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Guidance for Industry

Waivers of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles

Draft Guidance

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For questions regarding the draft guidance document, contact Marilyn Martinez, Center for Veterinary Medicine (HFV-130), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7577, e-mail: mmartin1@cvm.fda.gov.

Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville,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/cvm>.

**U.S. Department of Health and Human Services
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Center for Veterinary Medicine (CVM)
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Draft Guidance for Industry

Waivers of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles¹

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I. PURPOSE

This document describes how the Center for Veterinary Medicine (CVM) intends to evaluate requests for waiving the requirement for submitting *in vivo* 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,² particularly the section on Criteria for Waiver of *In Vivo* Bioequivalence Study.

II. BACKGROUND

In general, an abbreviated new animal drug application (ANADA) must include information to show that the generic product and pioneer product are bioequivalent.³ This requirement is patterned very closely on the human generic drug provision.⁴

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 generic and pioneer drug products when administered at the same molar dose under

¹ This draft guidance has been prepared by the Office of New Animal Drug Evaluation in the Center for Veterinary Medicine at the Food and Drug Administration.

² CVM Guidance for Industry # 35, "Bioequivalence Guidance," October 9, 2002.

³ Section 512(n)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the Act).

⁴ Section 505(j)(2)(A)(iv) of the Act.

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similar conditions.⁵ In certain circumstances, however, the demonstration of bioequivalence does not need to be established on the basis of *in vivo* studies.⁶ For several categories of drugs, including oral solutions, bioequivalence is considered self-evident under specified conditions.⁷ In certain circumstances, the bioequivalence of solid oral dosage forms can be documented using *in vitro* approaches.⁸ For highly soluble, highly permeable, rapidly dissolving, and orally administered drug products, documentation of bioequivalence using an *in vitro* approach is appropriate based on a biopharmaceutics classification system.⁹

CVM has not issued regulations regarding the bioequivalence requirement for generic products. It 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.¹⁰ The guidance states that: “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 physico-chemical characteristics as an approved pioneer product.”¹¹ This 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.

FDA’s guidance documents, including this guidance, 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 requirements are cited. The use of the word “should” in Agency guidances means that something is suggested or recommended, but not required.

III. DISCUSSION

This guidance describes how CVM intends to evaluate requests to waive the requirements for conducting an *in vivo* bioequivalence study, hereafter referred to in this guidance as “biowaivers,” for certain categories of animal drugs.

⁵ 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 Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, March 2003.

⁶ 21 CFR 320.21(b),(f) and 320.22.

⁷ 21 CFR 320.22(b)(3).

⁸ CDER Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, March 2003, Page 10.

⁹ *Id.* Additional information about these waivers and the biopharmaceutics classification system CDER uses are in: CDER Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000.

¹⁰ CVM Guidance for Industry # 35, “Bioequivalence Guidance”, October 9, 2002.

¹¹ *Id.*, Page 7.

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- A. **Waivers for soluble powder oral dosage form products.** CVM believes it will usually be appropriate to grant biowaivers for oral dosage forms known as “soluble powders.” Such products are intended for administration to animals via the drinking water that, under most husbandry systems, is provided on an *ad libitum* basis.

The conceptual basis for granting biowaivers for “soluble powders” is that once a drug is in solution prior to administration, the product's formulation will usually not influence the bioavailability of the active pharmaceutical ingredient (API). This is because, from a mechanistic perspective, the rate-limiting step in systemic drug absorption will be its permeability across the GI mucosal membranes, which is a drug dependent rather than formulation dependent event. Similarly, if a drug acts locally within the GI tract (not systemically absorbed), the local exposure to the dissolved drug in the generic and pioneer formulations will be equivalent if the drug is already in solution because the rate-limiting step is drug 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 contains substances that could cause adverse pharmacologic effects (e.g., altered gastrointestinal (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 waiver decisions for soluble powders, CVM intends to evaluate 1) solubility data provided by the sponsor to ensure that, prior to administration, the product will go into solution under the range of physical conditions that a user of the product would typically encounter when adding the soluble powder to animal drinking water in the field; and 2) the product's formulation to ensure that there are no ingredients in the generic formulation likely to cause adverse pharmacologic effects.

- B. **Waivers 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 drug substances have similar physico-chemical properties, particularly solubility. A soluble drug, present in a Type A medicated article and mixed into a feed matrix, rapidly dissolves when exposed to the fluids of the GI tract. From a mechanistic perspective, if such a drug 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. As such, CVM also intends to review biowaiver requests that involve APIs in Type A medicated articles on the basis of a demonstration of solubility and the product's formulation to ensure that there are no ingredients in the generic formulation likely to cause adverse pharmacologic effects. Determining appropriate methods for ascertaining product bioequivalence for Type A medicated articles that contain APIs that are not classified as water soluble may prove more challenging and are not the subject of this guidance.

1. ***Type A medicated articles and feed formulation effects.*** Feed constituents may affect the bioavailability of the APIs in a Type A medicated article. CVM believes, however, that

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this should not be a factor in considering a biowaiver request since the variability in feed constituents between the pioneer and generic 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 generic product or the pioneer product.

2. ***Type A medicated articles containing biomass products.*** Many antimicrobials, and some drugs in other pharmacologic classes, that may become the active ingredients of soluble powder oral dosage form 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 others may contain significant quantities, or even all, of the fermenting microorganisms 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 article to cause adverse pharmacologic effects 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.

- C. **Effect of a grant of a bioequivalence waiver.** The granting of a waiver of the need to submit *in vivo* bioequivalence study data does not imply that a product is approvable. For product approval, all of the applicable legal requirements must be met. For example, products containing a biomass may raise animal, food, or environmental safety issues that would have to be addressed.

If a waiver of the need to submit *in vivo* bioequivalence studies is granted, the sponsor may request a waiver for the need to submit tissue residue depletion data.¹² If CVM waives the requirement to submit a tissue residue depletion study, it will assign the withdrawal time established for the pioneer product to the generic product.

IV. GUIDANCE

For soluble powder oral dosage form products and Type A medicated articles, CVM recommends that requests to waive the requirement to establish bioequivalence through *in vivo* studies (blood level bioequivalence or clinical endpoint bioequivalence) be made either by a comparison of formulations or a demonstration of solubility. Sponsors may make these waiver requests prior to submitting an ANADA.

¹² As described in the CVM guidance #35, "Bioequivalence Guidance," October 9, 2002, Pages 24-26.

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- 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 generic 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 approved comparator product or article. If this approach is selected, CVM recommends that the generic sponsor provide: 1) sufficient evidence that the generic product contains the same active and inactive ingredient(s) as the pioneer product, 2) composition statements for both the generic product and the pioneer product and 3) a description of the generic and pioneer products' manufacturing process.
- B. **Demonstration of Solubility:** For **soluble powder oral dosage form products**, a biowaiver may be granted if the generic product contains the same API(s) as the pioneer product, the product is soluble under the range of **physical conditions that a user of the product would typically encounter when adding the soluble powder to animal drinking water in the field**; and there are no ingredients in the generic product's formulation likely to cause adverse pharmacologic effects.

For Type A medicated articles, a biowaiver may be granted without direct comparison to the pioneer product's formulation and manufacturing process if the generic product contains the same API(s) as the pioneer product, the API is soluble, and there are no ingredients in the generic product's formulation likely to cause adverse pharmacologic effects. CVM recommends that the sponsor demonstrate solubility using one of the following two methods:

1. **"USP definition" approach:** 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 1.¹³ In using this table, the product should be tested in a pH range of 1.2 (0.1N HCl) to 7.5.

Table 1. Values for estimating drug solubility based upon "USP definition"

Descriptive Term	Appropriate Volume of 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

2. **"Dosage adjusted" approach:** In this approach, the aqueous solubility (across a pH range of 1.2 to 7.5) should be evaluated according to the highest expected mg/kg daily intake of

¹³ The United States Pharmacopeia, USP 26, NF 21, 2003.

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a drug and the “gastric fluid volume” of the target animal species. If the daily dose can be shown to be soluble in the gastric volume under the most conservative intended conditions of use (largest dose to fluid volume ratio), CVM believes the drug should be considered soluble. This method of defining drug solubility is similar to that described for categorizing compounds when using the Biopharmaceutics Classification System (BCS)¹⁴ and to the BCS-based approach described in CDER guidance.¹⁵ In this case, the appropriate fluid volume for testing drug solubility depends upon the target animal species for which this medicated feed is intended.¹⁶ If the Type A medicated article is to be used in the manufacture of medicated feeds across several animal species, the most conservative condition (largest dose to fluid volume ratio) should provide the basis for determining whether the drug is “soluble.” The sponsor should provide the estimated daily drug intake (mg/kg body weight) based on the labeled drug concentration (e.g., grams of drug per ton) in the feed administered to the animal (e.g., a Type C medicated feed) and the amount of feed (kg/day) expected to be consumed by an individual animal. When using this approach, we recommend using the species-specific animal weight and fluid volume estimates summarized in Table 2.

Table 2. Values for estimating drug solubility based upon “dosage adjusted” method^{a,b,c}

Species	Body weight (for estimating drug intake)	“Gastric” volume (to be used as volume of solvent)
Cattle	400 kg	200 Liters (rumen)
Pre-ruminating calf	60 kg	2 Liters
Swine	200 kg	8 Liters
Horse	450 kg	18 Liters
Chicken	2.5 kg	0.1 Liters
Turkey	10 kg	0.4 Liters

^aGastric volume estimate for cattle, swine and horses are based upon values reported in, ME Ensminger, JE Oldfield and WW Heinemann, *Feeds and Nutrition*, 1990, Ensminger Publishing Company, California, p 53.

^bVolume, based upon daily water consumption, is based upon values reported in GD Goldstein and E Skadhauge, Renal and extrarenal regulation of body fluid composition, In: *Avian Physiology*, 2000, GC Whittow, ed., Academic Press, Florida, pp 265-291 and Average Daily and Annual Water Requirements, Government of Alberta Canada, http://www1.agric.gov.ab.ca/app19/calc/livestock/waterreq_dataentry2.jsp

^cAnimal weights are based upon the following references: NRC, Nutrient Requirements of Swine 1988), poultry (NRC, Nutrient Requirements of Poultry 1994), and beef cattle (NRC, Nutrient Requirements of Beef Cattle 1984).

¹⁴ GL Amidon, H Lennernas, VP Shah, JR Crison, A theoretical basis for a biopharmaceutics drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.*, 12 (1995), 413-420.

¹⁵ CDER Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000.

¹⁶ CVM assumes that most or all soluble powder oral dosage form products would use the USP definition approach. While the dosage adjusted approach is described in terms of Type A medicated articles, it is technically applicable to soluble powder oral dosage form products as well.

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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 assessment within a given target animal species be based upon only one solute/solvent ratio. If the daily dose can be shown to be soluble in the gastric volume under the most conservative intended conditions of use, the drug should be determined to be soluble.

When establishing solubility of the API under either the USP definition or dosage adjusted approach, we recommend that the following test conditions be followed:

The pH-solubility profile of the test drug substance should be determined at 37 ± 1 °C in aqueous media with pHs of approximately 1.2, 4.6 and 7.5. 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. 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. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. It is recommended that concentration of the drug substance in selected buffers (or pH conditions) be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products. If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data.¹⁷

As part of a waiver request based on API solubility, CVM also recommends that the generic sponsor include: 1) sufficient evidence that the generic product contains the same active ingredient(s) as the pioneer product; and 2) a composition statement for the proposed generic product.

¹⁷ These recommendations are based on CDER Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000, section titled “Determining Drug Substance Solubility Class” (page 3). CVM has modified CDER's recommendations to take into account the unique conditions associated with the use of animal drugs in drinking water and feed.

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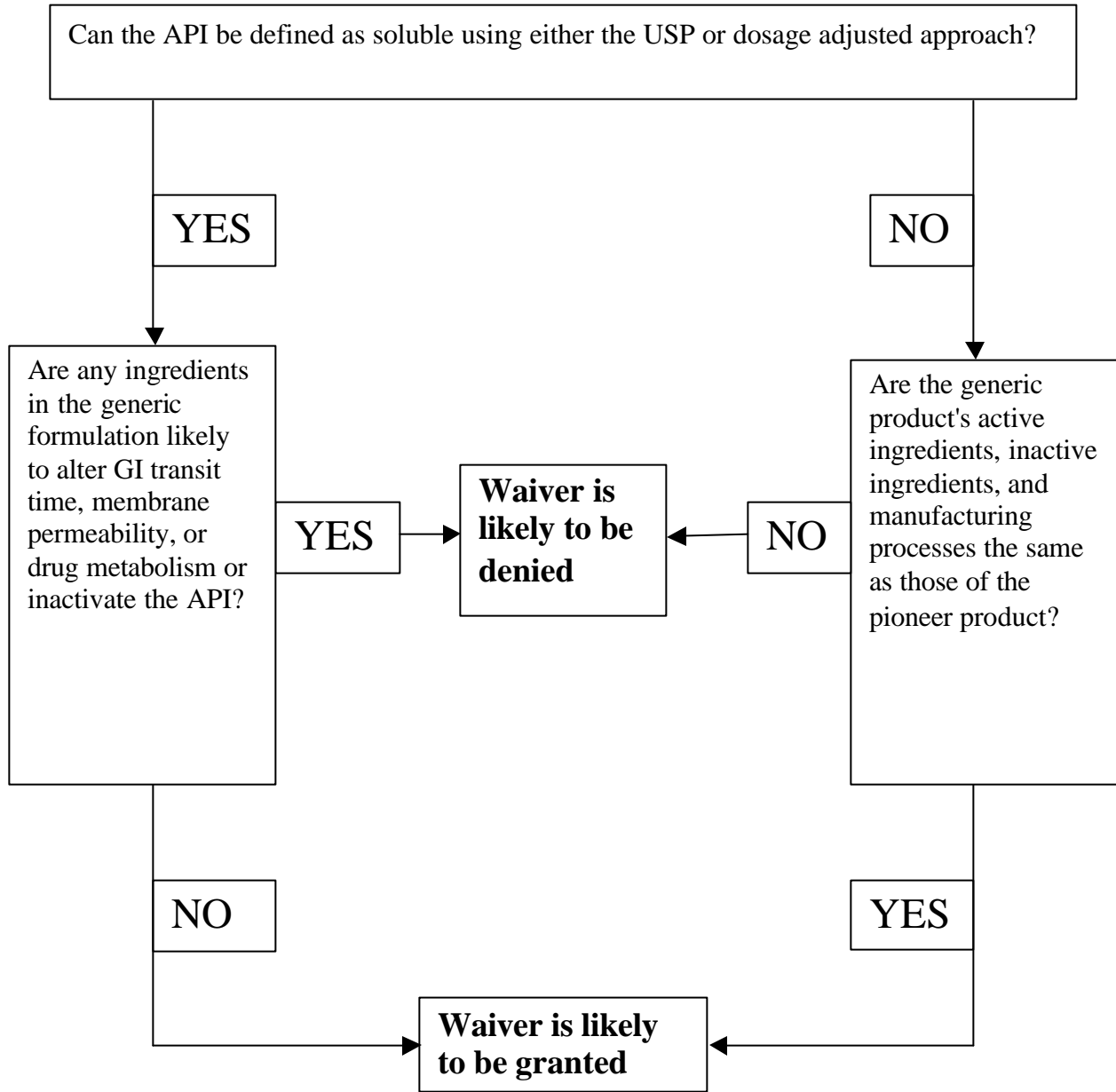


Figure 1- Flow diagram of a typical biowaiver decision tree for Type A medicated articles