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Solubility Criteria for Veterinary Drugs—Workshop Report

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ABSTRACT The objectives of this *Stimuli* article are to give a brief summary of discussions at a workshop, Solubility Criteria for Veterinary Products, that took place at USP headquarters in Rockville, MD, 7–8 November 2012, and to explain the new approaches that will be used to develop a new *USP* general chapter, *Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species* 1236.

INTRODUCTION

The workshop *Solubility Criteria for Veterinary Products* took place at USP headquarters in Rockville, MD, 7–8 November 2012. The main purpose of this workshop was to discuss topics presented in a *Stimuli* article, "Solubility Criteria for Veterinary Products," published in *Pharmacopeial Forum* (*1*) and to define a strategy for the development of the new *USP* general chapter, *Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species* 1236.

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BACKGROUND

The original Biopharmaceutics Classification System (BCS) proposed by Amidon et al. in 1995 (*2*) focused on conditions in the human gastrointestinal (GI) tract and classified drugs in accordance with their solubility and permeability characteristics. The BCS classified drugs as highly soluble and highly permeable (BCS class 1), poorly soluble but highly permeable (BCS Class 2), highly soluble but poorly permeable (BCS class 3), or poorly soluble and poorly permeable (BCS Class 4). In some cases, drugs that are

not inherently highly soluble may be classified as such for BCS purposes because of the administered dose and the inherent solubility of this low dose in the estimated 250 mL of gastric fluid. Thus, the dose number (mass of administered drug divided by gastric fluid volume) was a pivotal component of BCS. BCS has been used throughout the development and regulation of human pharmaceutical products to better define the drug and formulation variables that can influence in vivo drug product performance (*3,4*). On the basis of this system, FDA's Center for Drug Evaluation and Research issued a biowaiver guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf).

FDA's Center for Veterinary Medicine considered that extension of the BCS to veterinary species was a logical development and held several internal workshops to explore this possibility (*5*). This effort evolved into a USP initiative and resulted in the publication of a *Stimuli* article in 2004 (*6*). This article was an effort to directly apply human BCS principles to a species closely aligned (in terms of physiology, drugs administered, and the use of oral dosage forms) with human medicine, the dog. The article tried to establish criteria for dose number (administered dose vs. gastric volume) and permeability. The authors noted that although it would be feasible to establish an algorithm for estimating canine dose number, permeability would be difficult to estimate because of the absence of a validated in vitro system that replicates the canine GI tract. In 2006, the FDA Center for Veterinary Medicine first issued Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052493.pdf), which is, in part, based upon the application of the BCS to veterinary species and the concepts proposed by Amidon (*2*). The formulations represented in this guideline could be used in food animal species (i.e., cattle, swine, and poultry).

In 2010, the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) launched an extensive bioequivalence initiative that explored a wide range of bioequivalence issues that affect veterinary medicine. This initiative culminated in a *Supplement* to the *Journal of Veterinary Pharmacology and Therapeutics* (*7*). In that theme issue, several manuscripts examined the potential use of BCS criteria in animal health and explored criteria for defining a drug as “fully soluble” in veterinary species. This effort served as a springboard for relaunching the USP Veterinary BCS initiative in 2012. However, this new initiative differed from that in 2004 in two important ways:

- First, the concept of permeability was not considered as part of the deliberations. Rather, the focus was only on dose number.
- Second, following the elimination of permeability and the formidable challenge encountered with medicated feed (which often exhibits limited or no systemic bioavailability), the updated BCS initiative included both dogs (monogastric, carnivore) and cattle (ruminant, herbivore). Other veterinary species will be evaluated in the future.

This new initiative was discussed in a *Stimuli* article (*6*) that considered the relationship between species-specific GI characteristics and the appropriate criteria for describing drug solubility in veterinary species.

Summary of 2012 *Stimuli* Article

The science of solubility studies the interactions among factors such as polymorphic form of the active pharmaceutical ingredient, compound purity, particle size and shape; buffer composition, including pH and common ion effect; stability in solution; potential for molecular aggregation; time for attaining equilibrium; temperature; mixing conditions; and adsorption onto filter or vessel surfaces.

For human medicine, the three parameters considered when predicting drug oral bioavailability include: (1) *dose number* (D_o): the ratio of the dose to the amount of drug that will dissolve in 250 mL of test solution at the lowest solubility within the pH range from 1 to 7.5; (2) *absorption number* (A_n): the ratio of the GI transit time to the time needed for the solubilized drug to be absorbed (1/absorption rate constant); and (3) *dissolution number* (D_n): the ratio of the GI transit time to the time needed for in vivo drug dissolution (1/dissolution rate constant). With regard to solubility, dose number is the parameter of interest. The criteria used for classifying a drug as highly soluble must be clearly defined and must be firmly grounded in the GI physiology of the target animal species. Because the conditions under which dose number is defined reflect the GI tract of different veterinary species, it is likely that a compound that is fully soluble in one species may not be similarly categorized in another animal species. Furthermore, differences in dissolution number values are likely to occur across animal species.

Dogs

There are important differences between the GI tracts of different dog breeds and those of humans. The initial thought was that these GI differences render it inappropriate to apply the human criteria for drug solubility classification to dogs. In vivo dissolution of an oral medication in dogs must rely on residual stomach and intestinal water, and the human-based assumption of ingestion of 250 mL water is inappropriate. Fasting dogs may have a volume as low as 10 mL. Further, in humans solubility is based on the highest approved dose in mg. However, in veterinary medicine the dose is administered on a mg/kg basis. The potential effects of errors in estimated gastric volume on a compound's solubility classification, e.g., estimating that a compound is fully soluble (highly soluble) must be considered. The basal pH in the gastric fluid of dogs can be quite variable and depends highly on the portion of the stomach where the pH is measured. Evidence suggests that the gastric pH of the dog tends to be higher than that in humans because of the lower basal secretory rate of acid in the fasted dog. Despite species similarities in the amount of bicarbonate secreted, in the fed state the initial pH in the dog's duodenum is lower than that in humans because of the higher canine postprandial output of gastric acid. In other portions of the small intestine, the intestinal pH of dogs and humans are similar. Because of the range of pH values that affect drug solubility in dogs, it seems appropriate to use the same pH solubility criteria in dogs as is currently used for defining the solubility of human drugs.

Cattle

A number of points should be considered when one establishes conditions and criteria for classifying drug solubility in cattle: (1) the GI tract of the ruminant is markedly

different from that of humans; (2) the definition of highest dose is different in humans and cattle; and (3) the types of products are different (i.e., solid oral dosage forms vs. Type A medicated feeds). Because of the unique characteristics of the dosage form and ruminant GI tract, it may be necessary to factor time into the solubility assessment. Based on data from the literature, the duration of fluid transit through the rumen can be conservatively estimated as 8.6–11 h, and solubility must be determined after 8 h of testing. If a drug is considered fully soluble in the bovine rumen based on this conservative time estimate, the total dose should be dissolved within 8–9 h. The stomach of ruminant animals is composed of four compartments: the rumen, reticulum, omasum, and abomasum. The relative sizes of the 4 stomach compartments change with age. The total stomach capacity (fluid plus solid material) of an adult cow (all 4 compartments) is estimated to be in the range of 115–150 L, and extremes range from 95 to 230 L. Literature data support the hypothesis that drug entities reside in the rumen/reticulum for an extended period, thereby allowing drug dissolution before passage through the concentrating process of the omasum and into the acidic environment of the abomasum. Therefore, the rumen should be the compartment used for modeling drug solubility. Ruminants do not fast, and the ruminal fluids are complex mixtures because of their extensive fermentation activity. Generally these fluids contain large amounts of glucose, bacteria, volatile fatty acids, cellulose, digestive enzymes, vitamins, proteins, and lipids. These substances can act as surfactants, thereby affecting the solubility of a drug substance, and the relative proportions of these many constituents can vary as a function of diet. For these reasons, the question is whether or not one should consider the presence of these surfactants when developing testing conditions for drug substance solubility in ruminants.

Test Conditions for Determining Solubility

The gold standard for determining drug solubility is the shaker flask method. Other methods can be used with proper validation. Thermodynamic solubility is determined by several measurements, generally after 24–48 h of stirring the drug substance in aqueous medium. Equilibrium is considered to be achieved when at least two constant values of solubility are measured over time. The proposed conditions for determining if the drug is fully soluble are:

- dogs: 37 °C; pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer) and 7.5 (phosphate buffer) (volume and time are still to be defined)
- cattle: 38 °C; pH 5.1–7.5 (phosphate buffer), 50 L of fluid, 8 h.

TOPICS PRESENTED AT THE WORKSHOP

The following information summarizes and highlights some of the pivotal concepts presented during the workshop.

Physicochemical Basis of Drug Solubilization (Raafat Fahmy, PhD, U.S. FDA):

- Poor aqueous solubility and/or permeability of drug candidates often lead to poor absorption and bioavailability from the GI tract.
- Before absorption can occur, drug must first dissolve in the GI fluids before it can diffuse through the GI tract membranes and then reach systemic circulation.

- Poor solubility of the active ingredient is a major roadblock in formulation development.
- Thermodynamic solubility is performed using the solid crystalline form of a compound and defines the maximum amount of the compound in solution once equilibrium is reached.
- Strategies for enhancing the dissolution rate of poorly soluble drugs include particle size reduction; salt formation; complex formation with cyclodextrin; use of surfactants; solid dispersion formulations; lipid-based formulations, and others.

Influence of Drug Solubility on Formulation and Oral Drug Bioavailability (Marilyn Martinez, PhD, U.S. FDA, USP Solubility for Veterinary Drugs Expert Panel):

- Solubility of the active ingredient is key to developing successful formulations.
- Only dissolved drug is available to be taken up through the mucosa or to act at local GI target sites.
- There is only a negligible effect of formulation on the in vivo oral performance of highly soluble drugs that are intended for rapid dissolution.
- Variables that can influence the in vivo solubility of a compound include: excipients present in the formulation; presence of food and type of food (diet habits); and interspecies differences.

Testing Drug Solubility: Methodological Considerations (Bryan Crist, USP Solubility for Veterinary Drugs Expert Panel):

- Solubility determination is a prerequisite for pharmaceutical product development.
- Equilibrium solubility is the state at which the solution is saturated after compound solubilization and where an excess of undissolved compound remains.
- The rate of solubilization of drug substance depends on the interaction between the solute and solvent. The stronger the interaction, the more likely the drug will be highly soluble.
- Solubility classes vary from very soluble to practically insoluble.
- Solubility determination can be measured by the traditional saturation shake flask method.
- Other validated procedures can be used, e.g., with small amounts of compound and automation.

Solubility Criteria in Human Medicine and Its Application to Drug Development and Regulation (Alan Parr, PharmD, PhD, GlaxoSmithKline, USP Solubility for Veterinary Drugs Expert Panel):

- Solubility is influenced by many variables such as temperature; state of the solid; pH; composition; time; for ionizable compounds the presence or absence of certain counter-ions; and other factors.

- Potential in vivo challenges associated with poor solubility include poor or variable absorption; inefficacy; and the need for more complex and expensive delivery systems.
- The solubility of a compound is critical information during drug development.
- Regulatory flexibility: a compound's solubility is a parameter that can be considered to allow some regulatory flexibility (biowaivers according to the BCS).

Why We Cannot Simply Use Human Solubility Criteria in Veterinary Species (Marilyn Martinez, PhD, U.S. FDA, USP Solubility for Veterinary Drugs Expert Panel):

- Must consider how solubility is defined within the scope of human medicine.
- For humans, *highly soluble* is determined by the volume of an aqueous medium sufficient to dissolve the highest dose strength of a dosage form across a pH range of 1.2–7.5.
- A drug substance is classified as highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1.2–7.5 at 37 °C.
- Species-specific differences in drug solubility to consider: dose (based on animal body weight, route of administration, and transit time), interspecies differences in fluid volume in the GI tract, medium (i.e., composition and pH range of GI fluids), and temperature differences in the GI tract fluid across animal species.

Unique Physiological Attributes: Dog (Mark Papich, MS, DVM, North Carolina State University, USP Solubility for Veterinary Drugs Expert Panel):

- Anatomical and physiological differences between dogs and people are important.
- Physiological similarities exist between dogs and people with respect to: pH of stomach and intestine; and stomach emptying time (highly variable in both dogs and people).
- Different intestinal transit time—dogs compensate for a shorter intestine length by having longer intestinal villi that provide more surface area for absorption.
- The extent of oral absorption (F) of drugs between dogs and people does not correlate, but rate of absorption may have similar rank order for different formulations.
- Intestinal transporters may play an important role in oral absorption in dogs, and they may differ from human transporter systems.

Unique Physiological Attributes: Bovine (Mike Apley, PhD, DVM, Kansas State University, USP Solubility for Veterinary Drugs Expert Panel):

- The stomach of ruminant animals is composed of four compartments: rumen, reticulum, omasum, and abomasum. The relative sizes of the four compartments change with age.

- Studies using marker dilution have been used to evaluate rumen liquid turnover. These studies have yielded estimated turnover rates ranging from 11% to 18% of the liquid rumen content each hour.
- Estimates for the turnover time of rumen liquid contents have ranged from approximately 9 h up to 23 h in different studies.
- Rumen pH varies considerably depending on diet, intake, and time after a meal.
- Data support the assumption that drug entities reside in the rumen/reticulum for an extended period of time that allows dissolution before passage of these contents through the concentrating processes of the omasum and into the acidic environment of the abomasum.

WORKSHOP OUTCOMES

During the discussions at the workshop, participants expressed additional concerns regarding efforts to define dose number. In particular, numerous individuals considered dose number too restrictive with the potential to create an additional regulatory burden. Accordingly, participants agreed that the content of the general chapter would be limited to discussions about species-appropriate descriptions of conditions for testing in vitro drug solubility (C_s), including variables such as temperature and matrix composition (e.g., salts, natural surfactants, pH, etc.). Participants also agreed that because the default to date has been human-based solubility test conditions, veterinary species–specific assessments would provide more relevant information on which to base formulation assessments and product development and would be of value for those who deal with oral dosage forms for use in veterinary species.

The title of the proposed *USP* chapter will be *Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species* 1236. It will contain the laboratory procedure for the determination of thermodynamic solubility using the shake flask method but will allow the use of any other method that is shown to be equivalent and is appropriately validated. The duration of the test will be defined by the time needed to reach the equilibrium or saturation. For dogs the conditions will be: (1) media: USP buffers with pH of 1.2, 4.6, and 6.8; (2) temperature: 39 °C. For cattle the conditions will be: (1) media: pH 2.5 HCl, pH 3.5 acetate buffer, pH 5.0 and pH 6.8 phosphate buffer with possible addition of surfactants, and pH 6.8 phosphate buffer without surfactants; (2) temperature: 38.5 °C.

Future initiatives could explore description of the conditions for estimating in vitro drug solubility in other veterinary species and, potentially, any modification in existing specifications that may arise as additional information is acquired.

The activities involved in this project since 2002 and the next steps are summarized in *Figure 1*.

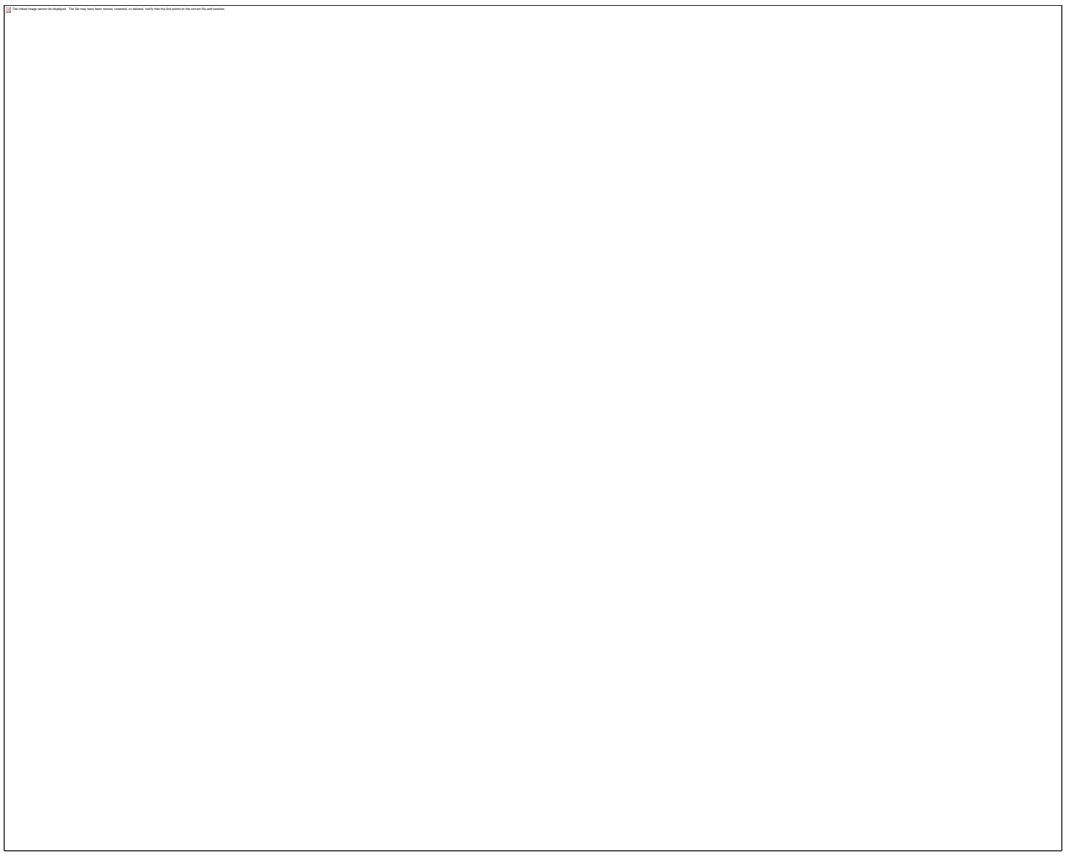

Figure 1. Summary of USP activities since 2002 and next steps. Cs = in vitro drug solubility.

NEXT STEPS

It is proposed that a revised *Stimuli* article be published in a future issue of *Pharmacopeial Forum* (*PF*) explaining the rationale for the new approach for the development of the new *USP* general chapter. This paper is going to be followed by the publication of the chapter proposal in *PF*. A broader promotion of the new chapter will be made through trade magazines.

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