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<1236> Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species

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Veterinary Drugs Stakeholder Forum
February 19-20, 2014

Expert Panel
Solubility Criteria for Veterinary Drugs

- Mario González, Ph.D., P'Kinetics International Inc. (Chair)
- Mike Apley, D.V.M., Kansas State University
- Mark Papich, M.S., D.V.M., Kansas State University
- Alan Parr, Pharm.D., Ph.D., GlaxoSmithKline Inc.
- Bryan Crist, Agilent Technologies
- Robert Hunter, M.S., Elanco Animal Health
- Jim Riviere, D.V.M, PhD, Kansas State University
- Marilyn Martinez, Ph.D., CVM, FDA
- Sanja Modric, D.V.M., CVM, FDA
- Margareth Marques, Ph.D., USP Liaison

Background

- Stimuli article – Pharm. Forum 30(6) [Nov. Dec. 2004]

Veterinary Application of In Vitro Dissolution Data and the Biopharmaceutics Classification System

Marilyn N. Martinez,[*] Mark G. Papich,[**] and Jim E. Riviere[**]

ABSTRACT The Biopharmaceutics Classification System (BCS) has been developed for human pharmaceutical compounds to predict oral drug absorption. A similar approach for evaluating in vitro data regarding dissolution, solubility, and permeability of veterinary oral dosage formulations has not been applied to predict oral absorption in animals. However, if reliable data can be generated, it may be possible to apply these principles to veterinary drugs. Before this can happen, obstacles must be overcome. Because of differences in anatomy and physiology between animals and people, extrapolations to veterinary drug formulations may not be applicable. Veterinary drug formulations also may differ in their size, excipient content, and use compared to human drug formulations. There is a clear need to examine the application of in vitro data regarding dissolution and permeability for product evaluation and regulatory decisions. This article and future scientific presentations will explore the potential for this application.

Upon resolution of these questions and following appropriate adjustments to testing methods for permeability, solubility, and dissolution assessments, we will be able to apply, with confidence, BCS principles to oral formulations intended for use in dogs. We believe that the extrapolation of BCS principles to oral formulations for use in canines will prove to be an extremely valuable contribution to veterinary medicine.

This *Stimuli* article on the potential applications of BCS to veterinary drugs was endorsed by the USP Veterinary Drugs Expert Committee. Reader comments about the suggested applications of in vitro solubility, permeability, dissolution data, and the BCS are invited. These comments should be directed to Ian F. DeVeau, Ph.D., at the Department of Standards Development, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, telephone: 301.816.8178; fax: 301.816.8373; e-mail: ifd@usp.org.

Background

- Stimuli article – Pharm. Forum 38(4) [July – Aug. 2012]

STIMULI TO THE REVISION PROCESS

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Solubility Criteria for Veterinary Drugs

Mike Apley,[a] Bryan Crist,[a] Mario A. Gonzalez,[a,b] Robert P. Hunter,[a] Marilyn N. Martinez,[a] Sanja Modric,[a] Mark G. Papich,[a,c] Alan F. Parr,[a,b] Jim E. Riviere,[a] Margareth R.C. Marques[d*]

ABSTRACT This *Stimuli* article is the first step toward the development of a general chapter addressing solubility criteria for veterinary drug products. The current criteria for classifying drug solubility are based on human gastrointestinal (GI) physiology. These criteria may not be appropriate to the unique conditions encountered within the GI tract of veterinary species. Thus, this article discusses the relationship between the species-specific GI characteristics and the criteria appropriate for describing drug solubility in veterinary species. Initially the discussion focuses on dogs and cattle, the most common veterinary patients in small- and food-animal practices, respectively. Later the discussion will include various other veterinary species of interest.

INTRODUCTION

The determination of drug solubility is important to facilitate an appreciation of the formulation variables that can influence drug absorption. Highly water-soluble compounds designed for immediate release tend to be far more forgiving with regard to the effect of formulation changes on oral product bioavailability compared to drugs that exhibit poor aqueous solubility (*1*). Furthermore, within veterinary medicine, drug solubility is one of the essential pieces of information needed to support the biowaiver of oral soluble powders and Type A medicated articles (premixes) (*2*).

The Biopharmaceutics Classification System (BCS) provides a foundation for the consideration of biowaivers and for predicting formulation variables that can influence human oral drug absorption (*3*). Initially proposed by Amidon et al. in 1995, the BCS is founded on an

Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredient for Veterinary Species

- Thermodynamic solubility
  - Use of shake flask method
  - Use of others validated techniques
  - Time to equilibrium or saturation

Workshop outputs (Nov 7 – 8, 2012)

- **Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredient for Veterinary Species**
- **Dogs**
  - Media composition: buffer according to USP
  - pH: 1.2, 4.6, and 6.8
  - Temperature: 39°C
- **Cattle**
  - Media composition: pH 2.5 HCl, pH 3.5 acetate buffer, pH 5.0 phosphate buffer and volatile fatty acids (VFA), pH 6.8 phosphate buffer, pH 6.8 phosphate buffer with VFA
  - Temperature: 38.5°C

Workshop Report

- Pharm. Forum 39(4) [July – Aug. 2013]

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Solubility Criteria for Veterinary Drugs—Workshop Report

Mike Apley,[a] Bryan Crist,[a] Mario Gonzalez,[a,b] Robert P. Hunter,[a] Marilyn N Martinez,[a] Sanja Modric,[a] Mark G Papich,[a,c] Alan F Parr,[a,b] Jim E Riviere,[a] Margareth RC Marques[c,d,e]

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 ⟩.

The objectives of this *Stimuli* article are to give a brief summary of discussions at the workshop and to explain the new approaches that will be used to develop the new *USP* general chapter.

Next steps

- Collect more information about the conditions for cattle
- Publish new Stimuli article with the rational for the new general chapter
- Develop the text for the chapter
- Next possible species: cats and pigs
- **Workshop** – March 14 – 15, 2016

Web Page for Veterinary Topics

- http://www.usp.org/usp-nf/key-issues/key-issue-standards-veterinary-drugs

Key Issue: Standards for Veterinary Drugs

Original Posting: 01–May–2013; Updated 22–Nov–2013

Contacts

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Consistent with its commitment to provide public standards for the quality, consistency, purity, identity, and strength of all medicines, USP is advancing its standards for drugs for veterinary use. These standards include monographs and general chapters (including those devoted to veterinary drug topics) applicable to any articles recognized in the United States Pharmacopeia–National Formulary (USP–NF), whether in the form of a manufactured product or a compounded preparation. USP has been active in setting standards for veterinary drugs for many years, and recently has expanded its mission statement to acknowledge this.

Current Activities

Solubility Criteria for Veterinary Drugs

A summary of the discussions during the Workshop on Solubility Criteria for Veterinary Products that took place at USP headquarters in Rockville, MD on November 7–8, 2012 was published in Pharmacopeial Forum 39(4), together with Stimuli articles that will provide explanations for the approaches to be included in a new USP General Chapter <1236>, provisionally titled Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species.

- Solubility Criteria for Veterinary Drugs—Workshop Report. Pharmacopeial Forum, Vol. 39, No. 4 [Jul.–Aug. 2013] (31–May–2013)
- Solubility Criteria for Veterinary Drugs. Pharmacopeial Forum, Vol. 38, No. 4 [Jul.–Aug. 2012] (31–May–2013)
- Veterinary Application of In Vitro Dissolution Data and the Biopharmaceuticals Classification System. Pharmacopeial Forum, Vol. 30, No. 6 [Nov.–Dec. 2004] (31–May–2013)

For additional information, contact Margareth Marques, Ph.D., Senior Scientific Liaison (mrm@usp.org or 301-816-8106).

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Questions

Thank You