Canadian regulation of animal health products

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Abstract
Several agencies are involved in regulating animal health products in Canada. Health Canada is responsible for protecting human and animal health and the safety of Canada's food supply. Veterinary Drugs Directorate of Health Canada evaluates and monitors the safety, quality and effectiveness, sets standards, and promotes the prudent use of veterinary drugs administered to food-producing and companion animals. The Pest Management Regulatory Agency of Health Canada is responsible for administering the Pest Control Products Act on behalf of the Minister of Health. The Canadian Food Inspection Agency aims to mitigate risks to Canada's animal resource base, animal feeds and animal products. The Canadian Centre for Veterinary Biologics of Canadian Food Inspection Agency is responsible for regulating the manufacture, testing, importation, distribution and sale of veterinary biologics. An Interim Notification Program is designed for Low Risk Veterinary Health Products (LRVHP) via North American Compendiums operating independently of Health Canada (a new notification program will be administered by Health Canada and replace the existing program). Canadian Animal Health Institute, a member of Health for Animals, is the trade association representing the developers, manufacturers and distributors of animal pharmaceuticals, biologics, feed additives and animal pesticides in Canada. Guidelines and policies have been developed on a variety of issues regarding veterinary drugs to provide further guidance.

Health Canada's regulatory background

Health Canada[1] is responsible for protecting human and animal health and the safety of Canada's food supply. Health Canada's Drug Product Database (DPD) contains product specific information on drugs approved for use in Canada. The database is managed by Health Canada and includes veterinary drugs, human pharmaceutical and biological drugs and disinfectant products. It contains approximately 24,000 products that are currently being marketed in Canada.

The regulatory framework of the past 100 years[2] can be summed up as follows:

- 1919: Federal Government departments were reorganised after World War I and the first Federal Department of Health was formed
- 1920: The first Food and Drugs Act was passed
- 1951: Drug manufacturers were required to file New Drug Submissions (NDS) and obtain Notice of Compliance (NOC)
- 1953: The current structure of the Food and Drugs Act was established, and there was rapid development of new drugs during and after World War II
- 1954: First Food and Drug Regulations
- 1963: Addition of "Division 8 – New Drugs" (eg, clinical trials and manufacturing, and control info)
- 1966: Annual Notifications – Emergency Drug Release (EDR)
- 1969: Medical Devices (Part K of Food and Drug Regulations)
- 1993: Tie Patent and NOC
- 1995: Fees
- 1998: Legislative renewal exercise aimed at replacing four acts with one
- 2003: Extensive consultations undertaken
- 2006: Blueprint for renewal to modernise the Food and Drugs Act. Extensive consultations hence Blueprint II
- 2008: Blueprint II (as Bill C-51) – the Canada Health Protection Act – was introduced in parliament to replace the Food and Drugs Act
- 2008–2011: A new separate regulatory framework for veterinary drugs with the degree of control proportional to the level of harm that products present (risk-based approach)
- 2012–2017: Launch of the five-year plan, the "Regulatory Roadmap for Health Products and Food."

Veterinary Drugs Directorate (VDD)

VDD[3] of Health Canada, located in Ottawa (Ontario, Canada), is part of the Health Products and Food Branch (HPFB). To protect human and animal health and the safety of Canada's food supply, VDD evaluates and monitors the safety, quality and effectiveness, sets standards, and promotes the prudent use of veterinary drugs administered to food-producing and companion animals. VDD applies the Food and Drug Regulations (Part C, Division 1 and Division 8) under the authority of the Food and Drugs Act, and administers fee regulations for veterinary drugs under the authority of the Financial Administration Act.

VDD is comprised of six divisions: Director General's Office (DG), Human Safety Division (HSD), Manufacturing and Chemical Evaluation Division (MCED), Clinical Evaluation Division (CED), Submission and Knowledge Management Division (SKMD), and Regulatory and International Affairs Division (RIAD).

All veterinary drug submissions must undergo rigorous scrutiny and fully satisfy all scientific requirements under the Food and Drug Regulations before any drug can be marketed in Canada. Guidelines and policies have been developed on a variety of issues regarding veterinary drugs to provide further guidance.

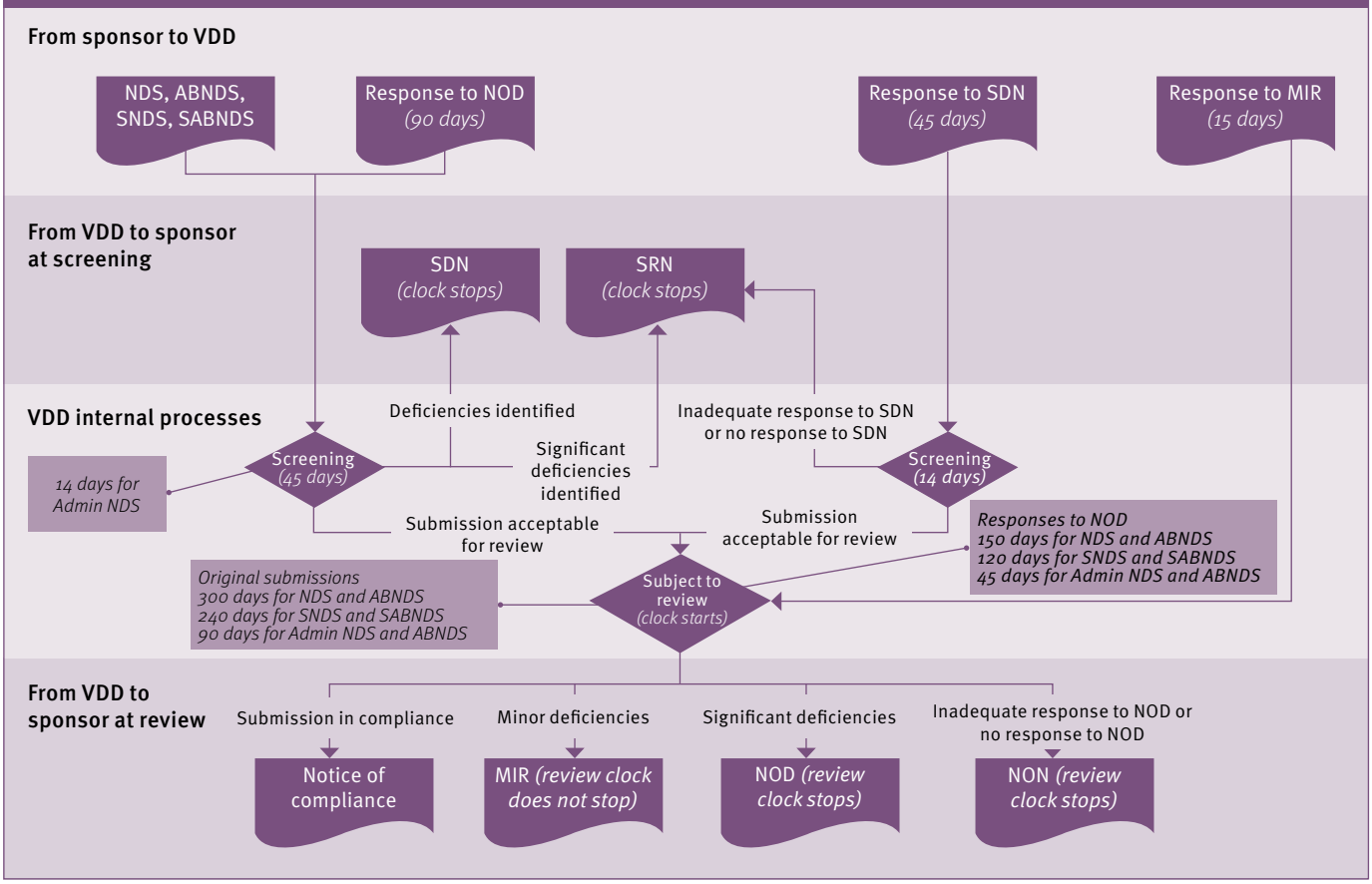
Marketing authorisation.[4] Sponsors can submit one of the following regulatory submissions to VDD to obtain a Drug Identification Number (DIN) for selling a veterinary drug in Canada:

- A DIN submission ("Not-New-Drug")
- A NDS
- An abbreviated NDS (ABNDS/Generics).

A drug may be sold in Canada without a DIN when any of the following submissions are filed and a written authorisation is obtained from VDD: an Experimental Studies Certificate (ESC), an Investigational New Drug (IND) submission and Emergency Drug Release (EDR).

Manufacturers may be authorised to sell IND to qualified investigators for the purpose of conducting clinical evaluations, and the Directorate may issue ESC to researchers to carry out specific projects. EDR may be issued by the Directorate to authorise the sale of limited quantities

Figure 1: VDD – Review and approval process of NDS, ABNDS, SNDS and SABNDS.



of drugs which are not approved for sale in Canada to veterinarians for emergency use.

Post approval obligations. VDD's "Appendix 2 to the Post-NOC Changes: Quality Guidance Document" is intended to clarify the classification of chemistry and manufacturing changes made to the quality information relevant to the approved veterinary drugs. The "Post-NOC Changes: Safety and Efficacy Document" is to assist with the classification of safety or efficacy related changes. Scientific amendments include:

- Supplement to a New Drug Submission (SNDS) or Supplement to an Abbreviated New Drug Submission (SABNDS)
- Notifiable Change (NC) submission

Administrative amendments include:

- Notification of commencement of sale: to notify VDD within 30 calendar days after commencing sale of a drug
- Annual drug notification: to confirm that all the information previously provided is still correct and current
- Cancellation of the DIN: the DIN of a drug can be cancelled either by VDD or by the DIN owner
- Reactivation of DIN: once a DIN has been inactivated, the sponsor is required to submit a new submission to regain marketing approval. Cross references to previously filed information may be permitted. However, additional information may be required by VDD to ensure that the submission complies with the current regulations and guidelines
- Changes to the product's brand name and DIN ownership.

Health Canada's VDD formalised its pharmacovigilance program to monitor the safety and efficacy of veterinary drugs used in animals, and the safety of humans handling these products and consuming food derived from treated animals. Canada's Food and Drugs Act and Regulations require manufacturers to report all suspected adverse drug reactions (ADR) to Health Canada. Although there are no regulations requiring veterinary practitioners to report ADRs, VDD encourages veterinarians to report suspected ADRs to any drugs which occur in their practices to the manufacturer or to VDD.

Target Performance Standards. VDD targets to issue its decisions and responses within the following target performance standards. Initial processing of all submissions takes up to seven calendar days (see Figures 1 and 2):

- NDS, ABNDS, SNDS, SABNDS: 45 days first screening cycle
- NC, Admin NDS, Admin ABNDS: 14 days first screening cycle
- NDS and ABNDS: 300 days first review cycle
- SNDS and SABNDS: 240 days first review cycle
- NC, Admin NDS, Admin ABNDS: 90 days
- Final label review: 45 days
- Sponsor's response to Screening Deficiency Notice (SDN): 45 days
- VDD's screening of response to SDN: 14 days
- Sponsor's response to Minor Information Request (MIR): 15 days
- Sponsor's response to Notice of Deficiency (NOD): 90 days
- VDD's screening of response to NOD: 45 days
- VDD's review of response to NOD is 150 days for NDS and ABNDS, 120 days for SNDS and SABNDS, and 45 days for Admin NDS/ABNDS.
- Sponsor's response to SDN and NOD: 30 days
- VDD's screening of response SDN and NOD: 14 days
- VDD's review of response to NOD: 60 days

Fees. Cost recovery fees[5] are in effect for evaluations of veterinary drug submissions and applications. The regulations can be found in *The Canada Gazette Part II*.[6] The schedules outlined below apply to all New Drug and Not-New-Drug submissions, with the exception of EDR

applications, which are invoiced after the application is received. For fees less than C$10,000, the full amount is payable when the submission or application is filed. For fees greater than C$10,000, 10% is due at the time the submission is filed and 40% when the submission is accepted for review. The remaining 50% will be invoiced for each individual component of the submission once its evaluation is completed.

If a submission or application is rejected at screening, 10% of the sum of applicable submission fees will be retained to cover services rendered.

For review of chemistry and manufacturing data, fees are C$4,840 for one strength of a single dosage form and C$2,420 for an additional strength. For review of efficacy and safety data, fees are C$15,980 for single route of administration, dosage form and indication in one animal species; C$9,680 for an anti-parasitic drug in one non-food animal species; and C$23,240 for two animal species or two indications in one animal species. Further fees in relation to efficacy and safety data are C$31,470 for growth promotion or production enhancement indication in one animal species; C$12,590 for an additional indication in one animal species and C$7,740 for concurrent use of two drugs approved for the same animal species.

For review of human safety data the fees are as follows: C$14,520 for toxicity, metabolism and residue depletion studies (RDS) when an acceptable daily intake (ADI) has already been established or to establish a temporary ADI, a maximum residue limit (MRL) and a withdrawal period (WP) for a single dosage form, dosage and route of administration in one species. It is C$21,790 if establishing an ADI with a safety factor (SF) of 1000, and $29,050 for a SF of less than 1000. The fees are C$2,900 for RDS to establish a WP for an additional (or a change in) dosage form, dosage or route of administration, and in generic submission for confirming that the WP(s) for each species falls within the conditions of use for the Canadian reference product (CRP). Lastly, it is C$7,260 to change an established ADI, MRL and WP; and C$5,810 for the concurrent use of two drugs in a species – the RDS to determine if an extension to existing WP is required.

Electronic submission.[7] Regulatory Activities for veterinary drugs provided in electronic-only format have been accepted by Health Canada since 2014. Effective since 1April 2017, VDD will no longer accept the paper copies and non-eCTD electronic-only will be the only format accepted. Electronic documents will be uploaded onto the Health Canada viewing tool, where they will be immediately accessible to Health Canada staff involved in the review of the regulatory activities.

Regulatory transactions should be provided on a certified virus-free labelled media (eg, on a single disc/drive. Duplicate copies are not required). Media and files should not be password protected and files stored on the media should not be zipped. A cover letter should be attached to the media in both electronic and paper format. Zipped folder structures can be used by adding documents in their respective folders (empty folders must be deleted before filing to Health Canada[8].

The recommended format is a PDF of no larger than 150 megabytes. It should be properly hyperlinked and bookmarked in a maximum of four levels, and generated from electronic source documents and not from scanned materials. PDF documents with attachments are not allowed. Presentations for meetings with Health Canada, eg, pre-submission meetings, can be provided in PowerPoint format. Documents may be signed with an electronic signature or the signature page can be signed and scanned.

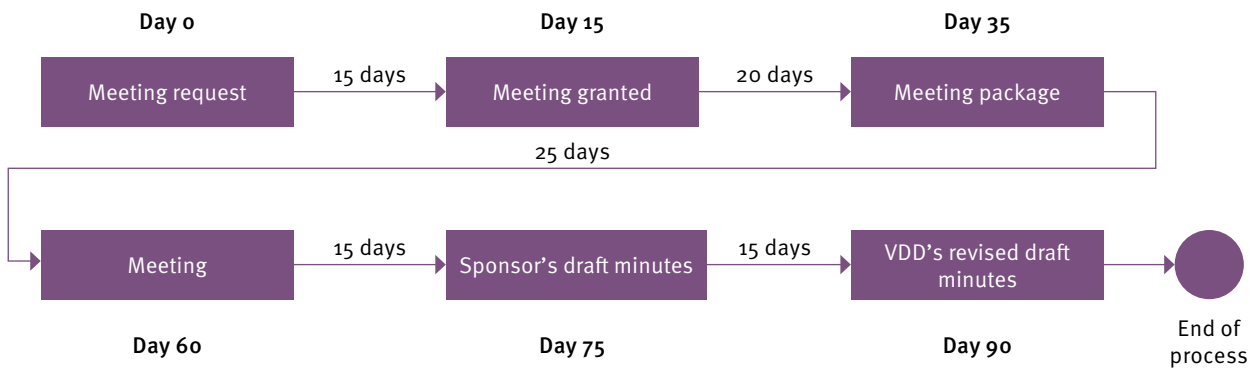
Regulatory transactions with the exception of Drug Notification Forms may only be sent to VDD via an email no larger than 20 megabytes (to skmd-so_dgps-cp@hc-sc.gc.ca), with the attachments only containing organised folders as a non password protected zipped file if the sponsor assumes the risk of transmitting Protected B information (from two main security categories "Classified" and "Protected A, B or C").

Pest Management Regulatory Agency (PMRA)

PMRA[9] is responsible for administering the Pest Control Products Act (PCPA) on behalf of the Minister of Health. The PCPA regulates the products used for the control of pests, stating that pesticides must be registered before they can be used in Canada. A pesticide is defined as any "product, device, organism or substance that is manufactured, represented, sold or used for controlling, preventing, destroying, mitigating, attracting or repelling any pest". Before any pesticide can be registered in Canada, PMRA must review the scientific information to make sure that it has value and there are no public health or environmental concerns related to its use. Determining value includes figuring out whether the pesticide is effective in dealing with the pest problem when used according to label directions. Health and environmental risks are considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the pesticide, based on its conditions or proposed conditions of registration.

As part of its assessment of potential risks to human health, Health Canada critically examines available scientific information, including toxicology studies (the study of the effects of toxic substances), and epidemiology studies (the study of diseases in human communities). Health Canada takes into consideration the effects of a single, multiple and/or lifetime exposure to a pesticide. Also, special consideration is given to more vulnerable people like infants and toddlers, pregnant and nursing mothers, and the elderly. Only those uses where human

Figure 2: VDD – Pre-submission meeting process.



exposures are well below 100–1,000 times lower than the no-effect level are registered for use in Canada.

To make sure that pesticides currently on the market continue to meet Canada's strict health and environmental protection standards, Health Canada re-evaluates registered pesticides every 15 years, or when new and relevant information suggests further study is needed. The pesticide companies are required by law to report all incidents related to their products to Health Canada. Health Canada has four types of pesticide incident reporting forms: Human Health Incident, Domestic Animal Incident, Environmental Incident, and Packaging Incident.

Canadian Food Inspection Agency (CFIA)[10]

The Canadian Centre for Veterinary Biologics (CCVB) of CFIA is responsible for regulating the manufacture, testing, importation, distribution and sale of veterinary biologics. Veterinary biologics include animal health products such as vaccines, antibody products, and *in vitro* diagnostic test kits that are used for the prevention, treatment, or diagnosis of infectious diseases in animals.

Veterinary biologics are evaluated on a case-by-case basis, and are licensed based on fulfilment of four criteria: purity, potency, safety and efficacy. The Canadian licensing requirements are similar to the United States Department of Agriculture requirements for veterinary biologics. Documents which are prepared using the United States Code of Federal Regulations (9 CFR) protocols and test procedures or equivalent, are accepted by the CCVB for review and licensing purposes.

CFIA also aims to mitigate risks to Canada's animal resource base, animal feeds and animal products. The chemical residue surveillance program of CFIA consists of three well-defined components. The first is monitoring sampling, which probes the food supply for potential contamination and is managed under the National Chemical Residue Monitoring Program (NCRMP). The second is directed sampling which focuses on identified chemical contamination issues, and the third is compliance sampling which seeks removal of food in violation of standards from the marketplace.

Limits for chemical residues and contaminants. Maximum Residue Limits (MRLs), Maximum Levels (MLs), guidelines, standards and tolerances are limits established by Health Canada to minimise potential health risks to Canadians from excessive exposure to chemical residues and contaminants in foods.

CFIA tests a variety of foods available in Canada for chemical residues and contaminants. When test levels are above the established limits for the food being analysed, results are referred to Health Canada for a risk assessment. Based on the outcome, CFIA makes a final decision on whether further action, such as product seizure or recall, is necessary.

Veterinary biologics establishment licence. Veterinary biologics licensed for sale in Canada must be manufactured at a facility that has been inspected and approved by CCVB. On approval of the facility, a Veterinary Biologics Establishment Licence is issued.

Veterinary biologics product licence. Veterinary biologics are licensed by issuance of a Veterinary Biologics Product Licence (for products manufactured in Canada), or a Permit to Import Veterinary Biologics (for products manufactured outside of Canada).

Serial release testing and quality assurance monitoring. On satisfactory review of the product dossier by CCVB, samples from pre-licensing serials are requested of the manufacturer along with the serial release test results, tested according to the production outline. These samples undergo confirmatory testing at the Biologics Evaluation Laboratory (BEL). Upon fulfilment of the licensing requirements, the manufacturer is then issued a Veterinary Biologics Product Licence for that product. The pre-licensing serials may then be released by CCVB, for sale by the manufacturer. For future release of serials of the vaccine, serial release test results are submitted by the manufacturer to CCVB and samples to the BEL for random confirmatory testing.

Post-licensure surveillance and compliance monitoring. Post-licensure compliance monitoring is done through the reporting and investigations of suspected adverse reactions and other consumer complaints, as well as review and approval of advertising material. The Health of Animals Regulations require manufacturers to notify CCVB of cases where there is any information or any evidence of a significant deficiency in safety, potency or efficacy of a veterinary biologic, within 15 days from the date the information is known.

Importation of veterinary biologics. Importation of a biological product into Canada requires that the importer obtain a permit to import veterinary biologics. CCVB issues permits for research and for commercial distribution and sale of veterinary biologics. A veterinary biologic produced in a foreign country must be licensed in that country prior to importation into Canada.

Interim Notification Program (INP) for Low Risk Veterinary Health Products (LRVHP)[11]

This is a voluntary program in which a notifier applies for a Notification Number (NN) with a third party program administrator – the North American Compendiums (NAC) – which operates independently of Health Canada. The INP originally applied to LRVHPs for sale in Canada that are for use in cats, dogs and horses that are not intended for food. LRVHPs may only contain substances that are found on the list of admissible substances including homeopathic medicines, botanicals, vitamins, minerals, fungi, bacteria, etc. Not covered under the INP are pet food products, dewormers, insect repellents and veterinary health products which are intended for food-producing animals. As of 23 March 2017 the scope has been expanded to a limited group of LRVHPs including oral calcium supplements and udder creams and lotions for dairy cattle only.

If the product meets the relevant conditions established by Health Canada, a NN would be issued. The notification is valid for one year and can be renewed using a simplified procedure. The program administrator will recover costs by charging fees for new notifications, annual renewals and amendments. Industry members may instead prefer to obtain a Notice of Compliance (NOC) and Drug Identification Number (DIN) through the normal regulatory process. Health Canada considers the INP to be a temporary measure pending the new veterinary drugs framework to improve the regulation of LRVHPs.

Health Canada may take enforcement action should it have reason to believe that a product is not compliant with the requirements of the INP, is unsafe or causes the public to be deceived. The issuance of a NN does not exempt any product from the application of legislation administered by other entities such as CFIA, PMRA or other government regulatory authorities. For example, if the product includes animal derived ingredients, it may be subject to the importation requirements of the Health of Animals Act. The notifier is responsible for ensuring compliance with applicable legislation.

Health Canada's regulatory changes related to VHPs will come into force on 13 November 2017. The new Notification Program will be administered by Health Canada and replace the existing LRVHP Program. Between 13 October 2017 and 13 November 2017 Health Canada will be preparing the new Notification Program for VHPs.

Canadian Animal Health Institute (CAHI)[12]

CAHI, located in Guelph, Ontario, is the trade association representing the developers, manufacturers and distributors of animal pharmaceuticals, biologics, feed additives and animal pesticides in Canada. CAHI is

a national association, whose members are responsible for sales of approximately 95% of the animal health product market in Canada. Sales by CAHI member companies in 2015 were approximately C$750 million. CAHI is also a member of the global organisation, Health for Animals.

Adherence to the provisions contained within CAHI's Code of Marketing Practice is a requirement of each CAHI member company. There are over 60 members in the CAHI. They fall into two categories, Full Members (companies that market licensed medications with animal health claims), and Associate Members (allied industries that include research firms, public relations companies, consultants and pet food manufacturers to name a few). CAHI is a registered, non-profit organisation, solely funded by annual membership fees and administered by a volunteer board of directors elected annually by the membership.

CAHI's stewardship program offers farmers an environmentally responsible way to dispose of old or unwanted product. It is offered in each province at least once every three years. Farmers drop off their obsolete materials at a designated collection site. Products are then transported to a high temperature incineration facility where they are safely disposed of.

In summary, the major players involved in Canadian regulation of animal health products are Health Canada and its Veterinary Drugs Directorate, as well as the Pest Management Regulatory Agency, the Canadian Food Inspection Agency and its Canadian Centre for Veterinary Biologics, Low Risk Veterinary Health Products program, and the Canadian Animal Health Institute.

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