# COMMENTARY

# Terminology Challenges: Defining Modified Release Dosage Forms in Veterinary Medicine

MARILYN N. MARTINEZ, DANIELLE LINDQUIST, SANJA MODRIC

Food and Drug Administration, Center for Veterinary Medicine, Office of New Animal Drug Evaluation, Rockville, Maryland 20855

*Received 16 September 2009; revised 30 December 2009; accepted 4 January 2010*

*Published online 8 March 2010 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22095*

**ABSTRACT:** Terminologies for describing dosage form release characteristics for human pharmaceuticals have been addressed by bodies such as the US Food and Drug Administration (FDA), the International Conference on Harmonization (ICH), and the US Pharmacopeia (USP). While the definition for terms such as "immediate release," "modified release," "extended release," and "delayed release" are now well accepted for human pharmaceuticals, confusion still exists within the veterinary community. In part, this confusion is attributable to differences between human and veterinary dosage forms (such as the preponderance of parenteral vs. oral extended release products for use in animals vs. the focus on oral extended release formulations for human use) which reflect interspecies differences in physiology and conditions of use. It also simply reflects a lack of attention to existing definitions. In an effort to remedy this problem, this manuscript reflects an initial effort to suggest definitions that may be appropriate for describing formulation effects in veterinary medicine. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3281–3290, 2010

**Keywords:** bioavailability; controlled release; formulation; pharamcokinetics; preclinical pharmacokinetics

## INTRODUCTION

The evolving sophistication of human and veterinary therapeutic objectives necessitates the development of innovative drug delivery systems. Often designed as modified release products, these formulations are invaluable for enhancing user compliance (by reducing dosing frequency) and user safety, minimizing patient discomfort, promoting safety and effectiveness of some active pharmaceutical ingredients by reducing the magnitude of peaks and troughs in systemic drug concentrations, or by delaying drug release (such as enteric coated products that reduce gastric irritation or targeted delivery systems that are formulated to release drug at the site of action). Examples of the therapeutic challenges and corresponding formulation and manufacturing concerns associated with the development of modified release dosage forms for veterinary use are discussed elsewhere.[1,2] Some of the critical variables associated with parenteral modified release dosage forms have also been previously reviewed.[3] Despite the large number of examples of these marketed platforms, the consistent terminology for describing the various subcategories of modified release products has been lacking, both among the human and veterinary pharmaceuticals. The term "modified release" is a broad overarching category that describes any non-immediately released dosage form for which there was an intentional change in the drug-release characteristics.

One of the problems that has occurred during this technology explosion is the tremendous variation in terminologies that has been used to describe these complex product formulations. Examples of terms that have been applied in both human and veterinary medicine include:

- Sustained release (SR).
- Long acting (LA).
- Extended release (ER).

The content of this manuscript reflects the opinions of the authors and does not reflect official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

*Correspondence to*: Marilyn N. Martinez (Telephone: 240-2768357; Fax: 240-276-8350;
E-mail: marilyn.martinez@fda.hhs.gov)

Journal of Pharmaceutical Sciences, Vol. 99, 3281–3290 (2010)

- Controlled release (CR).
- Timed release (TR).
- Modified release (MR).
- Delayed release (DR).
- Prolonged release (PR).

The many ways in which these products have been described have lead to tremendous confusion within the human and veterinary pharmaceutical communities. This lack of clarity is further complicated by the interchangeable manner in which these terms have been applied, leading to an uncontrolled proliferation of descriptive terms for various subcategories of modified release products. To illustrate this point, Posilac® (NADA 140-872), sometribove zinc suspension administered as a subcutaneous (SC) injection in lactating dairy cattle, is described as a "prolonged release" product.[4] However, in a manuscript titled "*Sustained Release* Veterinary Parenteral Products," Posilac® is listed in a table titled "Top Animal Health Parenteral Controlled Release Pharmaceuticals in 1999."[5] Another example further illustrating this confusion is the approval of Hava-Span *Prolonged Release* Bolus for cattle (NADA 093-329), which is described in the FOI Summary as a "Prolonged Release" bolus, but its dosage form is listed as a "Sustained release bolus." A comparable example among human pharmaceuticals is the brand Ritalin *SR*®, which (on "Drug Information.com") is said to have the generic name of methylphenidate *controlled release tablets*.[6]

Prefixes used in brand names only further add to this confusion. For example, inclusion of the prefix "Dura" in the brand name of a product may be interpreted as product exhibiting a prolonged duration of activity. However, this is certainly not the case. To illustrate this point, the product DuraPen™ (NADA 065-498) provides an extended exposure to penicillin, Duramycin 72-200® (ANADA 200-306) provides an extended release of oxytetracycline, but Duramycin 10 and Duramycin 324 (NADA 065-140) is a water-soluble tetracycline powder that is administered in drinking water to chickens, turkeys, pigs, and cattle (http://www.durvet.com/pl_div_products.html?div=Cattle). Further contributing to this ambiguity is that the same extended release penicillins that are contained within DuraPen™ are also contained within the products Longicil® manufactured by Fort Dodge Animal Health (NADA 065-087), and Dura-biotic® (also manufactured by Fort Dodge Animal Health, NADA 065-169). However, the "Dura" prefix is not contained in the comparable product, Dual-Cillin®, and manufactured by Teva Animal health (NADA 065-498) or in the other name used by Fort Dodge for their NADA 065-169, Flo-cillin®. Furthermore, none of these products appear when searching Drugs@FDA for products containing the terms "Prolonged Release," "Sustained Release," "Controlled Release," or "Extended Release." (Please note that due to the age of these products, sponsor names, brand names, and NADA numbers may vary with time. However, each of these products can still be found when using online search engines.)

This terminology quandary is exemplified in the US Food and Drug Administration (FDA) news release dated May 2007:[7]

FDA informed consumers and healthcare professionals of its intent to take action against companies that market unapproved *timed-release* dosage form of guaifenesin products, a substance commonly used in medicines to relieve cough and cold symptoms by stimulating removal of mucous from the lungs. These dosage forms are often described as *extended-release*, *long-acting*, or *sustained-release* products that release their active ingredients over an extended period of time, reducing the number of doses needed per day. Approximately 20 firms make unapproved timed-release products containing guaifenesin that have not undergone FDA review for safety and efficacy. Mucinex, Mucinex-D, Mucinex-DM, and Humibid are the only FDA approved *timed-release* guaifenesin (single ingredient or combination) products. Companies marketing unapproved products containing guaifenesin in *timed-release* form are expected to stop manufacturing them within 90 days and must cease shipping them in interstate commerce within 180 days. This action does not affect products containing guaifenesin in immediate release form.

Furthermore, within the human drug community, there are examples of products using an array of abbreviations such as SR, ER, CR, XL, XR, and others to represent extended release formulations. Each of these has been used to convey an extended availability of the active pharmaceutical ingredient (API) without a distinct definition of the timeframe associated with the dosing interval. For instance, Wellbutrin® SR and Eskalith® CR are both dosed every 12 h, even though one is labeled "SR" and the other is labeled "CR." In another case, Ritalin SR is dosed every 8 h as compared to the 12-h dosing interval of Wellbutrin® SR. In the case of veramapil HCl, two formulations have been approved, each that uses novel delivery systems that provide 24-h blood pressure control, while maximizing drug concentrations in the morning and minimizing drug concentrations during sleep.[8] There are currently two antihypertensive agents, Verelan® PM (NDA 20–943) and Covera® HS (NDA 20–552), which are both formulated as an extended release capsule that is intended for administration in the PM.

In an effort to ameliorate this problem, the US FDA Center for Drug Evaluation and Research (CDER), the US Pharmacopeia (USP), and the International