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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

(This version of the guidance replaces that which was made available on February 16, 2006. This guidance document has been revised to address some confusion among sponsors regarding the recommendations contained in the document. The revisions clarify the guidance's key concepts. No new concepts have been introduced and the scope of the guidance has not changed. The revisions: (1) update terminology to indicate that the GFI is not just applicable to applications for generic drugs; (2) move lengthy and informative footnotes into the body of the text so that they are not overlooked; and (3) restructure sections (specifically Section IV) to improve the flow and readability of the document and to highlight important details (e.g., analytical data) that the sponsor should submit to CVM in support of their waiver request.)

Comments and suggestions regarding this guidance should be sent 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 No. 2004D-0283. Comments also may be submitted electronically on the Internet at http://www.fda.gov/dockets/ecomments.

For questions regarding the guidance document, contact the following individuals:

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Additional copies of this 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.

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John K. Harshman, Center for Veterinary Medicine (HFV-104), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-8197, email: john.harshman@fda.hhs.gov.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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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[1]

This guidance represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statute(s) and regulation(s). If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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.

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

The recommendations in this 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 may not be appropriate to use the recommendations in the guidance to compare the solubility of two products where the 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 the applicability of this guidance document to that type of comparison.

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[1] This 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," November 8, 2006.

II. BACKGROUND

In general, an ANADA must include information to show that the proposed product and reference 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 proposed and reference drug products when administered at the same molar dose under 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.

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[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.

[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", November 8, 2006.

[11] Id., Page 7.

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.

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 ingredient. This is because, from a mechanistic perspective, the rate-limiting step in systemic drug absorption will be: a) the rate of gastric transit; and b) the permeability of the active ingredient across the gastrointestinal (GI) mucosal membranes. Both of these variables are formulation-independent. Similarly, if a drug acts locally within the GI tract (not systemically absorbed), the local exposure to the dissolved drug in the proposed and reference product 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 other than the active ingredient 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 active ingredient 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 differences between the reference and proposed product formulations likely to adversely affect the performance of the proposed product, e.g., cause adverse pharmacologic effects or alter active ingredient bioavailability.

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 active ingredients intended for administration to animals via drinking water and active ingredients 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 active ingredients 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 proposed formulation likely to cause adverse pharmacologic effects or inactivate active ingredients. Determining appropriate methods for ascertaining product bioequivalence for Type A medicated articles that contain active ingredients 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 active ingredients in a Type A medicated article. CVM believes, however, that this should not be a factor in considering a biowaiver request since 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 product or the reference 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 active ingredients typically are subjected to substantial extraction and purification following the fermentation process. While the active ingredients in some Type A medicated articles are virtually identical in purity to these soluble powder oral dosage form products, the active ingredients 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 medicated article to cause adverse pharmacologic effects or inactivate active ingredients 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 active ingredient bioavailability and whether a proposed 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 office of the Director, Office of New Animal Drug Evaluation.

C. **Effect of a grant of a bioequivalence waiver.** As noted above, 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.

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.

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 approved reference product or article. If this approach is selected, CVM recommends that the sponsor of the proposed product for which a biowaiver is being requested provide: 1) sufficient evidence that the proposed product contains the same active and inactive ingredient(s) as the reference product, 2) composition statements for both the proposed product and the reference product and 3) a description of the proposed and reference products' manufacturing processes. This approach is probably practical only for situations in which the sponsor of the proposed product also manufactures or, perhaps, formerly manufactured the reference product as well.

B. **Demonstration of Solubility**. The following sections summarize the main elements associated with the request for biowaivers based upon the demonstration of the solubility of soluble powder oral dosage form products or the solubility of active ingredients in the Type A medicated articles:

1. ***Composition Statement.*** The applicant should submit a composition statement for the proposed product.

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

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 the proposed product contains the same active ingredient(s) as the reference product, there are no ingredients in the proposed product's formulation likely to cause adverse pharmacologic effects or inactivate active ingredients, and 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 (i.e., well or municipal water) in the field.

   b. *Type A medicated articles.* A biowaiver may be granted if the proposed product contains the same active ingredient(s) as the reference product, the active ingredient is soluble, and there are no ingredients in the proposed product's formulation likely to cause adverse pharmacologic effects or inactivate active ingredients. CVM recommends the following criteria be used to support the request for a biowaiver of a Type A medicated article:

      i. Information about the Active Ingredient**.** CVM recommends that the active ingredient used to support a biowaiver request be provided from the same supplier of the active ingredient that will be used to formulate the proposed product during production. In addition to the information requested above, CVM recommends that the applicant provide the following relevant information regarding the active ingredient in the waiver request for the proposed product:

         1. *USP Active Ingredient.* Submit a certificate of analysis (COA) for an active ingredient that complies with a USP monograph. This may suffice as evidence of equivalence with the active ingredient of the reference product.

         2. *Non-USP Active Ingredient or Multiple Active Ingredients (e.g., bambermycins).* 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 active ingredient components are equivalent to those in the reference product.

         3. *Active Ingredients 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 Active Ingredient**.** CVM recommends that the applicant demonstrate solubility of the active ingredient using one of the two approaches described below in conjunction with the experimental guidelines described in Section iii below.

         1. *"USP definition" approach.* CVM believes that for an active ingredient 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] Solubility should be determined across a defined pH range (see Section iii below).

Table 1. Values for estimating drug 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

2. *"Dosage adjusted" approach.* In this approach, the aqueous solubility, across a defined pH range, should be evaluated according to the highest expected mg/kg daily intake of 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 the medicated feed is intended. If a 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.

[13] The United Stated Pharmacopeia, USP 30, NF 25, 2007.

[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.

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	600 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

[a]Gastric 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.

[b]Volume, 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

[c]Animal weights are based upon the following references: NRC, Nutrient Requirements of Swine 1988), poultry (NRC, Nutrient Requirements of Poultry 1998), and beef cattle (NRC, Nutrient Requirements of Beef Cattle 1996).

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.

iii. Experimental Test Conditions for Demonstrating Solubility. When establishing solubility of the active ingredient under either the USP definition or dosage adjusted approach, CVM recommends that the applicant submit data collected using the experimental conditions described below. 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.

1. The solubility data should be generated in aqueous media with pH values of approximately 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.

2. The temperature of the pH-solubility profile testing for the active ingredient should be maintained at 37 ± 1^{o}C throughout the study to ensure solubility is not affected by variation in temperature.

3. Solution pH should be verified after addition of the drug substance to the buffer. If the pH changes significantly after addition of the drug substance, then the buffers selected are either inadequate or the pH should be adjusted back to the original pH prior to testing for solubility.

4. 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.

5. As visual determination of solubility is insufficient, it is recommended that concentration of the drug substance in selected buffers (or pH conditions) be determined using a suitably validated assay procedure for the specific type of sample to be tested.

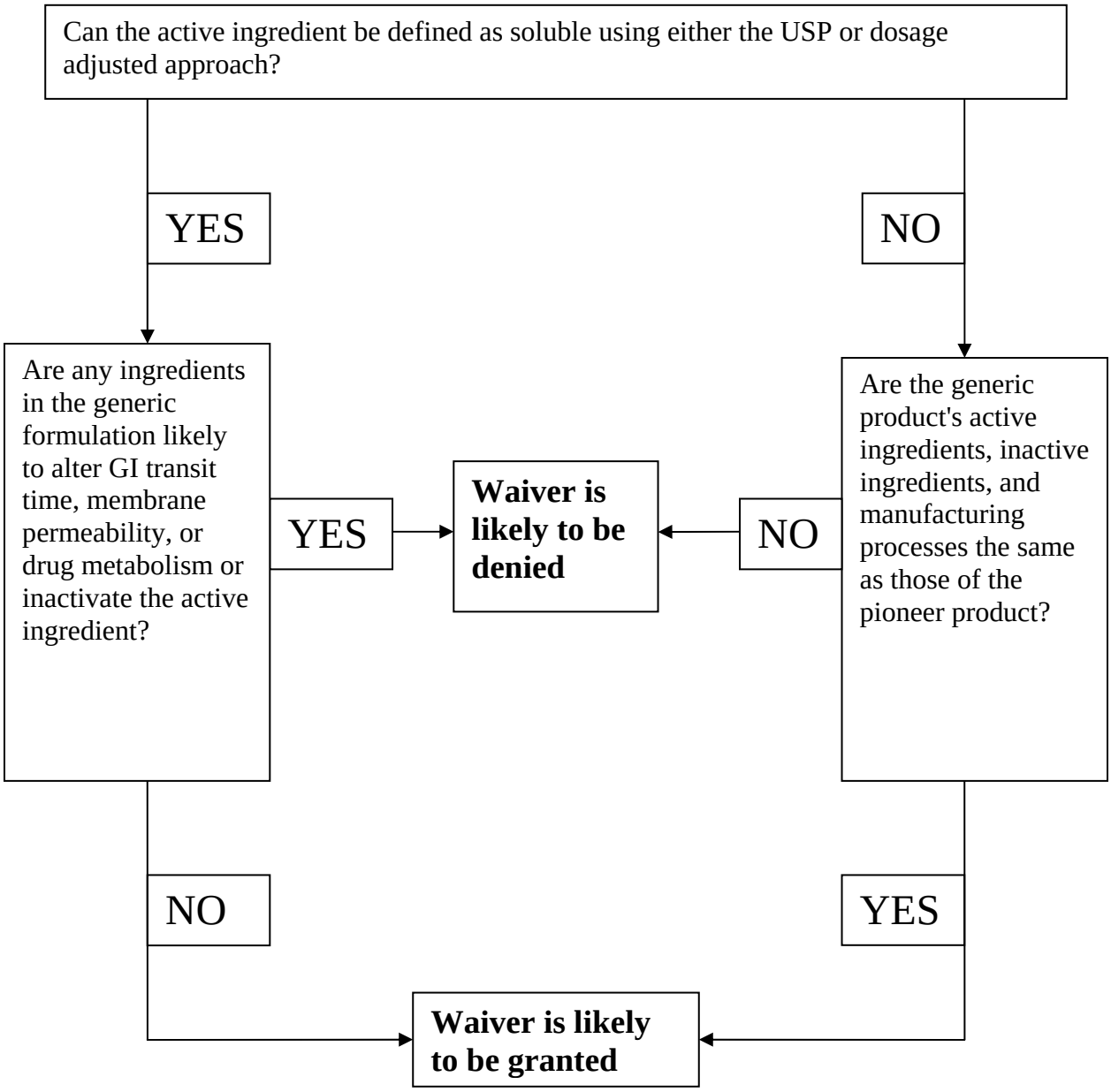

Figure 1 - Flow diagram of a typical biowaiver decision tree for Type A medicated articles