

## Drugs prohibited from extralabel use in food animals

Michael A. Payne, DVM, PhD; Ronald E. Baynes, DVM, PhD; Stephen F. Sundlof, DVM, PhD, DABVT; Arthur Craigmill, PhD; Alistair I. Webb, BVSc, PhD; Jim E. Riviere, DVM, PhD

**T**he Animal Medicinal Drug Use Clarification Act (AMDUCA), signed into law in 1994, amended the Food Drug and Cosmetic Act to decriminalize most instances of Extralabel Drug Use by veterinarians.<sup>1</sup> This privilege, however, is not *carte blanche*; specific conditions must be met before a veterinarian may legally use or prescribe drugs in an extralabel fashion for food-producing animals. These requirements<sup>2-4</sup> include a valid veterinarian-client-patient relationship and appropriate drug labeling and record keeping.

Certain drugs may not be prescribed or used even under AMDUCA auspices. Section 530.21 of the act clearly states that the FDA Center for Veterinary Medicine (CVM) may prohibit the extralabel use of approved new animal or human drugs for a number of reasons. Thus far, FDA-CVM has prohibited 8 drugs or drug classes, making their extralabel use in food animals illegal.

Veterinarians violating state or federal laws regulating the transport, sale, or use of drugs may face various sanctions, including warning letters, fines, temporary or permanent revocation of their state veterinary license, or incarceration. Extralabel use of any of the prohibited drugs in food animals represents one of the FDA's highest priorities for regulatory attention.

Because of the potential adverse human health effects resulting from the use of these drugs in food animals, FARAD will decline to routinely provide withdrawal intervals for them. However, in the event of accidental exposure, FARAD has consulted with veterinarians and regulatory officials to determine periods after which tissue and milk might be safely marketed.

This FARAD Digest provides background information to more clearly define the regulatory requirements regarding these compounds. The drugs are listed in the order in which they were prohibited. Except as described, these drugs should not be used in food animals.

**Diethylstilbestrol (DES)**—From 1941 to 1971, US physicians prescribed this potent nonsteroidal synthetic estrogen to between 0.3 and 3 million pregnant women to prevent miscarriage or other reproductive diseases.<sup>5</sup> The drug continued to be used despite considerable evidence, collected during the 1950s, that raised questions regarding efficacy for its label claims.<sup>6</sup> In 1971 a link between in utero exposure to DES and a rare vaginal cancer (clear cell adenocarcinoma) was established.<sup>7</sup> Between 35 and 90% of fetal-exposed female offspring will develop precancerous lesions,<sup>8</sup> which undergo malignant transformation in approximately 1 in 1,000 of those exposed.<sup>9</sup> In 1971, the FDA published an alert advising doctors against the use of DES in pregnant women. The FDA banned the use of DES in food animals in 1979.<sup>10</sup> The drug has applications in human and companion animal medicine, but DES-containing products are not currently being marketed.

**Chloramphenicol**—Reversible, dose-related bone marrow suppression resulting from treatment with chloramphenicol has been detected in numerous species including humans. Of more concern is a human-specific aplastic anemia, estimated to affect between 1 in 10,000 to 50,000 exposed people. Because this idiosyncratic toxicosis is often fatal, appears to be non-dose related, and could presumably be triggered by residues, use of chloramphenicol in food animals was prohibited in 1984. Several reports document human fatalities resulting from ophthalmic preparations containing chloramphenicol, with total exposure doses that could be achieved from food residues.<sup>11</sup> Several veterinarians have been fined or imprisoned for distributing or misbranding chloramphenicol for use in food animals.<sup>12,13</sup> A number of oral, injectable, and topical products containing chloramphenicol are approved and available for use in small animals. The prohibition against the drug's use in food animals extends to all formulations of chloramphenicol including ophthalmic ointments. Florfenicol (Nuflor), a synthetic member of the chloramphenicol family, is approved for use in beef cattle in the United States. This compound lacks the *p*-NO<sub>2</sub> group thought to be responsible for inducing aplastic anemia and has not been associated with the syndrome.<sup>14</sup> Florfenicol may be used in an extralabel fashion in food-producing species.

From the Food Animal Residue Avoidance Databank (FARAD), Environmental Toxicology Extension, College of Agricultural and Environmental Sciences, University of California, Davis, CA 95616 (Payne, Craigmill); FARAD, Center for Cutaneous Toxicology and Residue Pharmacology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Baynes, Riviere); FARAD, Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Webb); and the Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD 20855 (Sundlof).

**Nitroimidazoles**—Laboratory studies of members of this drug class (which include dimetridazole, metronidazole, and ipronidazole) have demonstrated mutagenicity and carcinogenicity.<sup>13</sup> After undergoing reductive activation *in vivo*, metabolites from these compounds attack DNA base pairs resulting in loss of helical structure, strand breakage, and possible inhibition of DNA repair mechanisms. Oral exposure to nitroimidazole compounds has caused carcinogenesis in rodents and mutagenic urinary metabolites in humans. Dimetridazole was approved in the mid-1960s for the treatment of histomoniasis (infectious enterohepatitis, blackhead) in turkeys. Despite available label alternatives, the FDA-CVM documented widespread extralabel use of the drug to treat and prevent swine dysentery. Food safety concerns led to withdrawal of its approval in 1987.<sup>16</sup>

Metronidazole is approved in humans for the treatment of trichomoniasis, amebiasis, giardiasis, and anaerobic bacterial infections. Short-term exposure in human patients does not appear to increase risk of developing cancer.<sup>17</sup> The drug has found extensive extralabel veterinary use for indications similar to those in humans, particularly in the treatment of giardiasis in companion animals. Metronidazole and ipronidazole (the latter also once labeled for histomoniasis) have been used to eliminate the bull carrier-state of the venereal disease trichomoniasis. With no approved veterinary nitroimidazole labels, the use of any member of this drug class in food animals is illegal.

**Sulfonamide use in dairy cattle**—As with the nitroimidazoles, concerns about sulfonamide residues have arisen as a result of observed carcinogenicity in laboratory animals. In 1988, the FDA National Center for Toxicologic Research reported an increase in thyroid follicular cell carcinomas and hepatocellular adenomas in rodents given large doses of sulfamethazine (SMZ).<sup>18,19</sup> These studies were of particular concern to regulatory agencies, as they coincided with reports of sulfonamide residues in up to 13% of swine carcasses and up to 73% of retail milk samples.<sup>20,21</sup> In swine tissue and milk, SMZ was by far the most common sulfonamide detected, because of the compound's widespread use, high oral bioavailability, long half-life, and stability in the environment.

A review of the causes and prevention of SMZ residues in swine is beyond the scope of this article, but excellent references are available.<sup>20,22</sup> Detection of milk residues was particularly disturbing because there are no SMZ products labeled for lactating cattle. Clearly, these residues were the result of extralabel use. New labeling for SMZ products, aggressive education efforts by the dairy industry, and intensified enforcement actions by regulatory agencies resulted in a dramatic decrease in SMZ residues in milk. Another consequence of the SMZ issue was the now familiar drug labeling and storage requirements, which were added to the Pasteurized Milk Ordinance in 1989. Only 1 of the 3 sulfonamides that have label indications for lactating cows, sulfadimethoxine (SDM), is currently being marketed. The FDA defines a lactating cow as any dairy cow (regardless of lactation status) older

than 20 months. Currently, use of any sulfonamide other than SDM in dairy cattle older than 20 months is illegal. Additionally, extralabel use of SDM in lactating dairy cattle is prohibited (for example, use of a higher dose or slow-release SDM boluses in dairy cattle is not permitted).

**Nitrofurans**—As with the nitroimidazoles and sulfonamides, the carcinogenicity and mutagenicity of nitrofurans has been documented in laboratory studies. Feeding trials with nitrofurazone have demonstrated the development of fibroadenomas in mammary glands of rats and benign mixed tumors and granulosa cell tumors in ovaries of mice.<sup>23</sup> Furazolidone has been shown to cause bronchial adenocarcinomas in mice fed the compound for life.<sup>24</sup> These drugs are also believed to cause occupational allergic contact dermatitis in humans.<sup>25</sup> On the basis of concerns related to carcinogenicity, approval for all human nitrofurazone products, except for dermatologic preparations, were withdrawn in 1974.<sup>26</sup> Nitrofurazone and furazolidone had been approved for a variety of protozoal and other infections in poultry and swine. On the basis of carcinogenicity and the absence of a reliable detection method, the FDA withdrew approval for systemic animal nitrofurans in 1991.<sup>27</sup> A number of nitrofurans-containing products are still available for topical use in dogs, cats, and horses. A limited number of topical nitrofurazone products labeled for "pinkeye in cattle, sheep and goats" and "surface wounds, cuts and abrasions on all livestock" were recently available. As a result of a FDA-CVM sponsored study demonstrating meat and milk residues following label use,<sup>28</sup> manufacturers of these products agreed to remove their food animal indications. The parenthetical reference to "approved topical" nitrofurans in AMDUCA will be omitted in the near future. Product with "old" labels, already in distribution, may be depleted through normal sale channels. Following this, with no approved food animal labels, the use of any member of this drug class in food animals will be illegal.

**Clenbuterol**—This synthetic sympathomimetic is approved in a number of foreign countries and is administered as either a bronchodilator in horses or as a uterine relaxant in cattle and sheep. A  $\beta$ -2 adrenergic agonist with lipolytic activity, this compound has been used illegally in food animals to increase weight gain and lean body mass. Such illicit use is reported to have resulted in > 1,000 emergency hospitalizations and several deaths in people in Europe.<sup>29,31</sup> In Spain and France, numerous humans have developed symptoms of toxicosis, with muscle tremors, tachycardia, and heart palpitations being the most commonly reported. Episodes are usually associated with consumption of liver, the edible tissue containing the highest residue concentrations.<sup>32,33</sup> Several factors may contribute to the high residue concentrations detected in poisoned humans. The dosage required for anabolic effects in animals is 5 to 10 times higher than that used for treatment of respiratory therapy<sup>32,33</sup> and cooking only decreases drug residues minimally.<sup>29</sup> Because muscle depletion and fat redeposition commences following

drug withdrawal (the "β-agonist reverse effect"<sup>34</sup>), producers may be tempted to market animals with little or no withdrawal interval.

Inappropriate use of clenbuterol is not limited to Europe. Two veterinarians were recently convicted on charges of conspiring to smuggle clenbuterol into the US from Canada.<sup>35</sup> Total fines in these cases approached \$100,000 and included an 8-month prison term. In addition, there have also been a disturbing number of regulatory actions involving American show animals.<sup>36</sup> With the recent US approval of clenbuterol (Ventipulmin Syrup) as a treatment for chronic obstructive pulmonary disease (COPD or "heaves") in horses, the FDA will be monitoring for illegal food animal residues and unusual sales patterns of the drug.<sup>37</sup>

**Dipyrrone**—A pyrazolon derivative, dipyrrone has historically been used in humans and animals as an antipyretic, anti-inflammatory, and analgesic. The drug has been associated with serious toxic effects in humans, including dose-independent teratogenicity, increased bleeding times, and a potentially fatal agranulocytosis.<sup>38,39</sup> Prompted by these concerns, the FDA removed approval for all dipyrrone-containing human medical products in 1977.<sup>40</sup> Dipyrrone products labeled for companion animals (but which the FDA had never approved) continued to be sold. On the basis of surveys indicating food animal use, the absence of an assay method, and lack of animal safety, residue, and efficacy data, regulatory discretion allowing veterinary product marketing ceased in 1995.<sup>39</sup> Because products are not available for either humans or animals, dipyrrone is not typically included on lists of extralabel prohibitions published by FDA-CVM. Old stockpiles of the drug, however, do occasionally surface. Any use of dipyrrone in food animals remains a violation of the Food Drug and Cosmetic Act and receives the same regulatory priority as other compounds described in this article.

**Fluoroquinolones**—Although antibiotic use has been shown to contribute to microbial drug resistance in food animals, the frequency, magnitude, and importance of such resistance in humans remains a hotly contested issue. A review of relevant research is beyond the scope of this article, but excellent summaries are available.<sup>40,41</sup> Of particular concern has been the question of increasing virulence of *Salmonella* sp, a pathogen estimated to account for between 500 and 4,000 human deaths in the United States annually.<sup>42,43</sup> One study observed a risk of death or hospitalization to be 20-fold higher for resistant than nonresistant *Salmonella* infections.<sup>44</sup> The emergence of the multi-drug resistant *Salmonella typhimurium* DT-104 strain has similarly fostered international attention on the question of zoonotic pathogen resistance.<sup>45</sup> Because the fluoroquinolones have remained a mainstay for treatment of antibiotic-resistant *Salmonella* infections in humans, the advisability of using this class of antibiotic in food animals has been questioned. Especially controversial has been data collected by the Centers for Disease Control and Prevention (CDC) suggesting a possible link between fluoroquinolone use in food animals and increasing human pathogen resistance in the

United Kingdom.<sup>43</sup> Although these and other data have not been sufficiently conclusive to prevent approval of sarafloxacin for chickens or enrofloxacin for chickens and beef cattle, it prompted FDA-CVM to prohibit extralabel use of these compounds in 1997.<sup>46</sup> Fluoroquinolone products labeled for either humans or companion animals may not be used in food animals. Any deviation from a food animal label (such as use with a different species, dosage, route of administration, or disease indication) is similarly illegal. In the case of the approved beef cattle formulation of enrofloxacin (Baytril 100), this prohibition extends to all nonbeef-production animals, including lactating and nonlactating dairy cows, heifer replacements, and veal calves.<sup>47</sup> Enrofloxacin may not be stored in dairy farm drug cabinets.

**Glycopeptides**—The only glycopeptide antibiotic available in the United States is the human product vancomycin (Vancocin). Because of its gram-positive spectrum and associated renal and ototoxicity, this compound has found limited application in humans except in the treatment of *Clostridium difficile* colitis and infections with beta lactam-resistant gram-positive cocci. Most important, vancomycin is often the treatment of last resort for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans. Although only demonstrated in the laboratory, widespread transfer of vancomycin resistance from strains of *Enterococcus* spp to MRSA could provoke a health care crisis in the form of a common, highly virulent, and untreatable infection.<sup>48</sup> Particularly worrisome are Danish and German data demonstrating vancomycin resistant *Enterococcus* spp in the feces and food products of poultry and swine fed the glycopeptide avoparcin.<sup>49,50</sup> Avoparcin, a compound chemically similar to vancomycin, has been used in European animal feeds as a growth promoter since the mid-1970s. On the basis of these and other data, FDA-CVM in 1997 issued an order prohibiting the extralabel use of all glycopeptides in food animals.<sup>46</sup>

The restriction of fluoroquinolone and glycopeptide use represents a novel exercise of FDA-CVM discretionary authority: restriction based not on the drug's direct toxicity, but on its potential for increasing human pathogen resistance. Besides these types of prohibitions, various other efforts now underway may help mitigate the drug resistance problem. A collaborative FDA, CDC, and USDA surveillance program will monitor changes in drug resistance patterns from both human and animal isolates.<sup>48</sup> In addition, CDC has funded a limited number of projects examining on-farm methods to minimize resistance development. Lastly, a number of professional, industry, and regulatory organizations have formed committees whose purpose is to develop procedures that will define prudent use of antimicrobials in food animals.

**Extralabel use of medicated feed**—Another prohibition generated by concerns of antibiotic resistance relates to the extralabel use of medicated feed. Section 530.11 of AMDUCA specifically prohibits the "extralabel use of an approved new animal drug or human

drug in or on an animal feed.”<sup>1</sup> As a matter of enforcement discretion, FDA-CVM generally has not objected to mixing a drug with an individual animal’s feed, but extralabel mass medication in feed is prohibited “without limitation or exception.” This prohibition extends to all drugs; not just those discussed in this article.

**Other dairy prohibitions**—The Grade-A Pasteurized Milk Ordinance states that unapproved or improperly labeled drugs will not be used to treat dairy animals and will not be stored in “the milkhouse, milking barn, stable, or parlor.”<sup>2</sup> With the exception of SDM, none of the drugs or drug classes listed in this article may be legally labeled for dairy cattle and, if found during an inspection, would trigger regulatory action. In addition to dipyrone, there are 2 drugs that are not currently on the AMDUCA prohibited list but which result in “debits” if found during a dairy inspection. These are dimethyl sulfoxide and colloidal silver. The use of ionophore compounds (ie, monensin, lasalocid) in lactating dairy cattle rations is prohibited.

**Status of aminoglycosides**—A number of veterinary organizations have established or support policies that discourage the extralabel use of aminoglycosides. These organizations include the Academy of Veterinary Consultants, the Society for Theriogenology, the American Association of Bovine Practitioners, the American Veterinary Medical Association, and a number of state veterinary medical associations. These position statements are nonbinding and should not be confused with the legal prohibitions described in this article.

**Treatment of companion animals**—The prohibitions described in this article pertain to food-producing animals only and not companion species, such as dogs and cats. FARAD receives a few inquiries related to the use of these compounds in companion animals that also are a members of a food producing species (ie, horses, llamas, pot bellied pigs). As long as they are never offered for slaughter, the FDA-CVM does not normally consider these to be food animals. Because the ultimate fate of such treated animals is often beyond the control of the veterinarian, a practitioner should reflect on the amount of liability that he or she is willing to accept. Practitioners who have used a prohibited substance in a companion or pack animal that subsequently enters the food supply would be subject to enforcement actions under the Food Drug and Cosmetic Act.

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Additional references available on request.



### Correction: FARAD Digest

In the FARAD Digest titled "Primer on estimating withdrawal times after extralabel drug use" (*JAVMA*, Oct 1, 1998, pp 966-968), the first sentence of the last paragraph of the left-hand column on page 967 should have read "...and from a 100-g initial dose..." rather than 10-g initial dose.