under the range of physical conditions that a user of the drug product would typically encounter when adding the soluble powder to animal drinking water in the field; and 2) the drug product's formulation to ensure that there are no differences between the reference and proposed drug product formulations likely to adversely affect the performance of the proposed drug product, e.g., cause adverse pharmacologic effects or alter the bioavailability of the API.

### B. Biowaivers for Type A medicated articles.

With respect to eligibility for a biowaiver, CVM believes there is no reasonable basis for drawing a distinction between APIs intended for administration to animals via drinking water and APIs intended to be administered via feed, provided these APIs have similar physicochemical properties, particularly solubility. A soluble API, present in a Type A medicated article and mixed into a feed matrix, rapidly dissolves when exposed to the fluids of the GI tract. If such an API readily goes into solution across the range of

physiological pH values, it will likely go rapidly into solution when exposed to the fluids in the GI tract. Accordingly, such medicated feeds will effectively behave as oral solutions shortly after administration. Therefore, CVM also intends to review biowaiver requests that involve APIs in Type A medicated articles on the basis of a demonstration of solubility and evaluate the drug product formulation to ensure that there are no ingredients in the proposed formulation likely to cause adverse pharmacologic effects or inactivate the API(s). Determining appropriate methods for ascertaining drug product bioequivalence for Type A medicated articles that contain APIs that are not classified as water soluble is not the subject of this guidance.

**1. Type A medicated articles and feed formulation effects.**

Feed constituents may affect the bioavailability of the API in a Type A medicated article. Therefore, CVM believes that the variability in feed constituents between the reference and proposed Type A medicated articles should not be greater than the natural variations that can occur in the final feed to which the animal will be exposed, whether that feed contains the proposed or reference drug product.

**2. Type A medicated articles containing biomass products.**

Many antimicrobials, and some drugs in other pharmacologic classes, that may become the APIs of soluble powder oral dosage form drug products and Type A medicated articles are produced through fermentation processes. In soluble powder oral dosage form products, the APIs typically are subjected to substantial extraction and purification following the fermentation process. While the APIs in some Type A medicated articles are virtually identical in purity to these soluble powder oral dosage form products, the APIs in other Type A medicated articles may contain significant quantities, or even all, of the fermenting microorganisms, their by-products, and nutrient substrate (biomass) associated with the fermentation process.

Because dried fermentation biomass derived from a number of different fermentation processes is a well-accepted and routinely used feed ingredient, CVM will consider the potential for the biomass component of a Type A medicated article to cause adverse pharmacologic effects or inactivate APIs in the same manner that it considers these effects with respect to other feed ingredients. Generally, CVM would deny a biowaiver on the basis of such potential feed ingredient effects only when it has information indicating that a specific feed ingredient may have such an effect.

However, whether a biowaiver would be denied based on potential adverse pharmacologic effects or effects on API bioavailability and whether a proposed drug product's approval would be denied because of safety concerns associated with inactive ingredients, such as biomass components, are two different issues. The latter issue is outside the scope of this guidance document, and questions related to this aspect of biomass Type A articles should be addressed to the Director, Office of New Animal Drug Evaluation.

### C. Effect of granting a biowaiver.

As noted above, the granting of a waiver from the need to submit bioequivalence study data does not imply that a drug product is approvable. For drug product approval, all of the applicable legal requirements must be met.

If a waiver of the requirement to demonstrate bioequivalence is granted, the sponsor may request a waiver for the need to submit tissue residue depletion data.[9] If CVM waives the requirement to submit a tissue residue depletion study, the withdrawal time established for the reference drug product will be assigned to the generic drug product.

## IV. GUIDANCE

For soluble powder oral dosage form products and Type A medicated articles, CVM recommends that requests to waive the requirement to demonstrate bioequivalence (e.g., blood level bioequivalence or clinical endpoint bioequivalence) be made either by a comparison of formulations or a demonstration of solubility. Sponsors should make these biowaiver requests before submitting an ANADA.

### A. Comparison of formulations.

For both soluble powder oral dosage form products and Type A medicated articles, CVM is likely to grant a biowaiver if the sponsor can show that the proposed soluble powder oral dosage form product or Type A medicated article contains the same active and inactive ingredient(s) and is produced using the same manufacturing processes as the RLNAD.

If this approach is selected, CVM recommends that the sponsor of the proposed drug product for which a biowaiver is being requested provide: 1) sufficient evidence that the proposed drug product contains the same active and inactive ingredient(s) as the RLNAD; 2) composition statements for both the proposed drug product and the RLNAD, demonstrating a similarity in concentration of all ingredients; and 3) a description of the proposed and reference drug products' manufacturing processes.

However, this approach is probably practical only for situations in which the sponsor of the proposed drug product also manufactures or, perhaps, formerly manufactured the RLNAD as well.

### B. Demonstration of solubility.

The following sections summarize the main elements associated with the request for a biowaiver based upon the demonstration of the solubility of soluble powder oral dosage form products or the solubility of the API(s) in the Type A medicated articles:

[9] CVM Guidance for Industry #35, "Bioequivalence Guidance," November 8, 2006 (see pages 7, 24-25).

**1. *Composition statement.***

The sponsor should submit a composition statement for the proposed drug product (i.e., quantitative and qualitative information for the API(s) and excipient(s)).

**2. *General criteria for soluble powders and Type A medicated articles.***

In order for a proposed drug product to be eligible for a biowaiver, CVM recommends the following criteria be met:

a. *Soluble powder oral dosage form products.*

A biowaiver may be granted if:

*1)* the proposed drug product contains the same API(s) in similar concentrations as the RLNAD;
*2)* there are no inactive ingredients in the proposed drug product's formulation likely to cause adverse pharmacologic effects or affect the bioavailability of the API(s); and
*3)* the proposed drug product is soluble (dissolves in water based on physical observation followed by confirmation using a validated analytical method) under the range of physical conditions that a user of the product would typically encounter when adding the soluble powder to animal drinking water (i.e., well or municipal water) in the field.[10]

b. *Type A medicated articles.*

A biowaiver may be granted if:

*1)* the proposed drug product contains the same API(s) in similar concentrations as the RLNAD;
*2)* each API is soluble; and
*3)* there are no ingredients in the proposed drug product formulation likely to cause adverse pharmacologic effects (e.g., influence the gastrointestinal transit time or influence drug permeability) or inactivate the API(s).

CVM recommends the following additional criteria be used to support the request for a biowaiver for a Type A medicated article:

i. *Information about the API.*

CVM recommends that the API used to support a biowaiver request be provided from the same supplier of the API that will be used to formulate the proposed drug product during production. In addition to the information requested above, CVM recommends that the applicant provide the following

[10] CVM Guidance for Industry #5, "Drug Stability Guidelines," December 9, 2008 (see page 45).

relevant information regarding the API in the biowaiver request for the proposed drug product:

1. *USP Active Ingredient(s).*
   Submit a certificate of analysis (COA) for an API that complies with a USP monograph. This may suffice as evidence of equivalence with the API of the RLNAD.

2. *Non-USP API or Multiple APIs.*
   CVM recommends that the applicant provide sufficient analytical evidence, including structural characterization (*e.g.*, nuclear magnetic resonance, mass spectroscopy), to confirm that the identity and/or ratio of the API components are equivalent to those in the RLNAD.

3. *APIs containing biomass materials.*
   CVM recommends that the applicant provide information about the composition of the biomass and identify the bacterial strain, including its source, used in the fermentation process.

ii. *Approaches for Demonstrating Solubility of the API.*

The applicant may demonstrate solubility of the API using one of the two approaches described in conjunction with the experimental guidelines described in Section iii below.

1. *"USP definition" approach.*
   In some situations (e.g., Type A medicated articles to be administered to ruminants) it may be acceptable to use the USP definition approach for demonstrating drug solubility. CVM believes that for an API to be considered "soluble" with respect to a biowaiver request, it should be "very soluble," "freely soluble," or "soluble" as these terms are defined in Table 1.[11] Solubility should be determined across a defined pH range (see Section iii below).

**Table 1.** Values for estimating API aqueous solubility based upon "USP definition"

| **Descriptive Term** | **Appropriate Volume of Aqueous Solvent In Milliliters Per Gram of Solute** |
|---|---|
| Very soluble | Less than 1 part solvent needed to dissolve 1 part solute |
| Freely soluble | From 1 to 10 parts solvent needed to dissolve 1 part solute |
| Soluble | From 10 to 30 parts solvent needed to dissolve 1 part solute |
| Sparingly soluble | From 30 to 100 parts solvent needed to dissolve 1 part solute |
| Slightly soluble | From 100 to 1000 parts solvent needed to dissolve 1 part solute |
| Very slightly soluble | From 1000 to 10,000 parts solvent needed to dissolve 1 part solute |
| Practically insoluble | More than 10,000 parts solvent needed to dissolve 1 part solute |

[11] The United States Pharmacopeia, USP 39, NF 34, 2016.

2. *"Dosage adjusted" approach.*
In this approach, the aqueous solubility is evaluated on the basis of the highest expected mg of API per mL of gastric fluid at any point in time. This assessment is determined based on the API concentration in the feed and characteristics of the gastric physiology of the target animal species.

   a. The API concentration can be calculated by using one of the following: 1) the highest expected daily intake of the API, or 2) the amount of API in the medicated article likely to be consumed per feeding event, e.g., dividing the daily dose into the number of feeding events the target animal species typically takes to consume their daily ration, such as five feeding events in a ten hour period.

   b. The animal physiology is critical as it determines the gastric residence time (how long it takes for the consumed medicated feed to exit the stomach or rumen), the gastric fluid volume of the target animal species (Table 2), the pH range over which solubility measurements must be made, and the temperature at which solubility should be determined (see Section iii below).

   If the highest expected daily dose (mg of API) can be shown to be soluble in the gastric volume determined under the most conservative intended conditions of use (e.g., the largest dose to fluid volume ratio, minimum time of dissolution, and the broadest pH range over which solubility is demonstrated), CVM believes the API should be considered soluble.

   If there are multiple species on the labeling, solubility should be based upon the most conservative mg/mL scenario (i.e., use the species that produces the highest dose to gastric fluid volume ratio). Additionally, CVM recommends the following criteria for determining API solubility:

   - Confirmation that API solubilization occurs during the minimum gastric residence time for the indicated species (Table 2).
   - Solubility determinations over a pH range that is inclusive of all the pH values expected in the gastric environment for all the species.

   When the conditions within the GI tract are markedly different across the labeled species, appropriate media composition for testing API solubility should be discussed with CVM.

This method of defining API solubility is similar to that described for categorizing compounds when using the BCS[12] and to the BCS-based approach described in CDER guidance.[13] In this case, the appropriate fluid volume for testing API solubility depends upon the target animal species/class for which the medicated feed is intended. For example, a conservative estimate of ruminal fluid volume (fluid volume available for drug solubilization) for steers is 47 L. The sponsor should provide the estimated daily drug intake (mg/kg body weight) based on the labeled drug concentration (grams of drug per ton) in the feed administered to the animal (e.g., the Type C medicated feed) and the highest amount of medicated feed (kg/day) expected to be consumed by an individual animal. When using this approach, CVM recommends using the species-specific animal weight and fluid volume estimates summarized in Table 2.

**Table 2.** Values for estimating API solubility under the "dose adjusted" approach

| **Species*** | **Gastric Fluid Volume in Liters (to be used as volume of solvent)** | **Gastric resident times (hours)** |
|---|---|---|
| Cattle[1] | 47# | 8 |
| Swine | 0.5 | 1 |
| Horse[2,3] | 1.5 | 0.25 |
| Chicken | 0.01‡ | 2 |
| Turkey | 0.04‡ | 2 |

*CVM acknowledges that the estimates for the indicated species are very conservative. If larger fluid volumes and or gastric resident times are used, it must be adequately justified. However, CVM notes that in certain instances the appropriate fluid volume may be less than that indicated in the table as is the case when dealing with younger animals.
#Fluid volume of the rumen.
‡Includes the fluid volumes of both the proventriculus and the ventriculus.

1 Martinez, M. N., Apley, M. D. Drug solubility classification in the bovine. J. vet. Pharmacol. Therap. 35 (Suppl. 1), 93–97, 2012.
2 American Association of Equine Practitioners: http://www.aaep.org/info/horse-health?publication=816.
3 Ontario Ministry of Agriculture, Food and Rural Affairs: http://www.omafra.gov.on.ca/english/livestock/horses/facts/info_digest.htm.

CVM assumes the amount of medicated feed consumed per day and the gastric volume will vary proportionally with animal age. Therefore, we recommend that the solubility determination within a given target animal species be based upon only one solute/solvent ratio. Assessments should be made by determining the API solubility under the most conservative conditions.

[12] GL Amidon, H Lennernäs, VP Shah, JR Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.*, 12 (1995), 413-420.
[13] CDER Draft Guidance for Industry, "Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," May 2015 (see pages 2-3).

There are several critical variables that need to be considered when using this approach. Therefore, sponsors are encouraged to discuss this approach with CVM before executing any experiments.

iii. *Experimental Test Conditions for Demonstrating Solubility.*

When establishing solubility of the API under either the USP definition or dosage adjusted approach, CVM recommends that the applicant submit data collected using the experimental conditions described below.

1. *Media.*
   a. Using the USP definition for solubility:
      The solubility data should be generated in aqueous media with pH values of 1.2, 4.6, and 7.5. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used after consultation with CVM.

   b. Dosage adjusted approach:
      In this approach, the composition of the media used for testing API solubility should be species appropriate. In all cases, solubility needs to be tested under the conditions that reflect the *in vivo* GI environment of the target animal species. The following conditions should be considered:

      - Monogastric: pH 1.2, 4.6 (acetate buffer), and 7.5 with the option of adding biorelevant surfactants;
      - Ruminants: a pH range of 4.5 and 6.8 with the option of adding biorelevant surfactants;
      - Poultry: the sponsor can justify the sets of conditions under which solubility will be tested. Without agreed upon justification, the default conditions would be the same conditions as those described for monogastric species.

2. *Solubility test methodologies.*

In most situations this is the approach recommended for defining API solubility. The evaluation of API solubility can be accomplished through the use of a variety of methods including the traditional shaker-flask procedure (pH stability during drug solubilization, drug complexation and/or aggregation may alter solubility), acid-base titration method (generally limited to uncharged ionizable molecules), and the column elution method (applicable primarily to low solubility compounds).[14]

[14] Avdeef, et al. (2000). pH-Metric Solubility. 2: Correlation between the acid-base titration and the saturation shake-flask solubility-pH method. *Pharm. Res*., 1**7**: 85-89.

It is essential to note that regardless of the procedure used, a visual determination of solubility is insufficient. For the determination of solubility the concentration of the API in selected buffers (or pH conditions) must be demonstrated using a validated assay procedure for the specific type of sample to be tested. CVM expects that sponsors will demonstrate full control of their test method through the submission of the method validation information, including the results from no less than three replicate samples.

3. *Other technical considerations.*
   a. Temperature:
      The variability of temperature used when generating the pH-solubility profile for the API should be maintained at 37 ± 1°C throughout the study to ensure solubility is not affected by variation in temperature, unless biologically relevant justification is provided for an alternative temperature.

   b. Media stability:
      Solution pH should be verified after addition of the API to the buffer solution. If the pH changes significantly after addition of the API, then the buffers selected are either inadequate or the pH should be adjusted back to the original pH before testing for solubility (i.e., the pH of the solution should be verified to be unchanged before measuring the solubility of the API).

   c. Replication:
      A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility.