

New Animal Drug Approval Canadian Guidelines

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In Canada, veterinary drugs are reviewed and approved under authority of the Federal Food and Drugs Act and regulations, as well as the Narcotics Control Act. Administrative responsibility for the evaluation and approval of veterinary drugs resides with the Health Protection Branch of Health Canada. The mandate of the Bureau of Veterinary Drugs includes the evaluation of human safety, animal safety, and drug efficacy. In order to carry out its mandate, the Bureau requires that new drug submissions include the following: manufacturing data which should include information on the drug substance, the dosage form of the drug, and information regarding drugs which are intended to be used as feed additives, pre-mixes and medicated feeds. The Bureau requires target species safety and efficacy data which must include information on margin of safety studies in the intended species, studies which address potential alterations in reproductive function, as well as clinical trials conducted under environmental and clinical conditions similar, if indeed not identical, to those of the intended use of the drug. Similarly, efficacy studies in support of new drug submissions also should include information derived from *in vitro* sensitivity where applicable, dose titration studies, challenge studies, and, again, clinical trials intended to address the efficacy of the drug under actual Canadian use conditions. Applications for new drug approvals in Canada typically include new chemical entities, new drug combinations or new claims or conditions of use for existing drugs. Human safety, as a function of the presence of residues of veterinary drugs in products of animal

origin, is of paramount importance to the Bureau of Veterinary Drugs and, indeed, to the Health Protection Branch of Health Canada. Typically, human safety is addressed through the conduct of classical laboratory animal toxicology studies, pharmacology studies and residue studies. While classical toxicological studies are generally conducted in laboratory animals, residue studies typically include radio-labelled residue depletion investigations, comparative metabolism and methods of residue analysis. The Canadian Bureau of Veterinary Drugs has adopted a six-step procedure for the human safety evaluation of new animal drugs intended for use in food production. These six steps include:

- 1) Metabolism studies in the target species
- 2) Comparative metabolism studies in the laboratory test species
- 3) Toxicity/Carcinogenicity testing, where applicable, to determine a safety level or acceptable level of risk for residues.
- 4) Determination of the safe concentration levels for total residues, target tissue, marker residue and tolerance.
- 5) Development of an analytical assay for the marker residue at the required level of measurement
- 6) Establishment of an appropriate withdrawal period required for the safe use of the drug

Notwithstanding the authorities derived from the Food and Drugs Act to review, approve and regulate the use of veterinary drugs in the production of food commodities, in Canada any practitioner

may lawfully prescribe any approved drug for any use, including indications not originally reviewed or approved as well as doses or species not originally labelled. The practice of prescribing non-approved drugs is often referred to as extra-label or off-label use. Surveys of clinical practitioners in Canada have revealed that 84% of those practitioners surveyed have made use of extra-labelled prescriptions at least some of the time. Further, of extra-label uses prescribed, practitioners responded that antibiotics were the most frequently prescribed and most often due to a lack of efficacy of previously approved labelled dosages. Practitioners also have indicated that the most widely prescribed extra-label drugs in small animal practice include Ovaban and Ivomec, whereas extra-label drugs used in large animals have included Banamine and Penicillin.