

CANADIAN VETERINARY
MEDICAL ASSOCIATION

GUIDELINES

FOR THE LEGITIMATE USE OF
COMPOUNDED DRUGS
IN VETERINARY PRACTICE



CANADIAN VETERINARY
MEDICAL ASSOCIATION



Health Canada Santé Canada

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P R E F A C E

This document has been prepared by the Canadian Veterinary Medical Association (CVMA) in consultation with a multi-member task force consisting of:

- Alberta Veterinary Medical Association (AVMA)
- Canadian Animal Health Institute (CAHI)
- Canadian Food Inspection Agency (CFIA)
- Canadian Veterinary Medical Association (CVMA)
- Health Canada, Health Products and Food Branch Inspectorate
- Health Canada, Veterinary Drugs Directorate
- National Association of Pharmacy Regulatory Authorities (NAPRA)
- Ontario Veterinary Medical Association (OVMA)
- Ordre des médecins vétérinaires du Québec (OMVQ)

The purpose of these guidelines is to summarize and clarify all existing legislation and policy regarding the compounding and prescribing of compounded products for use in animals. For the most part, the wording is a concise reflection of the text from various pieces of legislation^(1,2). However, the document is intended for guidance only; it is not to be used as a legal interpretation.

The CVMA believes that there is a significant need for information in this area. Concerns have been expressed about some current compounding practices. On occasions, compounding practices have crossed the line and become manufacturing. In these cases, veterinarians may unknowingly be assuming significant liability. Food safety could be placed at risk. There could be unknown threats to animal health. Inappropriate compounding practices may prove to be a disincentive to the development and approval of new animal health products.

This document is intended as guidelines for veterinarians and to provide veterinary practitioners with information needed to make appropriate professional decisions when considering whether or not to use a compounded product for the treatment of a patient.

BACKGROUND

The compounding of drugs is an ancient art and science that has been practiced by health professionals, including veterinarians, for centuries. The process involves combining two or more ingredients, at least one of which is a drug, to create a final product in an appropriate form for dosing. Compounding involves the use of raw chemicals or the alteration of the form of commercially available drug. **Compounded drugs are unapproved drugs that have not undergone the Health Canada approval process. They are not to be confused with generic drugs, which have undergone the Health Canada approval process.**

Compounding is both necessary and beneficial for the treatment of veterinary patients. However, a potential exists for causing harm to animals and the public when drugs are compounded without adherence to the principles of contemporary pharmaceutical chemistry and current good compounding practices, as outlined by provincial standards of practice for compounding by pharmacists⁽¹⁾. In the absence of adequate safety, potency, and efficacy data for the use of a compounded drug in animals, the potential exists for treatment failures, adverse reactions, including death. Furthermore, because the pharmacokinetics and residual depletion times for compounded drugs are not known, assigning an empirical withdrawal time may result in residues of concern being in food derived from treated animals. Inactive ingredients in compounded drugs, such as excipients and vehicles, may also pose additional risk.

GUIDELINES

- For the purpose of these guidelines, the term “compounding” refers exclusively to the making of veterinary pharmaceutical preparations within the practice of veterinary medicine or pharmacy, as permitted under the Canadian *Food and Drugs Act and Regulations*⁽²⁾. Accordingly, the term “Compounded drugs” refers only to pharmaceutical preparations that have been formulated in accordance with legitimate pharmacy and veterinary practices.
- Compounding and dispensing are licensed activities under provincial legislation that fall within the professional scope for pharmacists and veterinarians⁽³⁾. No person other than a licensed pharmacist or veterinarian may compound drugs for use in animals.
- These guidelines do not waive or diminish in any way the obligation by all parties to comply with all applicable federal and provincial laws and regulations, including the *Food and Drugs Act and Regulations*, insofar as they apply to manufactured drugs and to compounded pharmaceutical preparations. Accordingly, veterinarians must prescribe and dispense compounded pharmaceutical preparations according to federal, provincial and territorial acts and regulations.
- Further guidance as to what are considered to be compounding practices under the *Food and Drugs Act and Regulations* is provided in Health Canada’s policy document entitled *Manufacturing and Compounding Drug Products in Canada*⁽³⁾.
- Compounding is considered by Health Canada to be a legitimate practice in circumstances where the active ingredient is commercially available but a Health Canada approved veterinary or equivalent human product, labeled with a Drug Identification Number (DIN), is NOT. Alternatively, compounding is considered to be legitimate if the product is available but the appropriate method for dosing or dose concentration does not exist and a practical alternative does not exist. **Cost is not a defensible reason for prescribing a compounded drug.**

- Prescribing and dispensing a compounded drug is to be practiced only within the confines of a valid veterinary-client-patient relationship (VCPR), and informed consent from the animal's owner must be obtained.
- Prescribing a compounded drug is considered to be extra-label drug use (ELDU) and as such, the veterinarian is responsible for the safety and efficacy of the prescribed drug and, when used in food producing animals, for establishing adequate withdrawal times in order to avoid residues. The Canadian global Food Animal Residue Avoidance Databank (gFARAD)⁽⁴⁾ does not provide withdrawal times for compounded drugs. When prescribing a compounded drug, veterinarians are responsible for ensuring the potency and purity of the compounded drug.
- CVMA recommends that veterinarians:
 - Prescribe a compounded drug based on a specific patient need. Under certain circumstances, veterinarians may need to obtain a compounded drug in anticipation of reasonable prescribing needs or for use within their own clinical practice. In such instances, the veterinarian should ensure that the compounded drug is prescribed or used within its duration of stability, which could be as short as a few days for some compounded drugs.
 - Use the services of a registered pharmacist who has expertise in compounding procedures. Veterinarians should have appropriate expertise in pharmaceutical compounding if they are going to compound drugs for dispensing in their practice.
 - Establish a good working relationship with the compounding pharmacist. The veterinarian should request the compounding pharmacists to provide any information they have available that will aid in the veterinarian's critical assessment of the compounded drug(s). Such information includes the source of all active pharmaceutical ingredients (APIs), and the efficacy, safety, pharmacokinetic, and stability studies performed on the compounded product, as well as any potency or purity data that may be available.
 - Establish practical clinical assessment parameters for efficacy and toxicity prior to prescribing the compounded drug. Document and record therapeutic successes and failures experienced with compounded medications. Adverse reactions associated with the use of a compounded drug should be reported to Health Canada's Veterinary Drugs Directorate⁽⁵⁾ and the compounding pharmacist.
- There is a clear distinction between legitimate compounding and manufacturing activities. This includes:
 - Compounding activities performed by a person other than a licensed veterinarian or pharmacist (such as animal owner, breeder, feed mill operator, agricultural producer) not pursuant to a prescription, or outside the scope of a valid VCPR, will be considered manufacturing and subject to all applicable provisions of the *Food and Drugs Act and Regulations*.
 - Only establishments (usually pharmaceutical fabricators/distributors) that meet the requirements of Good Manufacturing Practices⁽⁶⁾ and are licensed under the Establishment Licensing Framework⁽⁷⁾, may manufacture drugs in Canada.

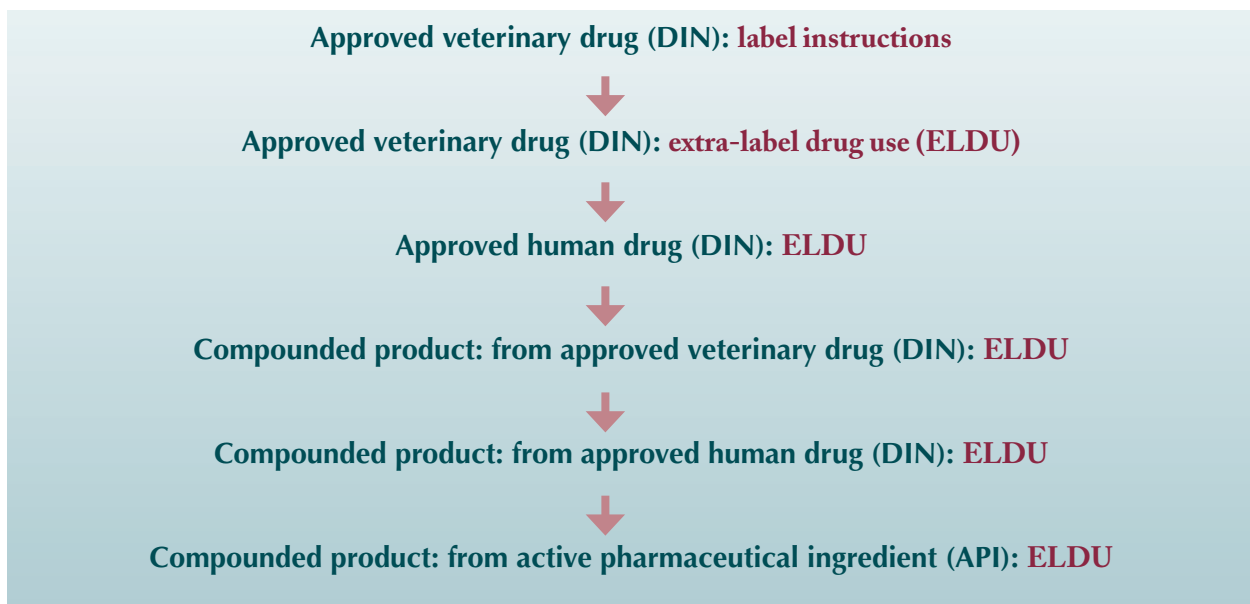
- Guidance from the Health Products and Food Branch Inspectorate⁽³⁾ states that bulk compounding intended for distribution or sale outside the established pharmacist-patient-prescriber relationship, or VCPR, for resale is considered to be manufacturing and thus subject to all applicable requirements from the *Food and Drugs Act and Regulations*.
- CVMA recommends that veterinarians be aware that:
 - Compounding of products for the treatment of an individual patient is to be used only for therapeutic purposes and only when there are no other commercially available options for that specific patient.
 - Restrictions in the *Food and Drugs Act and Regulations* also apply to compounding practices. Certain substances (for example chloramphenicol, 5-nitrofurans, 5-nitroimidazoles, clenbuterol, diethylstilbestrol and other stilbene compounds), are banned substances for use in animals that produce food or are intended for consumption as food⁽⁸⁾.
 - It is necessary to obtain informed consent from the client before prescribing a compounded product. The veterinarian is responsible for ensuring that the client is made aware of the potential risks and available alternative treatments.
 - Any drugs or raw material for compounding must be obtained legally.
 - As a basic quality requirement, oral and topical products should not be used to prepare parenteral formulations.

A compounded drug must include the following information on its label:

- Clear identification that it is a compounded drug; it must not be misrepresented as having a DIN
- A list of all active ingredients of the compounded product
- Generic name(s) of all active pharmaceutical ingredients (APIs)
- Date of compounding
- Patient's name/identification and owner's name (pursuant to a prescription)
- Prescribing veterinarian's name
- Expiration date based on known stability data. If stability data are not available, the CVMA recommends that the expiration date be short, usually limited to the duration of the prescription
- Dosage regimen and withdrawal times (if applicable), as prescribed by the veterinarian
- Name of the person (pharmacist or veterinarian) or pharmacy that compounded the drug
- Proper storage recommendations

DECISION CASCADE

When deciding on which medication to prescribe, the CVMA recommends that a veterinarian follow the course of the Decision Cascade and choose the level of least risk to the patient and public safety (food animals). Choose the first available level on the cascade below:



Foreign approved veterinary drugs obtained through Health Canada's Emergency Drug Release (EDR)⁽⁹⁾ may be an alternative option available to veterinarians when considering use of a compounded drug.

DEFINITIONS

Active Pharmaceutical Ingredient (API) - Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body. Bulk, pharmaceutically active substances that are used in the formulation of medicine in dosage form.

Adverse drug reaction - A noxious and unintended response (signs of toxicity, idiosyncrasy, hypersensitivity, intolerance, and incompatibility) to a drug that occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function. Also included are events related to a suspected lack of expected efficacy or noxious reactions in humans after being exposed to veterinary medicinal products.

Approved drug - A drug that has been assessed for its safety and effectiveness by Health Canada and meets the appropriate requirements of the *Food and Drugs Act and Regulations*. Includes innovative and generic products.

Banned drugs - Drugs banned by Health Canada from use in animals intended for use as human food.⁽⁸⁾

Compounding - The combining or mixing together of two or more ingredients (of which at least one is a drug or pharmacologically active component) to create a final product in an appropriate form for dosing. It can involve the use of raw chemicals or the alteration of the form and strength of commercially available products. It can include reformulation to allow for a novel drug delivery. Compounding does not include mixing, reconstituting, or any other manipulation that is performed in accordance with the directions for use on an approved drug's labeling material.

Compounded drug - Refers to pharmaceutical preparations formulated as per the definition for compounding and in accordance with legitimate pharmacy and veterinary practice.

Dispense - To provide a drug pursuant to a prescription; does not include the administration of the drug.

Drug - Includes any substance or mixture of substances manufactured, sold or represented for use in:

- The diagnosis, treatment mitigation, or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals;
- Restoring, correcting, or modifying organic functions in human beings or animals;
- Disinfection in premises in which food is manufactured, prepared, or kept.

End user - The person or corporation who actually administers a medicine to any animal.

Extra-label drug use (ELDU) - Often termed “off-label use,” refers to the actual use or intended use of any drug, whether it is a prescription drug or an over-the-counter (OTC) drug, in an animal in a manner that is not in accordance with the label or the package insert of the drug approved by Health Canada. This includes the use of all drugs (including unapproved bulk pharmaceutical substances and compounded drugs) that do not have a Canadian approved label.

Generic drug - A second and/or subsequent entry of a drug to the market, defined by reference to the generic drug’s equivalence to a Canadian reference product (a drug that is already approved for sale in Canada). In accordance with the Canadian *Food and Drugs Act and Regulations*, a Canadian reference product has a New Drug Submission approved by the Minister of Health, a Notice of Compliance, and a Drug Identification Number (DIN).

Maximum Residue Limit (MRL) - MRLs for specific drug residues are permitted in specified, edible animal products sold as food, as determined by Health Canada.

Medicine - Drugs and biological supplies for the prevention, treatment, control, or eradication of disease in animals.

Prescribe - Written or verbal directives for the compounding or dispensing and administration of drugs or for other medical services to an animal patient based on a diagnosed or determined need (an animal patient may be a group of animals with a similar diagnosed condition).

Repackaging - Subdividing or breaking up a manufacturer’s original package of a drug for the purpose of dividing and assembling the drug in larger or smaller quantities for redistribution or sale by retail.

Sell -

- Any transaction, activity, or operation relating to the transfer of possession (or of legal right) in a product or medicine from one person to another, including selling, loaning, bartering, leasing, consigning, or depositing with another for the performance of a service;
- Distribute, whether or not the distribution is made for consideration or;
- Having in possession, offering, or exposing with a view to accomplish any of the above.

Unapproved drug - A drug that does not have a valid Drug Identification Number (DIN) and whose sale has not been authorized.

Valid Veterinary-Client-Patient Relationship (VCPR) - A valid VCPR exists when these conditions apply:

- The client (owner or owner's agent of the animal[s]) has given the responsibility of medical care to the veterinarian and has agreed to follow the instructions of the veterinarian, and;
- the veterinarian has assumed the responsibility from the client for making clinical judgment regarding the health of the animal(s), the need for medical treatment, and for ensuring the provision of ongoing medical care for the animal(s), and;
- the veterinarian has sufficient knowledge of the health status of the animal(s) and the care received or to be received. The knowledge has been obtained through a recent examination of the animal(s) and the premises where they are (it is) kept or through a history of medically appropriate and timely examinations and interventions, and;
- the veterinarian is readily available, or has made the necessary arrangements with another veterinarian, for ongoing medical care in case of adverse reactions or therapy failure.

Veterinary facility - Any place or unit where veterinary medicine is practiced.

Withdrawal time - Time after cessation of treatment with a particular drug before the animal or any of its products may be safely or legally used as human food.

REFERENCES

1. Consolidation of the Canadian Food and Drugs Act and Regulations http://www.hc-sc.gc.ca/food-aliment/friia-raaii/food_drugs-aliments_drogues/act-loi/e_index.html
2. Section C.01A.002. of the Canadian Food and Drugs Act and Regulations
3. Manufacturing and Compounding Products in Canada- Health Canada, 2000 http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/pol_fram_man_comp_drug_prod_can_tc_e.html
4. Global Food Animal Avoidance Database (gFARAD) <http://www.gfarad.org>; phone: 1-866-CGFARAD
5. Veterinary Drugs Directorate (Health Canada) Pharmacovigilance Program 1-877-VET-REAC http://www.hc-sc.gc.ca/vetdrugs-medsvet/pharmacovigilance_e.html
6. Good Manufacturing Practices-Health Canada Guidance http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gmp_e.html
7. Establishment Licenses -Health Canada Guidance http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/establishment_licences_e.html
8. List of Drugs Banned by Health Canada (http://www.hc-sc.gc.ca/vetdrugs-medsvet/pub_banned_drugs_e.html)
9. Emergency Drug Release Program Veterinary, Drugs Directorate (Health Canada) http://www.hc-sc.gc.ca/vetdrugs-medsvet/edr_e.html