



*Canada's Independent Agri-Food  
"Think-Tank"*

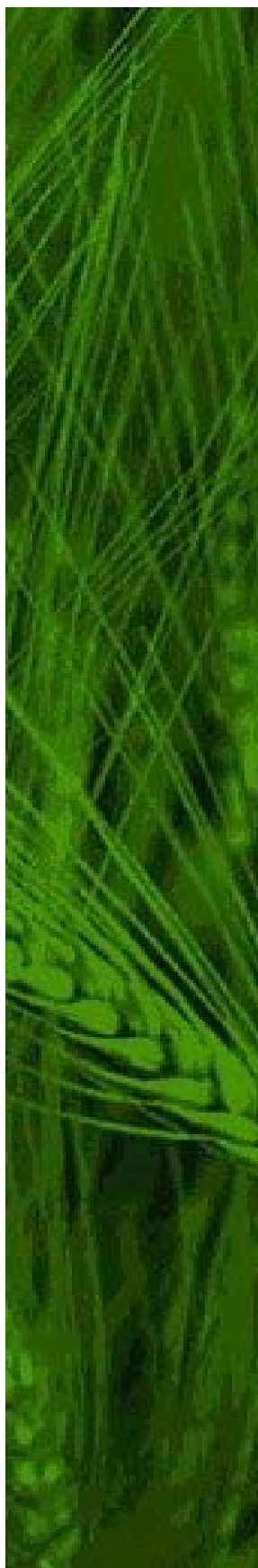
## **The Competitiveness Impacts of Canada's Agricultural Product Review Regulations**

### **FINAL REPORT**

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Date: February 13, 2004



## EXECUTIVE SUMMARY

Regulations are necessary for the organization of society. A good regulatory framework protects the health and environment of its citizens, contributes to economic growth, and promotes investments that will improve a nation's productivity and thus improve the standard of living. A dysfunctional regulatory system, however, hinders investment, productivity and innovation and reduces competitiveness and job opportunity.

One aspect of Canada's regulatory framework is its mechanism for approving new products used for curing or preventing diseases in farm and companion animals. We at the Centre have heard complaints about the approval process across a number of Market Access Regulatory Programs for years. Hence we approached the Canadian Animal Health Institute (CAHI) with a proposal to conduct an economic analysis of the approval process<sup>1</sup>. The resulting study, the results of which are presented here, had two underlying purposes:

- 1) Identify the impact of Canada's product registration system on companies operating in the animal health products industry in Canada, and ultimately, estimate the magnitude of the economic cost to the agri-food sector and the Canadian economy imposed by this system; and
- 2) Offer some alternative, potentially "optimum," solutions to the system and identify the costs/benefits of such a system.

The specific objectives of the project were:

1. To describe, compare and contrast the agriculture product approval systems in the United States, Australia, European Union and Canada with respect to the governing authority, structure and responsibility, marketing approval, applicant tasks, fees, time to approval and performance indicators.
2. To estimate the direct loss to companies, downstream losses to the agriculture industry and losses to the Canadian economy resulting from delayed product review for five case study products submitted to the Veterinary Drugs Directorate (VDD) for approval in Canada.
3. To develop recommendations based on the above analysis for improvements to the Canadian system.

To meet the objectives outlined above, the project was divided into three stages of work that parallel the objectives:

Stage 1 involved a literature review and (in some cases) personal interviews about the regulatory system for food animal and companion animal (animal health) product

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<sup>1</sup> This means that about half of the cost of the study was paid for by members of the industry, while the other half was paid for by the Centre itself. The Centre identified assessing the impacts of Canada's regulatory system on Canada's agri-food competitiveness as one of its major research focuses. Hence we regard it as a priority for investing our own resources.

approvals for the United States, Australia, European Union and Canada. The review addressed the governing authority, structure and responsibility, marketing approval and applicant tasks, fees, approval time and performance indicators.

Stage 2 involved the development of a series of case studies of the applications for approval of five products. The cases were chosen by companies within the industry to illustrate their experience with the system. The cases were also used to provide evidence on the economic and other consequences<sup>2</sup> of the Canadian system for animal health companies, their customers and the broader economy.

Stage 3 involved designing the 'optimum' registration system and estimating the costs and benefits of the proposed system to the Canadian economy. To accomplish this, the George Morris Centre conducted a focus group session with key members of the industry and government to develop the basic requirements for an 'optimum' system.

Comparing the structure and performance of the various national approval systems (section 2.0), provided the following insights:

- There are substantial structural differences in the systems among the countries, including internal disciplines designed to facilitate approval processes.
  - For example, until recently there was no appeal mechanism in Canada during the application process or once the drug decisions were made, but they exist in other systems. In December 2003, a blueprint for appeals was published by VDD; however, it is not an *independent* appeal mechanism as requested by industry. There still remains a need for an independent dispute mechanism.
  - For example, there are no mandatory pre-submission meetings (as in the EU) for applicants to get an understanding of what is required prior to submission.
- There are substantial differences in fees charged by regulators. Canada's is the highest when measured on the basis of market access gained.
- There are greater unanticipated delays in the approval system in Canada than in the other comparators.
- Total elapsed time until a decision is made is the slowest in Canada, by a wide margin. It is understood that, since the commission of this report (January 2003), there has been an effort on the part of the VDD to improve this situation but more improvements are needed to make this a world-class regulatory environment.
  - The Canadian system until recently made no commitment about time of review decision and does not adhere to its internal administrative standards. A draft management of submission policy document has recently been circulated for discussion and includes performance standards.

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<sup>2</sup> As will be seen, all of the consequences cannot easily be reduced to dollars and cents, especially in the companion animal area where delays in approval can mean suffering and death of people's pets.

- Canada has administrative or “provisional” standards of 180 days.
- US have implemented the Animal Drug User Fee Act (ADUFA) in which the legislation will impose performance standards on the CVM that are expected to improve the drug approval process to 180 days, 90% of the time by 2008.
- Australia aims to finish an approval in 240 days.
- The EU attempts to complete an approval process in 210 working days, not including “clock stop” days.
- Actual elapsed time until a decision was made in Canada is not related to the administrative standard.
  - Canada: exceeded its 180-day target 87% of time (2002).
  - US: exceeded its 180-day target 83% of the time (2002).
  - Australia: met its 240-day target 96.2% within timeframe (2001-02).
  - EU: limited data, but in the last 3 yrs has generally been within its timeframe of 210 days.

As will become clear in the text, the differences between Canada and the US compared to Australia are much greater than the 60-day difference in their standards.

The five case studies were analyzed to estimate the costs imposed as a result of the additional time required in Canada to make an approval decision. The analysis is done comparing Canada's performance against Australia's 240-day standard, not to the internal standard of 180 days. Costs resulting from delays were categorized into direct costs to the company sponsoring the application, indirect costs to the downstream industries, which are unable to source the product and its health benefits, and opportunity costs to the economy because of foregone economic activity. The three are not additive – they are separated for the purpose of providing an idea of the magnitude of losses to the different parts of the economy associated with these five cases.

The estimated economic impacts by category, of approval delays beyond 240 days in Canada for the five cases were:

- Approximately \$76 million in direct losses to the participating companies.
- Approximately \$91 million in indirect costs to the down stream agricultural industry.
- Approximately \$1.8 million in losses to the economy.

With the foregoing as background, a group of industry, and government personnel met to develop the desired characteristics of a stringent, yet timely product registration program for Canada. The group came up with a lengthy and detailed set of characteristics organized around the following headings that are presented in section 4.0:

- Objectives of the Legislation
- Procedures for market approval
- Applicant tasks
- Costs and Incentives

- Transparency
- Consistency
- Perceived Costs and Benefits

## **Conclusions and Recommendations**

While the foregoing are discussed in detail in section 4.0, one conclusion arrived at by the assembled group is inappropriate given subsequent information. That conclusion was that the underlying legislation does not need to change. Subsequent work by Rainnie and the Environmental Commissioner reveals what was already becoming evident to the Centre through a number of anecdotal observations – the problems are not just in approvals of animal health products. **As Rainnie and the Environmental Commissioners reports show, the problem is widespread in reviews of plant health products, and in reviews of consumer (companion animal) products.**

When one views the entire product approval system, one is left with the impression that it is out of the control of Parliament. The legislation and regulations have been developed piecemeal. There is no – or very little - reference to any economic or trade objectives of the legislation. Product reviewers, therefore, do not balance the narrow concept of risk prevention with the promotion of innovative advancements in health methodologies and products. By the same token, there is very little in the legislation that allows the public, though Parliament and its organizations such as the Auditor General, to hold regulators accountable for the economic consequences of their decisions -or non-decisions. At a time when government says it wants to increase “value adding”, “productivity” or “technology”, it must put regulatory processes in place that are consistent with its intents.

Therefore, our recommendation below goes farther than did the participants in the process for this project.

### Changing the System

1. Parliament needs to change the legislative intent to include a goal of enhancing industry competitiveness as well as protecting animals, people and the environment. They are not in conflict – no company will gain economic advantage for long by harming animals, people or the environment. In fact, everyone we know is looking for advantages by trying to do the right things, in part because it is perceived to be part of what most consumers want. Therefore, everyone will welcome an approval system that is tough but fast.
2. Parliament needs to extend this change across all product approval legislation, at least in the agri-food sector. The same problems occur for plant health, other input supplies and food labelling.
3. The system should:
  - Be transparent – applicants must be able to understand from the beginning what information is required to obtain an approval. Therefore,

- the regulatory procedures need to explicitly have clear guidelines for what is required of the applicant and what is required of the regulator.
- Be consistent – the same things should be expected for a certain type of registration every time. The current system is full of arbitrary decisions by regulators that mean each application is a new adventure.
  - Have well-understood timelines. They should be measurable and enforceable. They should likely include a “stop clock” concept so that both sides are accountable.
  - Have clearly defined gates (e.g., specific issues dealt with separately, i.e. it should be clear what the procedures and decisions are for trade issues separately from efficacy, separately from health, environment, etc.).
  - Function on fact-based processes.
  - Be properly resourced by government, including optimum use of appropriate outside expertise.
  - Include independent appeal mechanism(s).
  - Develop appropriate benchmarks and metrics to measure its performance against objectives and compare to best in class.

### Process for Change

The process clearly needs to pursue a number of efforts simultaneously:

1. Most fundamentally, CAHI needs to join forces with other segments of the agri-food sector to effect change since all are negatively affected by the larger system. This coalition also needs to get some form of consumer support for the principles. It needs to develop a united front and convince elected government to effect the changes.
2. Our experience is that the case studies are excellent vehicles to make the issues real for people who don't deal with product registrations every day. They clearly show the faults with the system and the frustrations that result. In addition, they provide a way to describe the magnitude of cost. A number of them need to be done in the other industries to assist in communication from a consistent framework.
3. In order to move forward, it is likely that the following initiatives need to be taken:
  - a. Contact potential champions among elected representatives to develop a strategy for convincing government of the need for change.
  - b. Contact the people in the “Smart” Regulation process to obtain their understanding and support (this has already started).
  - c. Bring together the affected industries in a series of conferences to establish common ground for the push to get change.

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## **1.0 Introduction**

Regulations are necessary for the organization of society. A good regulatory framework protects the health and environment of its citizens, contributes to economic growth, and promotes investments that, in turn, improve a nation's productivity and improve its standard of living. A dysfunctional regulatory system however, hinders productivity and innovation and reduces competitiveness and job opportunity (RIAS Inc.). We would add to the RIAS notions that protecting health and environment are not necessarily trade offs for competitiveness and innovation. A regulatory system that is slow and burdensome can actually do harm to human health and environment by stifling the very innovation that could improve them.

The intent of Canada's regulatory framework has been to protect Canadians while keeping its industries competitive through promoting investments and increasing productivity while protecting Canadians. The system, however, is not functioning well. The perceived result is a loss in growth opportunities and competitiveness across many sectors, including biotechnology, agri-food and financial services. In early 2000, the *Public Policy Forum* illustrated this increasing Canadian concern. The article stated that industry participants believe the federal government's regulatory regime continues to put Canadian enterprises at a significant competitive disadvantage and if the current system is not reformed, there is a risk that investment and employment will relocate outside of Canada. There is some evidence that this has already started.

One particular example of how the regulatory system hinders the growth of an industry occurs in the Animal Health sector, where the product registration procedure causes new animal health and companion animal products to be registered at a slower rate in Canada than in competitor countries.

### ***The Problem***

A lagging and non-transparent registration system affects company decisions about where and when to undertake research and development (R&D), as well as any subsequent manufacturing, and hence capital investment, that flows from the research and development. Regulatory processes can affect R&D as well as follow-up investment in a number of ways:

- *Lack of transparency in requirements for obtaining product approval* can cause unnecessary difficulty, cost, and delays in meeting the criteria;
- *Inconsistency of application of the requirements* can create a moving target that is difficult and sometimes impossible to hit;
- The longer *the time taken to obtain approval*:
  - The greater the time to access markets.
  - The greater the likelihood of new competition entering the market, and
  - The more costly the process.



- Use of non-regulated products in the form of imports from countries with access to innovative animal health management tools.
- The greater the unpredictability in the application of regulations, the less likely that the approval will be obtained and the more likely that investment will occur elsewhere.
- *Duplication of requirements* can increase costs by orders of magnitude if tests need to be replicated needlessly.

Delays in the regulatory process also have downstream impacts on the Canadian agricultural industry. For example, if a product has not been approved in Canada but is available in competing countries, the downstream industry in Canada suffers. Domestically, Canadian agriculture loses the benefits of the product, for example, productivity gains or a potential reduction in the incidence of disease. Therefore, Canadian agriculture also loses competitive advantage internationally.

These problems are amplified when the country in question is a relative “minor use” area, as Canada is often classified. If potential sales are limited by the size of the market, a slow and costly product approval system can discourage products from being registered. In turn, this discourages early stage R&D from being in Canada in the first place. Naturally, it may also mean that end users lose the value of improved products for some period of time – or forever, if the products are not eventually registered. This, in turn, can create “black markets” for access to non-registered drugs.

It should also be noted that all of the foregoing are not necessarily a problem. If Canada’s regulations were stringent, but the process was transparent and efficient, this could actually be an advantage. It is possible that Canada would become the preferred location for R&D, and follow-up manufacturing with its attendant investment, because of a regulatory regime recognized around the world as “tough but fast.” This could provide a significant competitive advantage for Canada.

## **1.1 Purpose and Objectives**

Given the problems identified above, there are two underlying purposes to this project:

1. Identify the impact of Canada’s product registration system on companies operating in the animal health products industry in Canada, and ultimately, estimate the magnitude of the economic cost to the agri-food sector and the Canadian economy imposed by this system; and
2. Offer some alternative, potentially “optimum,” solutions to the system and identify the costs/benefits of such a system.

The specific objectives are:

1. To describe, compare and contrast the agriculture product review systems in the United States, Australia, European Union and Canada<sup>3</sup> with respect to the governing authority, structure and responsibility, marketing approval, applicant tasks, fees, time to approval and performance indicators.
2. To estimate the direct loss to companies, downstream losses to the agriculture industry and losses to the Canadian economy resulting from delayed product approval for five case study products submitted to the Veterinary Drugs Directorate for approval in Canada.
3. To develop recommendations based on the above analysis for improvements to the Canadian system.

Fundamentally, the project addresses the cost of the above issues and provides direction on how to improve procedures so they are aligned with the stated “tough but fast” policy. In addition to these however, the following questions are important considerations for this analysis:

1. What are the costs of the current product approval system to companies that provide health products to animal agriculture and companion animal medicine? What would be the advantages of a system that is “tough but fast?” (This could be expanded to include crop protection products, feeds, seeds, disinfectants, etc.)
2. What are the costs to the agri-food sector of the current system and what would be the advantages of a faster system? If products are not available or are available more slowly than in competitor countries, then animal (and crop) agriculture will benefit from fewer efficiencies in Canada. This, in turn, means that farmers lose.
3. What are the impacts on the economy of the current approach? How much investment and employment could result from an improved product registration system?
4. What needs to change in the Canadian registration system to make it **facilitate investment and employment** rather than discourage it? What would be an “optimum” system? What are the possible economic benefits of an “optimum” system?

## **1.2 Methods**

To meet the objectives outlined above, the project was divided into three distinct stages of work.

Stage 1 involved a literature review and (in some cases) personal interviews about the regulatory system for food animal and companion animal (animal health) product

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<sup>3</sup> The Canadian review is of the Veterinary Drugs Directorate within Health Canada and does not include a review of the Veterinary Biologics Section of the Canadian Food Inspection Agency.

approvals for the United States, Australia, European Union and Canada. The review addresses the governing authority, structure and responsibility, marketing approval and applicant tasks, fees, approval time and performance indicators.

Stage 2 estimated the economic cost of the current system. To accomplish this, we gathered information from companies that previously experienced challenges with the registration process. Using information provided by participating companies regarding the precise procedures, information and costs required for approval of veterinary or agricultural products, individual confidential case studies were developed. The framework to estimate and aggregate the economic costs is based on the information gathered for the individual case studies and from conversations with regulatory personnel (from case study companies). The model attempts to capture not only the direct costs to companies, but also the indirect downstream costs to producers, processors and consumers. Where feasible, projections to the overall cost to the economy are made.

Although much more difficult to model, we also incorporate the effects of lost investment and lost employment to the Canadian economy as a result of delays in the registration system.

Stage 3 involved designing the 'optimum' registration system and estimating the costs and benefits of the proposed system to the Canadian economy. To accomplish this, the George Morris Centre conducted a focus group session with key members of the industry and government to develop the basic requirements for an 'optimum' system. This information was then used to identify the costs and benefits of the optimum system. In the analysis of the proposed optimum system are the costs to the government, as well as potential benefits in terms of tax revenues, investment and employment.

It is important to acknowledge that this research reviews a point in time and that numerous changes and advancements at the VDD have occurred since the onset and development of the research objectives. These changes have been acknowledged as accurately as possible in the document. However, there are some problems within the product review and approval process that continue to plague the Canada system. The recommendations component of Section 5 will identify what is required for Canada to have a world-class regulatory system.

## **2.0 Agricultural Product Approval Systems: United States, Australia, European Union and Canada**

Section 2.0 describes the registration system for food animal and companion animal (animal health) product approvals for the United States, Australia, European Union and Canada. The review discusses the governing authority, structure and responsibility, marketing approval and applicant tasks, fees, approval time and performance indicators.

### **2.1 United States<sup>4</sup>**

The Food and Drug Administration's Center for Veterinary Medicine (CVM) is responsible for assuring that animal drugs and medicated feeds are safe and effective and that food from treated animals is safe to eat. This authority is derived from the Federal Food, Drug, and Cosmetic Act (1938). The Act was amended in 1968 to include sections that specifically address animal drugs. These amendments were designed to ensure that animal drugs are safe and effective for their intended uses and that they do not result in unsafe residues in foods.

One of CVM's highest priorities is assuring the safety of the food supply.

CVM works to educate consumers as well as the regulated industry; evaluates data on proposed veterinary products before permitting them to be marketed; discovers volatile marketed products through surveillance programs, and initiates legal action, if necessary, to bring violators into compliance with the law; and conducts research to support Center activities.

#### Structure and Responsibility

Before a new animal drug can be marketed in the United States, it must be approved by the Food and Drug Administration (FDA) on the basis of quality, safety, and efficacy. When the drug is for use in food-producing animals, not only must animal safety be demonstrated, but so too must the safety of food products derived from the treated animals intended for human consumption.

Once approved products are on the market, the Center monitors the use of the products through surveillance and compliance programs.

The Federal Food, Drug, and Cosmetic Act allow the Secretary of Health and Human Services to delegate authority to the CVM. Among these re-delegated functions are:

- Authority to approve New Animal Drug Applications and their supplements and Abbreviated New Animal Drug Applications (for generic drugs).

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<sup>4</sup> USFDA, 2003

- Authority to issue proposals, notices, and orders relating to refusal to approve and withdrawal of approval of New Animal Drug Applications and corresponding new animal drug regulations.
- Authority to approve the use of certain food additives.

The CVM consists of the Office of the Center Director, the Office of Management, the Office of New Animal Drug Evaluation, the Office of Surveillance and Compliance and the Office of Research.

The major responsibility of the Office of New Animal Drug Evaluation (ONADE) (a division of CVM) is to review information submitted by drug sponsors who require approval to manufacture and market animal drugs. A new animal drug is deemed unsafe unless there is an approved new animal drug application. Virtually all animal drugs are "new animal drugs" within the meaning of the term in the Federal Food, Drug, and Cosmetic Act.

### Marketing Approval

ONADE determines whether an animal drug should be approved for marketing. Before a new animal drug receives FDA approval, it must be clinically tested for effectiveness and safety. If a product is intended for use in a food-producing animal, it must also be tested for safety to human consumers, and the edible animal products must be free of unsafe drug residues. The sponsor must also develop analytical methods to detect and measure drug residues in edible animal products. It is the responsibility of the drug sponsor (the individual or firm seeking FDA approval of the drug product) to conduct the necessary tests.

ONADE performs the following tasks in their review of applications:

- Determines the adequacy of information submitted for proposed use of investigational new animal drugs (INAD).
- Evaluates the safety and effectiveness of new animal drugs.
- Evaluates the safety for human consumption of drug residues in food derived from treated animals.
- Evaluates the effect of animal drugs on the environment.
- Evaluates manufacturing methods and procedures for new animal drug products.
- Recommends to the Center Director appropriate action on new animal drug applications and abbreviated new animal drug applications (for generic drugs).
- Coordinates the development and implementation of regulations and policies pertaining to new drugs intended for animal use.

There are two main processes involved in regulating the interstate shipment of animal drug products. The first process, the Investigational New Animal Drug exemption, involves the interstate shipment of experimental drugs used for testing in animals. This testing may require that drugs be given to animals that will later be used to produce

human food products. FDA must ensure that the food products derived from the experimental animals are safe for human consumption.

The second process is the New Animal Drug Application (NADA) review. It includes evaluating data regarding an animal drug's safety to the treated animal and to humans who might consume products from the treated animal, in addition to evaluating the drug effectiveness (for the purposes claimed). To be legally marketed, a new animal drug product must be approved under a NADA.

ONADE is divided into several different groups charged with the evaluation of both INAD and NADA submissions. Efficacy and safety information for the animals are evaluated by two therapeutic use groups (food animals and non-food animals), and by a group that evaluates production drugs. There are additional groups responsible for reviewing other aspects of submissions. For example, the human food safety group evaluates the safety to the public, the user (the producer or veterinarian), analytical methods, withdrawal times, and provides the drug tolerances so that safe residue levels and conditions of use are provided to the public. The manufacturing chemistry group evaluates the manufacturing processes, quality control and environmental safety. The biometrics group provides statistical support to ONADE and the rest of the Center.

The various groups in ONADE review the information and any amendments in the NADA. A decision is then made to determine whether the information provided in submissions concerning the new animal drug illustrates that the product will be safe and effective for its intended use. If the information shows the drug is safe and effective, a recommendation is provided to the Center Director that the NADA should be approved. If the Director agrees, he/she approves the application and a notice of approval is published in the Federal Register.

A sponsor must conduct certain tests to show that a drug is safe for the target animal, has the intended effect, and that edible products derived from treated animals are safe for human consumption. If animals receiving an investigational drug are to be slaughtered for consumption, authorization to do so is needed from the FDA. These animals must be slaughtered in a federally inspected facility. The USDA, in coordination with the FDA, provides a USDA inspector to monitor the slaughter of research animals intended for human consumption.

Usually drug approval process begins with the sponsor submitting a request for an exemption to use a particular substance for experimental purposes. CVM can grant this under an INAD. Once an INAD exemption has been granted according to the requirement of the Federal Food Drug and Cosmetic Act (FFDCA), the sponsor must do the following:

- Assure the proper and safe packaging and labelling of investigational drugs.
- Report the names and locations of investigators to whom drugs are shipped.

- Maintain records of all drug shipments and of all reports received from investigators.
- Notify FDA immediately if a safety problem is observed.
- Notify FDA or USDA prior to slaughter of animals treated with the investigational drug.
- A request for a categorical exclusion from an Environmental Assessment.
- An important function in the INAD process for all ONADE staff is review of submitted protocols for experimental work conducted to provide the necessary information needed for the approval of the NADA.
- A sponsor may submit individual completed technical sections (such as target animal safety, effectiveness, human food safety, freedom of information (FOI), and labelling) for "phased review" under the INAD, or the entire requirements for approval may be provided in one submission as an NADA.
- An "original" NADA (the initial application for approval of a new animal drug) should contain all of the following information:
  - A signed copy of the FDA 356V (New Animal Drug Application).
  - A well-organized summary of the information in the application.

When the applicant feels that sufficient data has been generated to establish the safety and efficacy of their product, they are ready to apply for approval. A New Animal Drug Application must be submitted in triplicate to the CVM along with all the data obtained during the clinical trials.

### Approval Time

Approval time can vary greatly depending on the completeness and accuracy of the safety and efficacy data submitted. The CVM has a statutory review time of 180 days, which implies that an approval decision must be made, or the sponsor must be advised why an application cannot be approved (refer to Appendix B for an assessment timeline of new drug submissions). This 180-day timeframe is a provisional timeframe in that after the sponsor has been advised; the final decision can often take much longer than the 180 days. The applicant is however, notified of the progress of the application.

### Appeals Procedure

The CVM appeal procedure was developed to deal with problems that occur between the sponsor and the group reviewing the application, during the application procedure. When a sponsor disagrees with a decision regarding science or policy, he/she may submit an appeal in writing to the Division Director responsible for the group reviewing the sponsor's application. The initial appeal should contain documentation of the sponsor's viewpoint and must not contain new information that has not been reviewed.

If the issue involves animal safety or effectiveness, the Division Director has the responsibility of preparing a written response to the sponsor's appeal and for obtaining the concurrence of his or her Office Director with that response.

## Fees

On November 18, 2003, "The Animal Drug User Fee Act (ADUFA) of 2003" was signed by President Bush. ADUFA amends the Federal Food, Drug, and Cosmetic Act and authorises the FDA to collect fees for certain applications and establishments, products and sponsors of those applications in support of the review of animal drugs.

The driving force for the implementing of user fees by the CVM was to supplement the extra manpower that has been increasingly required to handle all the applications that the CVM receives.

The Act establishes a fee schedule for FY 2004 through to 2008, including total fees for animal drug products, establishments, and sponsors.

Each category is expected to generate 25 per cent of the required revenue, each year. The CVM expects to generate the following revenue once ADUFA has been implemented:

- FY 2004: \$5M
  - *Drug Application Fees*: \$1.25M (25%) (Includes New Animal Drug Applications and Supplementary Animal Drug Applications)
  - *Establishment Fees*: \$1.25M (25%)
  - *Sponsor Fees*: \$1.25M (25%)
  - *Product Fees*: \$1.25M (25%)
- FY 2005: \$8M
- FY 2006-2008: \$10M

To provide the CVM with revenue predictability, 75% of the fees will be collected at the beginning of the year as product, establishment and sponsor fees. The remaining 25% will be collected as application fees at the time of submission.

The applicant will still be responsible for funding all the clinical and field tests required to submit their product to the CVM.

As mentioned above, ADUFA sets out certain revenue goals, beginning in FY2004 and ending in FY2008. As of January 14, 2004, the specifics of the fee make-up had not yet been published under the Federal Register, but the Animal Health Institute has provided a preliminary overview of the fees (refer to Table 2.1).

According to this animal drug user fee program, the majority of the revenue generated by fees will come from drug application fees, particularly new animal drug applications. In FY2004, the average expected NADA fee is \$35,370, rising to \$71,500 by FY2006. Sponsor fees and supplementary new animal drug (sNADA) fees are expected to start between \$17,600 and \$17,850 in FY2004 and increase to between \$35,200 and \$35,700 by FY2006.



**Table 2.1 US Animal Drug User Fee Program**

Type of Fee	FY2004 (\$5MM)	FY2005 (\$8MM)	FY2006-2008 (\$10MM)
Product Fee	\$1,600 (C\$1,815)	\$2,550 (C\$2,893)	\$3,190 (C\$3,619)
Establishment Fee	\$15,625 (C\$17,728)	\$25,000 (C\$28,365)	\$31,250 (C\$35,456)
Sponsor Fee	\$17,600 (C\$19,969)	\$28,200 (C\$31,996)	\$35,200 (C\$39,937)
NADA Fee	\$35,750 (C\$40,562)	\$57,150 (C\$64,842)	\$71,500 (C\$81,124)
sNADA Fee	\$17,850 (C\$20,253)	\$28,575 (C\$32,421)	\$35,700 (C\$40,505)

\* Canadian amount based on April 9, 2003 Bank of Canada Exchange Rate: 0.8814 (1.1346) (Bank of Canada, 2003).

Source: AHI, 2004

### Performance Indicators

In addition to providing funding for the agency, the legislation will impose performance standards (on the agency) that are expected to improve the drug approval process. Performance goals were set out for the CVM under ADUFA. The five-year goals (to be implemented by September 30, 2008) are as follows:

- Review and act on 90 percent of:
  - Complete animal drug applications (NADAs) and reactivations of such applications within 180 days after submission date.
  - Non-manufacturing supplemental animal drug applications (i.e., supplemental animal drug applications for which safety or effectiveness data are required) and reactivations of such supplemental applications within 180 days after submission date.
  - Manufacturing supplemental animal drug applications and reactivations of such supplemental applications within 120 days after submissions date.
  - Investigational animal drug study submissions within 180 days after submission date.
  - Investigational animal drug submissions consisting of protocols, that the Agency and the sponsor consider to be an essential part of the basis for making the decision to approve or not approve an animal drug application or supplemental animal drug applications, without substantial data within 50 days after submission date.
  - Administrative animal drug applications (NADAs submitted after all scientific decisions have been made in the investigational animal drug process, i.e., prior to the submission of the NADA) within 60 days after the

submission date.  
 Source: USFDA/CVM ADUFA Website, 2004

These goals are further detailed in the table below. The goal for original and reactivated NADAs, is to reduce the review time from 295 days in FY2004 to 180 days by FY2008, and to be on time 90% of the time. Similarly, for supplemental NADAs and reactivated supplements, the target is to reduce the review time to 180 days by FY2008, from 320 days today.

**Table 2.2 ADUFA Performance Standards**

Goal	% on time	FY1	FY2	FY3	FY4	FY5
Original and reactivated NADAs	90%	295d	270d	230d	200d	180d
Supplemental NADAs and reactivated supplements (excluding mfg.)	90%	320d	285d	235d	200d	180d
Supplemental NADAs and reactivated supplements (mfg.)	90%	225d	190d	140d	120d	120d
Administrative NADAs	90%	90d	85d	80d	70d	60d
INAD studies with Data	90%	320d	285d	235d	200d	180d
INAD Protocols without Data	90%	125d	100d	80d	60d	50d
Fees		\$5MM	\$8MM	\$10MM	\$10MM	\$10MM

Source: USFDA/CVM ADUFA Website, 2004

These performance standards choose predictability over timelines. Slightly longer timelines are expected in order to have a 90% predictability of meeting the timeframes. One of the key reasons for this, is that industry has indicated it is critical that statutory timeframes be met by the fifth year.

A review of CVM review times for FY2002 was undertaken by the Animal Health Institute (AHI). The cumulative results for all divisions of the CVM are shown in the table below.

**Table 2.3 – Animal Health Institute Survey of CVM Review Times for FY2002**

<b>Cumulative Results (All Divisions)</b>					
	Number Reviewed on Time	Number Overdue	Percent Overdue	Average Elapsed Time of Overdue Review in Days	Longest Elapsed Time in Days
Protocol with no data (50 days)	40	89	69%	100	314
Protocol with data (100 days)	2	4	67%	207	252
Study with minor data (100 days)	10	11	52%	192	622
Study with substantial data (180 days)	25	37	60%	385	1174
Phased technical section (180 days)	34	56	62%	361	1193
Original NADA (180 days)	1	5	83%	352	562
Administrative NADA (45 days)	2	4	67%	148	180
Supplemental NADA (180 days)	64	68	52%	338	1113
Reactivation of an original NADA (180 days)	1	3	75%	378	695
Amendment to Original NADA (180 days)	7	3	30%	292	452
Reactivation of supplement NADA (180 days)	1	2	67%	238	259
Amendment to supplement NADA (180 days)	22	14	39%	291	480
Amendment to reactivation (180 days)	0	0		n/a	n/a
Amendment to reactivation of a Supplement (180 days)	0	0		n/a	n/a
<b>505 Total Submissions</b>	209	296	59%		

Source: AHI, 2002.

For the 2002 fiscal year, the CVM 180 day standard was overdue 83% of the time for an original New Animal Drug Application (NADA). Note that this is an improvement from the 90% overdue rate in 2001 (original NADA's). The longest elapsed time to complete an approval in this category was 562 days (862 days in 2001 (AHI, FY2001)). In the

supplemental NADA – the category with the most submissions – the CVM 180 day standard was overdue 52% of the time, with the longest elapsed time to complete the review at 1113 days (897 days in 2001 (AHI, FY2001)). Again, this is an improvement from FY2001 when CVM was overdue 79% of the time. It is important to note that the CVM had more submissions (total 505) in the 2002 fiscal year; however, there were slightly fewer submissions in both categories examined above<sup>5</sup>.

## **2.2 Australia<sup>6</sup>**

The regulatory system in Australia responsible for agricultural and veterinary chemicals is the National Registration Authority for Agricultural and Veterinary Chemicals (NRA). It operates a national system that evaluates, registers and regulates agricultural and veterinary chemicals. The NRA must approve any new agricultural and veterinary chemical product intended for the market, or any changes to those products already on the market. The NRA also reviews products that have been on the market for many years.

In March 2003, the NRA changed its name to the Australian Pesticides and Veterinary Medicines Authority (APMVA) in an attempt to more clearly identify the organization's role and area of focus. The APMVA name will be used in all public communications, however, all decisions and formal processes will continue under the name of the NRA until the legislative amendment comes into effect.

Prior to March 1995, the Commonwealth held responsibility for the evaluation and assessment of selected agvet chemical products and their clearance for registration. The States and Territories were responsible for the registration and control of use of all agvet chemical products.

In July 1991, the Commonwealth, States and Territories agreed to establish the National Registration Scheme (NRS) for agricultural and veterinary chemicals. The development of the NRS sought to place under one national umbrella the assessment and registration of all agvet chemical products previously undertaken independently by the Commonwealth and each of the States and Territories.

The NRA was established in 1993 as a Commonwealth Statutory Authority, with responsibility for the evaluation, registration and review of agricultural and veterinary chemicals, and their control up to the point of retail sale. The States and Territories retain responsibility for control-of-use activities, such as licensing of pest control operators and aerial spraying.

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<sup>5</sup> In FY2002 there were a total of 6 original NADA and 132 supplemental NADA submissions. In FY2001 there were a total of 10 original NADA and 142 supplemental NADA submissions.

<sup>6</sup> NRA, 2003

An overall focus for the NRA has been to establish openness and transparency in the decision-making process. When there are new chemical products, or major extensions of product use being assessed, public opinion is sought before the final decisions on registration are made. Initiatives such as the Existing Chemicals Review Program are developed with the benefit of community and industry consultation.

### Structure of the NRA

The NRA falls within the Ministry of Agriculture, Fisheries and Forestry. It employs approximately 120 people and is managed by a Chief Executive Officer who is responsible for the Board of Directors.

The NRA's board is comprised of one part-time Chair and eight part-time Directors, selected for their expertise in policy development, agricultural and veterinary chemicals regulation, the agricultural and veterinary chemicals industry, the rural sector, occupational health and safety and consumer interests.

Consultations and communication are high priorities in the NRA and to emphasize this they set up three committees that allow participation in the decision making process at the industry, state and community levels. The Registration Liaison Committee operates at the state level and provides a mechanism for the States and Territories to co-ordinate their functions and responsibilities. The Industry Liaison Committee meets to discuss fees for the cost recovery program and management issues as they affect the NRA's customers. Finally, the Community Consultative Committee offers community advice on registration and public information issues.

### Legislation Governing the NRA<sup>7</sup>

The NRA was established on June 15 1993 under the Agricultural and Veterinary Chemicals (Administration) Act 1992. The NRA is an independent statutory authority. It implements the legislative powers and functions provided to it under the legislation on behalf of all jurisdictions. It has responsibility, in particular, for the implementation of the Agvet Codes.

Legislation regarding the National Registration Scheme consists of seven acts: three dealing with registration activities and four dealing with registration fees and charges. The Agricultural and Veterinary Chemicals Code (the 'Agvet Code') scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*, contains the detailed operational provisions for registering chemical products and provides the NRA with its full range of powers, including the evaluation, registration and review of agricultural and veterinary chemical products (including active constituents and product labels); the issuing of permits; the control of the manufacture of chemical products; controls regulating the supply of chemical products; and provisions ensuring compliance with, and for the enforcement of the Code. The last four Acts in the package contain the cost recovery

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<sup>7</sup> NRA Website, Legislation Governing the NRA

mechanisms - in particular, the imposition, assessment and collection of a levy on sales of chemical products - which establish the NRA as an independent, self-funding regulatory body.

The Agvet Code is a law of the Commonwealth that only applies in the Australian Capital Territory. To enable the Agvet Code to have national coverage, each of the States and the Northern Territory enacted complementary legislation that has the effect that the Agvet Code of the Australian Capital Territory is applied as a law of each State and the Northern Territory. Taken together they are referred to as the Agvet Codes.

Statutes:

[\*Agricultural and Veterinary Chemicals \(Administration\) Act 1992\*](#) [No. 262 of 1992]  
<http://www.nra.gov.au/publications/nrafact200.pdf>

This Act, which came into effect on 15 June 1993, establishes the NRA as a statutory authority. The NRS is a partnership between the Commonwealth and the States/Territories under which the NRA was established as a Commonwealth Statutory Authority, with responsibility for the evaluation, registration and review of agricultural and veterinary chemicals, and their control up to the point of retail sale. The States and Territories retain responsibility for control-of-use activities, such as licensing of pest control operators and aerial spraying.

[\*Agricultural and Veterinary Chemicals Act 1994\*](#) [No. 36 of 1994]  
[http://www.nra.gov.au/about\\_us/AgVetChemAct94.rtf](http://www.nra.gov.au/about_us/AgVetChemAct94.rtf)

This Act, which was part of the National Registration legislation and thus commenced on 15 March 1995, contains the constitutional and other legal provisions that enable the Agvet Code to have effect. The essence of the legislative arrangements that give effect to the NRS is, by means of complementary adoptive legislation, for the Commonwealth Parliament to pass a law establishing the Agvet Code in the Australian Capital Territory. This Act does this. The Agvet Code then is applied by the legislatures of the States and the Northern Territory as a law of those jurisdictions by state/territory complementary Acts - the Agricultural and Veterinary Chemicals [State/Northern Territory] Acts 1994. This federal Act also contains the Commonwealth provisions that partly 'federalised' the applied Agvet Codes. This 'federalisation' of the applied laws was explained in the earlier part of this Appendix. This Act also repealed the Agricultural and Veterinary Chemicals Act 1988.

[\*Agricultural and Veterinary Chemicals Code Act 1994\*](#) [No. 47 of 1994]  
[http://www.nra.gov.au/about\\_us/AgVetChemCode94.rtf](http://www.nra.gov.au/about_us/AgVetChemCode94.rtf)

This Act, which was part of the National Registration legislation and thus commenced on 15 March 1995, contains as a schedule the Act, the 'Agvet Code', which has the detailed provisions allowing the NRA to evaluate, approve or register, and review active

constituents and agricultural and veterinary chemical products (and their associated labels); to licence the manufacture of chemical products; and to issue permits. The Agvet Code also contains detailed offence provisions allowing the NRA to regulate the control of agvet chemicals and it has other provisions for ensuring compliance with, and enforcement of, the Agvet Code. As well, the Code contains provisions for data protection compensation for review data.

### The Assessment Process

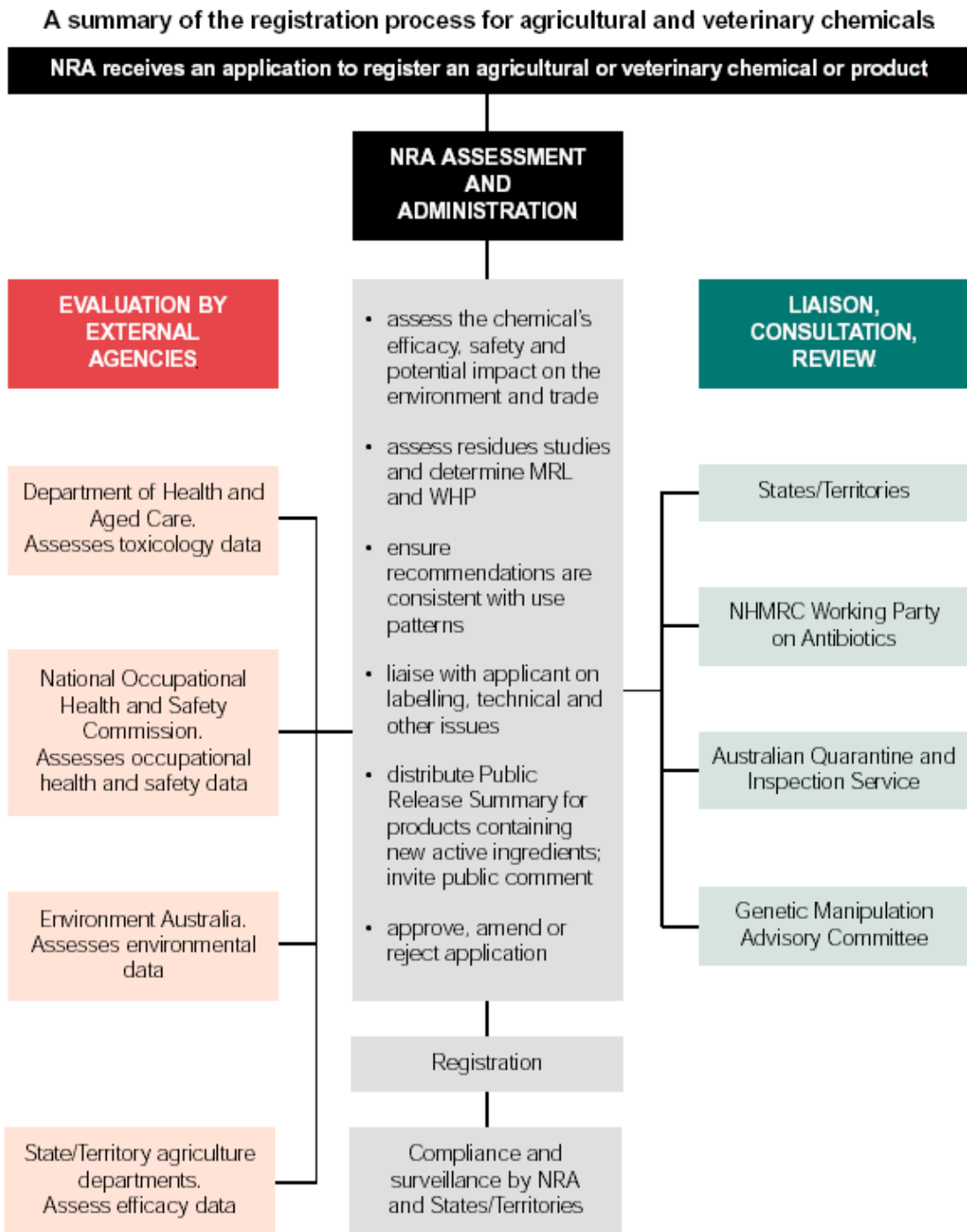
Before applying to register a new agricultural or veterinary chemical product, it is expected that companies undertake extensive product development, testing and field trials to generate data to justify registration of the product and to meet the standards required by the NRA assessment process. The amount of time it takes to complete the necessary field trials varies depending on the complexity of the product, but rough estimates indicate that it takes five years plus.

When an application is received, the NRA undertakes a detailed, independent assessment of all the data to ensure it meets the high standards of quality, safety and efficacy and that the product will not have an unacceptable adverse effect on public health. Residue studies on food-producing crops and animals are performed to establish a Maximum Residue Limit (MRL) and withholding period (WHP).

Specialist advice during the assessment process comes from three Commonwealth agencies: the Chemicals and Non-Prescription Drugs Branch, Environment Australia and The National Occupational Health and Safety Commission.

Figure 2.1 summarizes the registration process for agricultural and veterinary chemicals.

**Figure 2.1 Summary of the Australian Registration Process for Agricultural and Veterinary Chemicals**



Source: NRA Facts, 1999



Following assessment, the product may be registered or rejected. In many cases, the NRA proposes amendments to the product label as a requirement of registration. Depending on the product, this process may take months, or even a year or more to complete. It depends on the type of product and the nature of the testing involved.

Each year the NRA registers between 30 and 40 new agricultural and veterinary active constituents and approximately 1000 new products based on existing active constituents. In addition, approximately 1300 applications to vary existing products, ranging from repacks of currently registered products through to major variations in formulation, are registered each year.

The next section discusses the fee scheme and the assessment time-frame in more detail.

### Fee Scheme and Assessment Timeframe

The NRA recovers most of its operational costs through fees and levies paid by the agvet chemicals industry. These are recovered through:

- Application fees;
- Annual registration renewal fees; and
- Levies on disposals of registered products.

**Application Fees:** imposed under the authority of the Agricultural and Veterinary Chemicals Code (scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*). They vary according to the type of application and the assessment required. Registration applications are assessed as soon as the necessary data is presented and the appropriate fee is paid. Companies can apply for a partial rebate of the application fee paid if the timeframe for approval is exceeded.

**Registration Renewal Fees:** good for one financial year and are based on the product's disposals for the previous calendar year. The term disposal refers to Australian products sold, used or given away in Australia by the manufacturer; and imported products sold, used or given away in Australia by the importer.

**Levies:** the NRA imposes levies on disposals of registered agvet chemical products through three Acts: *the Agricultural and Veterinary Chemical Products Levy Imposition (General) Act 1994*, *Agricultural and Veterinary Chemical Products Levy Imposition (Excise) Act 1994*, *Agricultural and Veterinary Chemical Products Levy Imposition (Customs) Act 1994*.

The following table outlines the typical fees and assessment periods that various applications undergo in the assessment process, as mandated under the authority of the NRA.

**Table 2.4 Australian Fees and Assessment Periods for New Products**

<b>Fees and Assessment Periods – New Products</b>		
Description	Assessment Period (mths)	Fee
New Active - Primary Application	15	\$ 20,260 *(17,857 CAD)
New Active - Secondary Application	15	\$ 2,060 (1,815 CAD)
New Combination, approved actives - primary application	8	\$ 12,370 (10,900 CAD)
New combination, approved actives - secondary application	8	\$ 1,030 (908 CAD)
New Product, approved active - new situation	8	\$ 12,370 (10,900 CAD)
Repack	3	\$ 620 (546 CAD)
Major Formulation Change	3	\$ 12,370 (10,900 CAD)
<b>Fees and Assessment Period - Variations to Registered Products</b>		
Major Extension	8	\$ 10,310
Minor Extension	5	\$ 2,060 (1,815 CAD)
Minor Formulation Change	3	\$ 1,030 (908 CAD)
Administrative Label Change	3	\$ 620 (546 CAD)
Technical Label Change	8	\$ 2,060 (1,815 CAD)
<b>Fees and Assessment Periods - Modular<sup>1</sup></b>		
Description	Assessment Period (mths)	Fee
1.Application	No set period	\$ 620 (546 CAD)
2. Chemistry Assessment	5	\$ 1,030 (908 CAD)
3. Toxicology (full package)	15	\$ 9,690 (8,540 CAD)
4. Toxicology (partial package)	12	\$ 5,980 (5,270 CAD)
5. Toxicology (acute studies only)	8	\$ 2,475 (2,181 CAD)
6. Residues Assessment	8	\$ 2,475 (2,181 CAD)
7. Occupational Health and Safety Assessment	5	\$ 1,030 (908 CAD)

8. Environmental Assessment	12	\$ 3,095 (2,728 CAD)
9. Efficacy Review - Category One	6	\$ 3,095 (2,728 CAD)
10. Efficacy Review - Category Two	5	\$ 2,060 (1,815 CAD)
11. Efficacy Review - Category Three	5	\$ 1,030 (908 CAD)
12. Minor Use - requiring one or more MRL's	8	\$ 620 (546 CAD)
13. Any other Assessment	5	\$ 620 (546 CAD)
<p><sup>1</sup> Applications not fitting into the new products or variations to products category are assessed under the modular category. In addition, where a submission contains several applications it will be assessed under the modular fees list.  * Canadian amount based on April 9, 2003 Bank of Canada Exchange Rate: 0.8814 (1.1346) (Bank of Canada, 2003).</p>		

Source: NRA, 2003

Legislation governing the NRA allows for 15 months for the worst-case category of an application (or more if there are major deficiencies in the application) for new active constituent products (refer to Appendix A for an assessment timeline of new drug submissions). Shorter timeframes are allowed for less complex applications (e.g., new use for already registered product). This allows time for screening an application, consultation where necessary, and hands-on evaluation of the data submitted. There are two stages in the registration process: administration screening to ensure that the application is complete and properly prepared, and technical evaluation.

Possible delays in the registration of a product may result from:

- Insufficient data supplied;
- Application fee not included;
- Labels not prepared according to the relevant labelling code; and
- Applications submitted without necessary letters for support.

### Appeals Procedure

Applicants have the right to obtain a formal written statement from the NRA setting out the findings of an evaluation, with references to the materials on which those finding were based and reasons for the NRA's decision. Applications must be in writing and should be lodged with the NRA Corporate Secretary within 28 days of a decision.

An applicant may apply, in writing, for the NRA to reconsider a decision under section 166 of the Agvet Code. Following reconsideration, the NRA may either confirm, set aside or vary its decision.

In addition, under section 167 of the Agvet Code, the Administrative Appeals Tribunal (AAT), subject to the Administrative Appeals Tribunal Act 1975, can review the decision

of the NRA to vary the conditions of a registration and to approve a label. An application to the AAT must be in writing, accompanied by the required filing fee and be lodged within 28 days of the NRA's notice.

Performance Indicators

According to an NRA spokesperson<sup>8</sup>, the NRA meets their legislative timeframes 97-98% of the time. The 2001-02 Annual Report for the National Registration Authority for Agricultural and Veterinary Chemicals gives an overview of how the system performed in the 2001-02 period (NRA, 2002). Of the 2,529 applications for registration, variation of registration or label approval finalized in the 2001-02 period, 96.2% were completed within the NRA's statutory timeframes. The following table analyzes veterinary registrations approved in the 2001-02 period according to their class of application and the amount of time it took for the product to be approved or finalized.

**Table 2.5 NRA Veterinary Registrations in 2001-02**

Class of Application	Total No. Registered or Approved	No. finalized or approved versus statutory timeframe			Average clock time to finalise (months)	Average elapsed time to finalise (months)
		<100%	100-120%	>120%		
15 Month	16	11	3	2	12.5	26.6
13 Month	3	3	0	0	11.5	43.3
12 Month	1	1	0	0	10.6	36.4
8 Month	56	54	2	0	6.2	15.9
5 Month	122	115	5	2	3.5	9.7
3 Month	830	825	1	4	0.7	3.7
<b>Total</b>	<b>1028</b>	<b>1009 (98.1%)</b>	<b>11</b>	<b>8</b>		

NRA Annual Report, 2002

The above table illustrates that the NRA often meets their statutory timeframe and in all cases the average clock time required to finalise a submission was below the statutory timeframe. As noted above, companies can apply for a partial rebate of the application fee if the timeframe is exceeded.

A review of the NRA system drew the following conclusions about the registration of Agvet chemical products that are safe and effective for their intended use and satisfy requirements for safety to people, animals, the environment and trade:

<sup>8</sup> A note on Australia's registration system in comparison with Canada and other countries from Peter Raphael at the NRA: "Australia has participated in an international benchmarking study of pesticide registration conducted by consultants. Canada also participated and it's possible that the PMRA may let the George Morris Centre have access to the report. There have been several independent Australian reviews that have concluded that the NRA is at 'world's best practice'. Companies with worldwide experience usually do not complain about the Australian system with much conviction and acknowledge that <the Australian system> is both cheaper and quicker than comparable countries".

- There was improved industry compliance with registration requirements due to better information and feedback;
- Decisions about active constituents and chemical products were made within statutory framework;
- Registered products in the marketplace meet legislative requirements for performance and safety due to sound decision-making.

### **2.3 European Union<sup>9</sup>**

The registration of veterinary drug products in the European Union falls under the authority of the European Medical Evaluation Agency (EMA). The EMA is in charge of co-ordinating scientific resources existing in Member States<sup>10</sup> with a view to evaluating and supervising medicinal products for both human and veterinary use. On the basis of the Agency's opinion, the European Commission authorizes the marketing of innovative products and arbitrates between Member States for other medicinal products in the case of disagreement.

The EMA was established in July 1993 by Council Regulation (EEC) 2309/93, which lays down the community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishes a European agency for the evaluation of medicinal products<sup>11</sup> (Official Journal L214, 24/08/1993, p.0001-0021).

#### Structure and Responsibility

The Agency is comprised of:

- A management board which consists of two representatives per Member State, two representatives of the Commission, and two representatives appointed by the European Parliament.
- Three committees responsible for preparing the Agency's opinion on questions relating to medicinal products for human use (CPMP – Committee for Proprietary Medicinal Products), for veterinary use (CVMP) and for the designation of 'orphan drugs' for rare diseases. The CVMP consists of two members nominated by each Member state.
- An executive director.
- A secretariat.

The Council Regulation (EEC) 2309/93 sets out the core tasks of the EMA as:

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<sup>9</sup> EMA, 2003

<sup>10</sup> The Member States includes the 15 Member Countries of the European Union (United Kingdom, Ireland, Germany, Austria, Spain, Portugal, Italy, Greece, Netherlands, Sweden, France, Belgium, Luxembourg, Denmark and Finland) as well as the European Free Trade Association states (Norway, Iceland and Liechtenstein).

<sup>11</sup> <http://www.noah.co.uk/legislation/932309en.pdf>

- The scientific evaluation of quality, safety, efficacy of medicinal products for human and veterinary use.
- The assessment reports, summaries of products characteristics, labels and package inserts.
- The supervision of medicinal products (pharmacovigilance).
- Providing scientific opinions regarding MRLs.
- Ensuring compliance with good manufacturing practice, good laboratory practice and good clinical practice.
- Facilitating cooperation between Member States, the Community and international organizations and third world countries.
- Reviewing the status of marketing authorizations.
- Advising companies on the conduct of various tests and trials.

### Gaining Marketing Authorization through EMEA

A veterinary product may only be placed on the market in the European Union when a marketing authorization has been issued by the competent authority of a Member State for its own territory (national authorization), or when authorization has been granted in accordance with Regulation (EEC) 2309/39 for the entire community (Community Authorization).

#### *National Authorizations*

The competent authorities of the Member States are responsible for the granting of marketing authorizations for medicinal products which are placed on their markets, except for medicinal products which are authorized under Regulation (EEC) No 2309/93 (Community Authorizations, see below).

In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State. For the majority of conventional medicinal products, a decentralized procedure exists and is based on the principle of mutual recognition of national authorizations. It provides for the extension of marketing authorizations granted by one Member State to one or more Member States as identified by the applicant. When the original national authorization cannot be recognized, the points in dispute are submitted to the EMEA for arbitration. The opinion of the scientific community is then submitted to the European Commission.

#### Community Authorizations

The Community is responsible for the granting of marketing authorizations for medicinal products:

- Developed by means of one of the biotechnological processes referred to in Regulation (EEC) No 2309/93, Annex, Part A<sup>12</sup>, which may only be authorized by a Community authorization following an evaluation according to the centralized procedure;
- Medicinal products referred to in Regulation (EEC) No 2309/93, Annex, Part B<sup>13</sup>, for which the applicant has chosen the centralized procedure leading to a Community authorization.

In order to obtain a Community authorization, an application must be submitted to the EMEA.

The scientific evaluation of the application is carried out within the Committee for Veterinary Medicinal Products (CVMP) of the EMEA, and a scientific opinion is prepared. The opinion is sent to the European Commission, which drafts a Decision. Having consulted through the relevant Standing Committee, normally the Commission adopts the Decision and grants a marketing authorization.

Such a marketing authorization is valid throughout the Community and confers the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State.

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<sup>12</sup> **Part A Products:** Veterinary medicinal products including those not derived from biotechnology, intended primarily for use as a performance enhancer in order to promote the growth of treated animals or to increase yields from treated animals.

Any veterinary medicinal product in the composition of which there is a proteinaceous constituent obtained by means of a biotechnology process, falls under the scope of Part A, irrespective of whether or not the constituent is an active substance of the veterinary medicinal product. This also applies where a biotechnology manufacturing step is introduced into the manufacture of a proteinaceous product after the granting of a marketing authorization.

Examples of new biotechnology products which would be considered obligatory for the Centralized Procedure are given below:

- Product intended for gene therapy;
- Vaccines from strains developed by means of recombinant DNA technology, including gene deletion;
- Any veterinary medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process;
- Cell therapy products, which are the result of any biotech process referred to in Part A of the Annex to Regulation (EEC) No 2309/93

<sup>13</sup> **Part B products** - applicants may use the Centralized Community procedure at their own discretion. Includes medicinal products intended for use in animals containing a new active substance which, on the date of entry into force of Council Regulation (ECC) No 2309/93, as amended, was not authorized by a Member state for use in a medicinal product intended for use in animals.

## Application Procedure

*Pre-Submission* - The EMEA emphasizes the importance of pre-submission meetings with applicants. These meetings should take place 4-6 months prior to the anticipated date of submission of the application. These meetings are a vital opportunity for the applicant to obtain procedural, regulatory and legal advice from the EMEA. This process helps applicants submit applications that are in conformity with the legal and regulatory requirements and result in a quicker validation.

## Application Fees

Table 2.6 illustrates the fee structure used by the EMEA, under the authorization of the Council Regulation (EC) No 2743/98 of December 14, 1998.

**Table 2.6 EMEA Fee Structure**

<b>EMEA Fee Structure</b>		
<b>Type</b>	<b>Fee</b>	<b>Description</b>
<b>Full Fee</b>		
Basic Fee	100,000 Euro (156,830 CAD)*	For a single strength associated with a pharmaceutical form
Additional Fee	+10,000 Euro (15,683 CAD)	For each additional strength and or pharmaceutical form submitted at the time of initial application
	+ 5,000 Euro (7,841 CAD)	For each additional presentation of the same strength and pharmaceutical form submitted at time of initial application
<b>Full Fee – Vaccines</b>		
Basic Fee	50,000 Euro (78,415 CAD)	For a single strength associated with a pharmaceutical form
Additional Fee	+ 5,000 Euro (7,841 CAD)	For each additional strength and or pharmaceutical form and or presentation submitted at the time of initial application
<b>Reduced Fees</b>		
Basic Fee	50,000 Euro (78,415 CAD)	For a single strength associated with a pharmaceutical form
Additional Fee	+10,000 Euro (15,683 CAD)	For each additional strength and or pharmaceutical form submitted at the time of initial application
	+ 5,000 Euro (7,841 CAD)	For each additional presentation of the same strength and pharmaceutical form submitted at time of initial application
<b>Reduced Fee – Vaccines</b>		
Basic Fee	25,000 Euro (39,208 CAD)	For a single strength associated with a pharmaceutical form



Additional Fee	+ 5,000 Euro (7,841 CAD)	For each additional strength and or pharmaceutical form and or presentation submitted at the time of initial application
<b>Extension Fee</b>		
	25,000 Euro (39,208 CAD)	For a new strength; a new pharmaceutical form; a new target species; a new indication; a new route of administration
	5,000 Euro (7,841 CAD)	For a new presentation of an already authorised strength, pharmaceutical form or route of administration
<b>Extension Fee – Vaccines</b>		
	5,000 Euro (7,841 CAD)	For a new strength; a new pharmaceutical form; a new target species; a new indication; a new route of administration
<b>Renewal of a Marketing Authorisation</b>		
Renewal Fee	5,000 Euro (7,841 CAD)	For each strength associated with a pharmaceutical form
Inspection Fee	15,000 Euro (23,525 CAD)	For any inspection within or outside of the EU
<b>Maintenance of a Marketing Authority</b>		
Annual Fee	20,000 Euro (31,366 CAD)	Covering all authorised presentations of a given medicinal product
<b>Scientific Advice Fee</b>		
	up to 30,000 Euro (47,049 CAD)	Request of scientific or technical advice concerning research and development, to lead to an application for a marketing authorisation or extension of an existing marketing authorisation
<b>Maximum Residue Limits</b>		
Establishment of MRL	50,000 Euro (78,415 CAD)	Fee will be deducted from the fee for an application of a marketing authorisation or for an extension of the medicinal product containing the substance subject to the MRL and submitted by the same applicant

\* Canadian amounts based on the April 9, 2003 Bank of Canada Exchange Rate: 1.5683 (0.6376)  
 Source: EMEA, 1999

The following is a list of definitions to accompany Table 2.3 (EMEA, 1999).

### Strength

- For single-dose preparations, total use, the strength is defined as amount of active substance per unit of dose.
- For single-dose preparations, partial use, the strength is defined as the concentration expressed in the amount of active substance per ml, per puff, per drop, per kg in percentage as appropriate.

- For multi-dose preparations, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, as appropriate.
- For powder for reconstitution (powder for oral solution or suspension, powder for solution for injection, etc.) the strength is defined as the concentration after dissolution or suspension (reconstitution) to the volume and liquid recommended.
- For concentrates for solutions (for injection or for infusion) the strength is defined as the concentration of the concentrate before dilution.

*Pharmaceutical Form:* According to full terms in the “Standard Terms” published by the Council of Europe.

*Presentation:* Each unit/entity of a certain strength and form of a pharmaceutical product which will be individually authorized and eventually marketed.

### Evaluation Timeframe

The maximum timeframe for a marketing authorization application under the Centralized Community Procedure is 210 days (does not include pre-submission meeting 90 days prior to the official start date), excluding clock stops when additional written or oral information is required by the CVMP with regards to a response to a question asked by the CVMP (refer to Appendix B for an assessment timeline of new drug submissions).

The EMEA will send the applicant an acknowledgement of the receipt of a dossier and, within 10 working days following the receipt, will complete its validation. At the end of the validation process the EMEA will start the procedure. If within a month from the start of the procedure any other member of the CVMP has not received the requested parts of the dossier from the applicant, they will stop the clock.

The following table (2.7) is the complete EMEA evaluation process by days and action.

**Table 2.7 EMEA Evaluation Timeframe**

Day	Action
-90	Pre-submission Meeting
1	Start the procedure
70	Receipt of the Assessment Report from the Rapporteur by the co-Rapporteur, the CVMP members and the EMEA Secretariat. Rapporteur's. Assessment report is also sent to the applicant without confidential aspects by the EMEA Secretariat.
85	Receipt of the Co-Rapporteur's critique of the Rapporteur's Assessment report by the Rapporteur, CVMP members and the EMEA secretariat. The Co-Rapporteur's critique is also sent to the applicant
100	Comments from members of the CVMP
115	Receipt of draft list of questions (including overall conclusions and overview of the scientific data) from (Co-) Rapporteur by CVMP members and EMEA.
120	CVMP adopts the list of questions as well as the overall conclusions and overview of the scientific data to be sent to the applicant by the EMEA. <i>Clock Stop</i>
121	Submission of the response, restart of the clock (on 11 official dates per year). Submission of all 11 updated language versions of the summary of product characteristics (SPC), labelling and Package insert.
150	Common Response Assessment Report.
150-190	Review of all translations of the SPC, labelling and package insert by the Quality Review of Documents group. Comments also sent to applicant.
170	Deadline for comments from CVMP Members.
180	CVMP discussion and decision on the need for an oral explanation by the applicant. If needed, clock is stopped while applicant prepares for discussion.
181	Restart of the clock and oral explanation.
195	Final draft of English version of SPC, labelling and package inserts by applicant.
By 210	CVMP opinion + CVMP draft Assessment Report.
BY 215 at latest	Applicant provides CVMP and EMEA members with all translations of SPC, labelling and package inserts.
225	Applicant prepares final revised translations of SPC, labelling and package inserts.
240	Transmission of opinion to applicant, Commission and Member States in all languages.
By 300	Finalization of EPAR in consultation with applicant (for confidentiality purposes) Source: EMEA, 1995-2004

### Appeals Procedure

There is no formal appeals procedure at the EMEA.

### Performance Indicators

The 2001 Seventh Annual Report (EMEA, 2001) of the EMEA provides information on how the system performed in 2001. In 2001, the EMEA received 9 applications for new and innovative products which fall under Part A and Part B of the Annex to Council Regulation (EEC) 2309/93, compared to 6 applications in 2000 and 4 applications in 1999. The target range for applications is 10.

The average number of calendar days required to finalise an application in 2001 was 678 days. Of this 678 days, 210 days were the assessment phase, 30 days were post-opinion phase, 94 days were the decision process and 344 days were company stop time days. The average number of days in 2001 to finalise an application is greater than 1999 and 2000. This is mainly attributed to the number of company stop time days.

A benchmark study based on the joint EMEA-European Federation of Animal Health (FEDESA) questionnaire on the use of the centralized system of authorization was completed in 2001 and shows a high level of satisfaction on the part of the European veterinary pharmaceutical industry with the centralized system and support for the EMEA, reflecting a consistency in full compliance with regulatory deadlines. The survey also found that there was an increase in the number of pre-submission meetings for products in 2001 (94%) compared to 2000 (66%).

EMEA has continued to efficiently register and approve new medicinal products. In 2002 the Committee for Veterinary Medicinal Products (CVMP) at the Agency granted authorization for the registration of Draxxin and the active ingredient Tulathromycin (EMEA, 2003) submitted by Pfizer Limited. Tulathromycin is intended for the treatment of bacterial respiratory disease in cattle and pigs but not intended for use in lactating cattle. Pfizer conducted numerous toxicological and pharmacokinetic studies prior to submitting an application based on the requirements of the CVMP. The drug was subsequently approved in a timely fashion. Pfizer initiated the application procedure on October 16<sup>th</sup>, 2002, and the positive opinion was granted 182 days later, on July 23<sup>rd</sup>, 2003 (EMEA, 2003). In this case, the approval of the drug was faster than the 210-day requirement within the EMEA.

## **2.4 The Canadian<sup>14</sup> Animal Health Product Approval Registration System**

The Bureau of Veterinary Drugs (BVD) of Health Canada conducted animal health product reviews and approvals in Canada prior to 2001. The mission statement of the BVD stated at that time that, “The Bureau was responsible for evaluating drugs for use in animals to ensure that:

1. Their use would not leave potentially harmful residues in food products of animal origin (meat, milk, eggs fish and honey);
2. They were efficacious and safe in the target animal;
3. Standards of manufacturing and quality control were acceptable.”

(Price Waterhouse, 1996)

At the end of 2001, the Veterinary Drugs Directorate was formed from the Bureau of Veterinary Drugs. For the purpose of consistency throughout the document, the Bureau of Veterinary Drugs will be referred to as the Veterinary Drugs Directorate, *regardless* of the time period being discussed. This is particularly important in Section 3, the case studies, as many of the companies began the review process with the Bureau of Veterinary Drugs.

The Canadian Animal Health Product Approval Registration system for both food animal and companion animal drugs is subject to the approval of the Veterinary Drugs Directorate of Health Canada. The Veterinary Biologics Section of the Canadian Food Inspection Agency is the regulatory body responsible for the licensing of all vaccines and veterinary biologics from manufacturers who wish to sell their products on the Canadian market. The Veterinary Biologics Section has not been reviewed in this research.

### The Veterinary Drugs Directorate (VDD)

The Veterinary Drugs Directorate (VDD) is part of the Health Products and Food Branch of Health Canada. The VDD ensures safety of foods such as milk, meat, eggs, fish and honey from animals treated with veterinary drugs. They also ensure that veterinary drugs sold in Canada are safe and effective for animals.

### Structure and Responsibility

The aim of the VDD is to enhance the efficiency of operations and to streamline the review of veterinary drug submissions and experimental studies certificates. A focus is on advancing areas of information management and processing, communications with Canadians and working in partnership with stakeholders and addressing a growing requirement of regulatory agencies worldwide.

The VDD is headed by a Director General and has six divisions: Human Safety Division, Manufacturing and Chemical Evaluation Division, Clinical Evaluation Division,

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<sup>14</sup> Source: VDD Health Canada Website, 2003

Submission and Knowledge Management Division, Strategic Planning and Stakeholder Relations Division, and Executive Services.

Within the Clinical Evaluation Division is a Pharmacovigilance Unit. The strategic focus of the Pharmacovigilance Unit is on post-market safety surveillance to improve the monitoring of veterinary drugs in Canada.

### Approval Process for New Veterinary Drugs

Veterinary drugs are used to prevent and treat diseases in animals caused by micro-organisms and parasites. Some drugs may help to promote growth, control reproduction or provide humane means of restraint and relief of pain in animals.

A new veterinary drug is approved for sale in Canada only if Health Canada is satisfied that:

- The drug is safe for the animals to be treated and effective for the purpose it is being marketed;
- It does not leave potentially harmful residues that could pose any health hazard to humans eating food products from treated animals (meat, milk, eggs, fish and honey);
- The drug must be manufactured according to strict specifications and must remain stable up to its expiry date.

Review of new veterinary drugs is conducted by the Health Products and Food Branch, through the work of the Veterinary Drugs Directorate.

For a new drug to be reviewed, the manufacturer must:

- Submit a 'New Drug Submission' which contains details on manufacturing and quality control as well as results of toxicity, pharmacology, residue and clinical studies;
- Provide the VDD with substantial evidence to support the product's quality, safety and efficacy;
- Prove that proposed labels for the new drug reflect the data submitted and specify adequate directions for use, including withdrawal periods for drugs used in food-producing animals.
- Note that unlike other countries, Canada does not require manufacturers to provide information pertaining to non-scientific issues, such as social and economic impacts (positive or negative), in their product review.

Manufacturers must also submit information, in a Supplemental New Drug Submission, if they wish to make significant manufacturing changes or modify conditions of use (labelling) for previously approved drugs.

If required, the VDD will ask for further information. This process continues until the VDD approves or rejects the application. Scientists in the VDD review the claims and

findings of a company in the submissions and ensure that the information that will be provided to veterinarians and consumers is clear and unequivocal.

When there is no clear consensus among its scientists, or when the VDD would benefit from outside advice, it may also convene an expert advisory panel to review data and recommendations made by scientists.

Following the review of all existing data which could also include an expert panel review, the scientists who have evaluated the submission assess the risks and benefits and make recommendations to their supervisors to either accept or reject the submission. The Head of the Veterinary Drugs Program, taking into account the recommendations of the scientists and scientifically trained managers, accepts or rejects the submission.

If a submission is accepted and the product is approved, the manufacturer will receive a 'Notice of Compliance' from Health Canada specifying the terms and conditions under which the drug can be sold and used. The drug must bear a Drug Identification Number (DIN) on its label.

### Approval Times

The Canadian performance standard for a 'New Drug Submission' (includes Abbreviated and Supplemental New Drug Submissions) is 180 days (refer to Appendix B for an assessment timeline of new drug submissions). Note that the 180 days to reach a decision is an administrative standard, not a performance goal that must be met. For Corporate or Brand Name changes, the performance standard in Canada is 90 days.

### Appeal Procedure

Until recently there was no appeal mechanism in Canada during the application process or once the drug decisions were made. In December 2003, a blueprint for appeals was published by VDD; however, it is not an *independent* appeal mechanism as requested by industry.

To serve industry clients more efficiently and enhance transparency, the Veterinary Drugs Directorate (VDD) developed a blueprint for the appeal process for veterinary drug submissions. The appeal process will be applicable to several VDD procedures including VDD's new Submission Management Policy (being developed). The blueprint is based on Health Canada's Health Products and Food Branch policy entitled *Appeals Procedures for Drug Submissions* and respects the principles and practices described therein (VDD Appeals Website, 2004).

There will be three levels of appeal, two of which were initiated by industry (not the regulator). In each case, the supporting information provided by the industry client will

be given due consideration and will be reviewed by scientific evaluators and external experts.

#### Level One Appeal

When a manufacturer is dissatisfied with a decision made by VDD that is related to a veterinary drug submission, the sponsor now has the right to appeal that decision. The manufacturer may contact the Chief or Director of the applicable Division within VDD to discuss the disagreement. At that time, VDD will conduct a peer review of the data and determine whether the sponsor has provided sufficient data (VDD Appeals Website, 2004).

#### Level Two Appeal

If the industry client does not agree with the decision made in the Level One Appeal and wishes to proceed further, an appeal may be made to the Director General of VDD. The Director General will review the information, and will consult with VDD's Science Issues Review Committee (SIRC). SIRC is comprised of a group of scientific experts and other members of the VDD management team (VDD Appeals Website, 2004).

#### Level Three Appeal

At the discretion of the Director General and/or the recommendation of SIRC, the appeal may be referred for further examination to an external peer review or an ad hoc committee. The final decision rests with the Director General of VDD.

In all appeal requests, a written explanation of the decision will be provided (VDD Appeals Website, 2004).

Given the above description, it is clear that there still remains a need for an independent dispute mechanism.

#### Fee Structure<sup>15</sup>

Examples of fees for frequently filed submission types are illustrated in Table 2.8.

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<sup>15</sup> The regulations for the fee structure can be found in the *Canada Gazette* Part II, Volume 130, No. 6, page 1100.



**Table 2.8 Examples of Fees for Frequently Filed Submission Types for Veterinary Drugs in Canada**

ACTIVITY OR SERVICE	ANIMAL SAFETY/ EFFICACY	HUMAN SAFETY	MANUFACTURING	TOTAL
NDS: New Entity/Food Species/1000 SF	\$ 15,980	\$ 21,790	\$ 9,680	\$ 47,450
NDS: New Entity/Food Species/100 SF	\$ 15,980	\$ 29,050	\$ 9,680	\$ 54,710
NDS: New Entity/Food Species/100SF/GP	\$ 31,470	\$ 29,050	\$ 9,680	\$ 70,200
NDS: New Entity/Non-Food Species	\$ 15,980	-	\$ 9,680	\$ 25,660
Abbreviated NDS: Food Species	\$ 2,900	\$ 2,900	\$ 9,680	\$ 15,480
Abbreviated NDS: Non-Food Species	\$ 2,900	-	\$ 9,680	\$ 12,580
SNDS: Another Food Species	\$ 15,980	\$ 14,520	-	\$ 30,500
SNDS: Another Non-Food Species	\$ 15,980	-	-	\$ 15,980
SNDS: New Indication, Same Food Species	\$ 12,590	-	-	\$ 12,590
SNDS: New Indication, Same Non-Food Species	\$ 12,590	-	-	\$ 12,590
Concurrent Use in Food Species	\$ 7,740	\$ 5,810	\$ 1,450	\$ 15,000
Concurrent Use in Non-Food Species	\$ 7,740	-	\$ 1,450	\$ 9,190
INDS: New Entity/Food Species/Temporary ADI	\$ 4,840	\$ 14,520	\$ 4,840	\$ 24,200
INDS: New Entity/Food Species/1000 SF	\$ 4,840	\$ 21,790	\$ 4,840	\$ 31,470
INDS: New Entity/ Food Species/ 100 SF	\$ 4,840	\$ 29,050	\$ 4,840	\$ 38,730
INDS: New Entity/ Non-Food Species	\$ 4,840	-	\$ 4,840	\$ 9,680
ESC: Food Species/Original	-	-	-	\$ 2,900
ESC: Food Species/Repeat	-	-	-	\$ 480
ESC: Non-Food Species/Original	-	-	-	\$ 960
ESC: Non-Food Species/Repeat	-	-	-	\$ 480
DIN: Application	-	-	-	\$ 720
DIN: Drug Status Information	-	-	-	\$ 500
Corporate or Drug Name Change	-	-	-	\$ 250
EDR: Food Species	-	-	-	\$ 100
EDR: Non-Food Species	-	-	-	\$ 50
SF: Safety Factor				
GP: Growth Promotant				
ADI: Acceptable Daily Intake				

Source: VDD (Doing Business with VDD Website), 2003

The following is a list of definitions to accompany Table 2.8.

Definitions:

- Schedule I New Drug Submission (NDS)
- Schedule II Supplement to a New Drug Submission (SNDS)
- Schedule III Abbreviated New Drug Submission and Supplement to and Abbreviated New Drug Submission (ANDS, SNDS)
- Schedule IV Drug Identification Number (DIN) Application
- Schedule V Preclinical (Investigational) New Drug Submission (INDS)
- Schedule VI Experimental Studies Certificate
- Schedule VII Emergency Drug Sale (EDR)

Bill C-212, a private members bill (sponsored by Roy Cullen, MP, Etobicoke North), was passed unanimously through the House of Commons in September 2003. The Bill, which will likely go to the Senate for consideration in February of 2004, would require fee-charging federal departments and agencies to: consult with stakeholders prior to establishing a fee; show that a clear private benefit is linked with the fee; establish an independent resolution system; and, set performance standards in exchange for the fee charged (Business Coalition on Cost Recovery, 2003).

The Bill would also provide fee reductions when performance standards are not met, as this has proved useful within the Australian and United States in encouraging fee-charging government agencies to meet performance commitments.

### Performance Indicators

An independent report by Regulatory Data Services (RDS) analysed the market access times for veterinary drug products in Canada between 1995 and May 2003<sup>16</sup>.

This report found that the average approval times for New Drug Submissions (NDS) were increasing from 1996 to 2002. The average number of days to approval in 1997 was 402 days, compared to 818 days for 2002.

From 1995 to 2002, the average approval time for NDS was 567 days. The minimum number of days to approval was 116 days and the maximum number of days was 1,828 days.

The report also found that NDS approval times exceeded the 180-day performance standard 87% of the time and that the predictability of NDS approvals is falling. The 95% confidence range tended to get broader from 1996 to 2002, with the standard deviation at 428 days in 2002 (ranging from 601 to 1035 days). Marketing decisions for a new product get more difficult as the standard deviation gets larger.

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<sup>16</sup> Data for this report is collected from the Veterinary Drugs Directorate of Health Canada via the Freedom of Information Act.

The report indicates that the average approval time for Corporate or Brand name changes has shown some improvement, but is still generally above the 90-day performance standard. As well, approval times for Abbreviated New Drug Submissions (ANDS) and Supplements to a New Drug Submission (SNDS) have seen upward trends with the average approval time in 2002 for ANDS being over 700 days and for SNDS it was approximately 574 days (over three times the performance standard).

The conclusions of a comparative study conducted by D.J. Rainnie at the Atlantic Veterinary College (Rainnie, 2002) show similar results. Their study compared the regulatory requirements of the Centre for Veterinary Medicine (CVM) in the United States to VDD with respect to drugs for use in companion animals. Rainnie concluded that although the regulatory requirements for both agencies are essentially the same, the CVM documents that lay out the requirements are more specific, numerous and detailed and therefore are less open to interpretation and resulted in more consistency in CVM reviews.

Rainnie's report also highlighted that the CVM was more formally standardized and less flexible in all processes throughout the approval process. Therefore, quality control and consistency in the approval process was always higher in CVM when compared to VDD. Rainnie also found that the review process at CVM to be team oriented, but at VDD it was more individualistic. Finally, Rainnie found that the interpretation of data from the field studies was generally the same in both agencies. This finding should encourage more collaboration between the two agencies thereby reducing any recreation of field data and reducing the amount of time required during approval decision process.

It is important to note that there have been numerous actions taken by the Veterinary Drugs Directorate of Health Canada to improve the regulatory process and the time required for a decision on new drug submissions. Like anything, new processes take time before the improvements are reflected, for example, in reduced time for drug approval decisions and backlog reduction. Table 2.9 identifies some of the actions taken by VDD for improvement in the regulatory process since 2001.

**Table 2.9 Veterinary Drugs Directorate: Progress on Key Issues**

2001	2002
27 Employees	80 employees
No outreach	Education and outreach unit
No stakeholder relations	Stakeholder committee in place
No consultations	Consultations – e.g., AMR, MRLs/AMRLs
No strategic planning	Strategic planning unit operational
Limited capacity for international activities	VICH – Steering Committee and Working Groups, CODEX bilateral activities with the CVM
No IM/IT capacity	Submission and knowledge Management Division operational, new Submission Management Policy in progress: E-review
No formal adverse drug reaction reporting	Pharmacovigilance unit in place
Significant submission backlog	Significant submission backlog reduction
Backlog of corporate name changes	Corporate name change backlog eliminated
37 MRLs	65 AMRLs/MRLs

Source: Kirkpatrick presentation slides at CAHI Annual Meeting, 2003

## 2.5 Summary

Despite improvements in the Canadian regulatory system, the foregoing reveals several issues that remain:

- Expense of applications
  - Canada has a new drug application fee that is among the highest of the countries compared, particularly when the size of the Canadian market is considered.
    - Canada: C\$25,660-70,200
    - US: C\$30,000-60,500
    - Australia: C\$17,650
    - EU: C\$157,000 for access to 15 member countries
- The time frame for an approval decision is too long.
  - The Canadian system makes no commitment with regard to time of approval decision and does not adhere to its administrative standards.
    - Canada: 180 days – administrative standard
    - US: 180 days – currently a provisional standard. The US have implemented the Animal Drug User Fee Act (ADUFA) in which the legislation will impose performance standards on the CVM that are

- expected to improve the drug approval process to 180 days, 90% of the time by 2008.
- Australia: 240 days
  - EU: 210 working days (does not include clock stop days)
  - Total elapsed time until a decision made is slowest in Canada, by a wide margin. It is understood that, since the commission of this report, there has been effort on the part of the VDD to improve this situation but more improvements are needed to make this a world-class regulatory environment.
    - Canada: exceeded NDS target 90% of time (2002)
    - US: exceeded target 83% for NADA (2002)
    - Australia: 96.2% within timeframe (2001-02)
    - EU: no data – last 3 yrs within timeframe
  - Until recently there was no appeal mechanism in Canada during the application process or once the drug decisions were made, but they exist in other systems. In December 2003, a blueprint for appeals was published by VDD; however, it is not an *independent* appeal mechanism as requested by industry.
    - There still remains a need for an independent dispute mechanism.
  - There are no mandatory pre-submission meetings (e.g., the EU) for applicants to get a better understanding of what is required prior to submission.

### **3.0 The Regulatory Approval System: Case Studies of Past Product Approvals**

In Section 2.0, evidence is provided that the approval process in Canada appears to present problems for the industry. Section 3.0 provides evidence of the costs and the distribution of costs among market participants created by those problems by undertaking a series of case studies. The section further defines the need for the case study analysis, reviews the RIAS model, which was developed to estimate the economic impact of regulatory product approval delays by RIAS Inc, and reviews two case studies RIAS completed some time ago. The final section introduces the case study methods and the George Morris Centre cases.

#### **3.1 Case Study Analysis**

Delays in government regulatory approval cause delays for the introduction of new products in markets. These delays have high costs to businesses and their customers. Estimating the empirical real costs of these delays and explaining the costs to regulators can be a difficult task.

A measure of the tangible costs associated with the Canadian animal health products regulatory system can be made based on the actual experience of firms in the industry introducing new products into the Canadian market. This experience includes the evidence that was initially requested by regulators, requests for further evidence and the time from approval submission to ruling on approval. The purpose of the case studies is to document these experiences and their associated costs.

#### **3.2 RIAS Inc. Case Study Summary**

*RIAS Inc.* in previous research addressed some of the difficulties identified above. Section 3.2 is a summary of two *RIAS Inc.* case studies (2000), which illustrate the economic impact of the regulatory product approval delay in Canada.

The following is an example of lost revenue from a delayed drug approval in Canada. The product was a drug designed to be efficacious against a wide variety of parasites in dogs and cats. After submission in Canada, it took 67 weeks to obtain regulatory approval. Recall that the 'goal' for veterinary drug approvals in Canada is 180 days. Thus, the approval exceeded the goal by 289 calendar days. The same product was introduced in the United States eight months *before* the Canadian approval. As the first single entity product against a broad range of parasites, this product was a real innovation in its category and was a great success and was widely adopted in the United States.

The Canadian regulatory delay cost the company 12% of the value of the drug over five years. That is, the company lost 12% of what it would have earned in Canada if the market approval had been within the maximum allowed time.

The financial loss due to the regulatory delay was 17% of the total annual Canadian sales in animal health products for that firm. Implications of this loss include fewer new products introduced for clinical testing and less employment in the business.

In the synopsis of the RIAS case, they identify that the extreme regulatory delays mean many of the company's new animal health products in use elsewhere will not be made available at the same time in Canada. Canadians and their companion animals lose out. In addition, consumers are going to the United States and importing the product for their use. This is a loss of income for Canadians and inflicts undue hardship on the companion animals that are denied the products during the excessive delay.

A second scenario concerns the submission of a growth promotant for livestock. At the time of submission, the product was not approved in the US or European Union and it was a unique opportunity for the food production sector to gain a production advantage in domestic and export markets. The product took six years to gain approval through the Bureau of Veterinary Drugs. Note that the European Union and the US did not register the product. Again, the *RIAS Inc* impact model was used to determine what the costs were to the consumer and the Canadian economy. The company lost 85% of the forecast revenue over its first ten years. Canadian food producers also lost because they did not have access to the product for the six years it took to gain approval. This affected Canadian firms by impacting their incentive to develop and market animal health products in Canada and as a result research and development took place in other countries.

Clearly, there are impacts to the agri-food industry, consumers and the Canadian economy from regulatory delays for product approval in Canada.

### **3.3 George Morris Centre Case Studies**

Section 3.3 contains a complete description of the case study process, interview results and economic impacts for each of the cases analyzed.

For the purpose of consistency throughout the document, the Bureau of Veterinary Drugs has been referred to as the Veterinary Drugs Directorate, *regardless* of the time period being discussed. This is particularly important in this section, as many of the companies began the product review process with the Bureau of Veterinary Drugs.

### 3.3.1 Case Study Evaluation

George Morris Centre researchers conducted five case study interviews and analyzed the economic impacts to the company and to the agricultural industry as part of this research. The case studies selected were examples of product submissions that were delayed in the Health Canada 'queue' for approval. It should be noted that, to date, some of the cases analyzed are still pending an approval decision. For this reason, the cases are described quite generically in what follows – all companies requested that their cases be treated confidentially.

The case studies were selected from among several companies in the Canadian Animal Health Institute. Anonymity of the product and manufacturer is retained throughout this report; for identification purposes each case is assigned a verification number, for example 'Case 1'.

A series of questions was developed as a guide for the interviewers (see Appendix A), i.e., a structured survey was not used. Interviews were conducted with staff from animal health product firms by George Morris Centre research staff.

#### *Estimating the Economic Impacts*

There are three types of loss accounted for when the economic impacts were estimated in each of the cases: direct losses, downstream losses and more general impacts to the Canadian economy. Each type is explained in the bullets below<sup>17</sup>.

- *Direct Losses to the Company:*
  - The cost of providing additional data and information for Canadian regulators; i.e., information/data that were not anticipated or required for other jurisdictions' approvals.
  - Lost market potential due to the delayed approval decision. When estimating the lost market potential, the net present value<sup>18</sup> was calculated from the estimated market losses every year the company waited for approval. In 2003, losses were estimated at present value. It should be noted that these calculations take into account the approval target of 240 days. Thus, the calculations of potential market losses start 240 days after the submission of an approval for each company. For example, if Company X submitted a product for approval in January 2000, potential market losses would begin to accumulate in September 2000.
- *Downstream Losses:*

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<sup>17</sup> It should be noted that there were several types of direct costs that we did not calculate as they were considered negligible in the big picture. One example is the opportunity cost to the company associated with sunk capital.

<sup>18</sup> A discount rate of 5% was used for the net present value calculations.



- Losses to the agriculture industry due to not having the drug available, including the potential loss of livestock and/or the loss in productivity.
- *Losses to the Economy:*
  - In some cases the cost of lost opportunities was estimated. For example, a company may have budgeted to hire new personnel specifically related to the drug pending approval. If the company was unable to hire the personnel as a result of the approval delays, the job losses were classified as an opportunity loss to the economy.

In estimating the economic impacts the following assumptions were made:

- When estimating the direct loss to companies, foregone sales are used. Ideally, foregone profits would be used, but the cooperating companies did not have profit projections. Profitability of these products could be highly variable, depending on whether they require new capital expenditure, and on a host of accounting procedures. For readers who want to think in terms of lost operating profits, experience suggests that profits on these types of products would range in the area of 7 – 30% of earnings before interest, taxes, depreciation and amortization (EBITDA).
- Each of the products reviewed would eventually receive approval.
- Industry losses occur when there is a delay in approval beyond 240 days. Note that VDD's administrative review standard is 180-days. However, 240 days was selected as a more reasonable expectation of approval. This review time corresponds with Australia's system, as Australia was shown in the previous section to be the fastest and most consistent at reaching their approval targets.
- The categories of loss described above cannot be added together to determine a total economic impact, as it would result in double counting. Specifically, part of the direct losses to manufacturers are measured by lost sales, while the losses downstream are measured as lost productivity. If the two values were added together, it would double count the loss because in order for industry to obtain the productivity gains they must purchase the product from the manufacturer. By purchasing the product, the manufacturer no longer experiences the loss in sales.

To estimate the economic impacts (direct, downstream or economy), compounded net present value calculations were used with a 5% discount rate. Equation 1.0 below illustrates the calculation used in this analysis. The value of *X* in the equation can be interpreted several ways. For example, it can be interpreted as losses to the company (e.g., lost sales), agricultural industry losses (downstream impacts), or losses to the economy (for example research opportunities) depending on the calculation being analysed.

Equation 1.0:

$$TL = \frac{X_n}{(1.05)^{-n}} + \dots + \frac{X_1}{(1.05)^{-3}} + \frac{X_2}{(1.05)^{-2}} + \frac{X_3}{(1.05)^{-1}} + X_4.$$

Where:

- TL is the sum of  $X_n \dots X_4$  and estimates the total loss
- X is the estimated present value of the loss
- n represents the year the estimated loss would have occurred
- negative exponent in the denominator represents the number of delayed years
- $X_4$  is the estimated losses for 2003 (present value).

As an example, suppose a company submitted a new drug submission (NDS) to the Veterinary Drugs Directorate in April of 1998. Based on the application submission date and an expected approval time of 240 days (8 months), the company could expect their product to be approved and would prepare for market penetration in January of 1999. If approval were not obtained until December 2003, losses would accrue each year the company did not receive approval (since 1999). Using the equation above for our example, in 1999 (the first year of losses) the value of lost sales would be represented by  $X_n$ . The negative exponent in the denominator would have the value of four, the number of years that the losses have been accruing. The value of  $X_1$  is the lost sales for the marketing year 2000 and 'n' in this case equals negative three. This process is repeated for each of the years, with  $X_4$  as the lost sales in 2003 (present value). The sum of each X value equates to the total losses (in present value terms) from not obtaining product approval in January 1999.

The following sections summarize the interview discussions and resulting economic impacts for the five drug products.

### 3.3.2 Case Study Results

Three of the five cases conducted by the George Morris Centre are products for the commercial livestock industry, while the remaining two are for companion animals. Each of the cases is summarized below to provide:

- An indication of the length of time until an approval decision was made (or, how long to date when a decision has still not been made)
- A brief description of the reasons for approval delays
- Estimates of the resulting economic impacts (direct, downstream, or impact on the economy).

Participating companies are very concerned about confidentiality. This concern stems in part from the normal business desire to not signal competitors about potential new products and a desire to maintain a good working relationship with VDD. For this reason, no details are given in the analysis of cases about the products or the dates of

application and approval. In addition, none of the detail of actual events of the individual cases is provided.

*Length of Approval Delays*

For each of the five cases, significant delays occurred in the amount of time required for approval. The table below illustrates the number of months that elapsed (to date, in some cases) beyond the 240 days (8 months) required for approval.

<b>Product</b>	<b>Delay in Approval Time</b>
1	36 months (1,080 days)
2	50 months (1,500 days)
3	134 months (4,020 days)
4	37 months (1,110 days)
5	60 months (1,800 days)

*Reasons for Approval Delays:*

Throughout the cases, the impacted companies identified a number of reasons for the delay in their product approval. These examples have been listed below in no particular order:

- **Employee problems within the VDD**
  - In the mid to late 1990's and in early 2000, delays in product approval were linked to a particular employee (reviewed product submissions) fighting with the managers. In addition, there were rotating directors and a lack of management guidance within the VDD.
- **Lack of communication between divisions and case files.**
  - Information that was required for a submission was available in another division of VDD, but was not made available to the reviewer. The VDD reviewer needed to cross-reference information from a previously submitted human safety file. The review was held up as a result of not being able to access the human safety file.
- **VDD misplaced information/data and required resubmission.**
  - The company was requesting approval for a product that was a new formulation of an already approved product. VDD indicated they lost the data from the original approval and that the company would have to resubmit it.
- **VDD requested additional “new” data and information.**
  - Many companies noted requests for *unexpected* new data, information or further testing.

- **VDD requested additional research studies not required for approval in other countries.**
  - It took 17 months from the original submission for VDD to indicate they needed additional efficacy data that would require a major clinical study. It should be noted that this clinical data was available from the clinical trials completed in another country, but VDD required a new study to obtain Canadian data.
- **Emerging antimicrobial resistance (AMR) issues.**
  - As AMR became an emerging issue of concern with consumers and government, companies found their product submissions were further delayed if their product was classified as an antibiotic.
- **VDD re-evaluated research in the submission file that had been previously accepted.**
  - Research submitted for the approval had been accepted. Several years later during the review process, additional time was taken by VDD to review the research once again.
- **Company changed the composition of an inactive ingredient of a previously approved drug and VDD required resubmission as a new drug.**
  - Required significant amounts of new data and testing.
- **Lack of communication from VDD for extended period of time.**
  - A 36-month period lapsed during which no contact was made from VDD to the Company, until an information request was made almost three years after the original submission.

These delays among others have resulted in significant economic impacts. The following is a brief description of the direct losses to the companies, downstream impacts to the agriculture industry and impacts to the economy that resulted.

#### DIRECT LOSSES

Company 1 incurred direct costs totalling \$21.6 million, which were the result of lost potential sales, and facilitation costs.

- The first direct cost resulting from the delay in Product 1's approval was approximately \$276,282<sup>19</sup>. These costs were the result of Company 1 having additional expenses for consultants over a four-year period to provide advice and facilitation to aid in the approval process between Company 1 and VDD. Additional internal costs for continued activities with this file have not been quantified.

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<sup>19</sup> Assumes \$50,000 in consultation fees compounded each year starting in 1999.

- Product 1 was approved in the United States in 1998. As a result, Company 1 estimated a two-year delay for the product to reach the Canadian market, and estimates they have been losing sales since 2000. Company 1 estimated that it would capture 15% of this segment of the Canadian market and estimates total lost sales of \$20 million over the last four years. These losses were estimated at \$3.8 million, \$4.8 million, \$5 million, and \$6.4 million for each consecutive year on the market. The net present value of Company 1's estimated market losses is \$21,340,975.

Company 2 estimated a total market potential of \$8 million in Canada, of which, 20% would be captured in the first year, 30% in the second year, 40% in the third year and 50% thereafter. The net present value of their estimated market losses was calculated at \$11.9 million.

Company 3 incurred direct costs totalling \$19.5 million, the result of lost potential sales and a safety study requested by VDD.

- The first direct cost resulting from the delay in Product 3 approval was approximately \$90,000. This represents the value of an additional safety study requested by VDD.
- Company 3 also incurred direct costs totaling \$19.4 million, which were the result of lost potential sales. In 1992, Company 3 submitted information to VDD regarding efficacy and safety testing for Product 3. Company 3 assumed that after this submission the approval would proceed as normal and within a reasonable approval period (~240 days). Therefore, Company 3 expected to begin marketing the product in the later part of 1992, and has incurred lost sales since then. Company 3 estimated that Product 3 would have captured 10% of the market for the first three years and 17.5% thereafter. Company 3 estimated the market for this drug at approximately \$9.5 million in Canada, but indicated the market shrank to \$7 million in 2002. The net present value of Company 3's estimated market losses is \$19.4 million.

Estimating the direct losses for Company 3 is a precarious situation because there were six years where the company did not actively pursue approval of their drug. This was due to frustration with the review process, as Company 3 did not agree with VDD's decision. At this time, there was no avenue for Company 3 to appeal the decision, so they opted not to pursue the drug approval.

Company 4 incurred direct costs totalling \$3.38 million, which were the result of additional data requested by VDD and lost potential sales.

- Company 4 incurred direct costs totalling \$37,500 resulting from labour<sup>20</sup> costs required to compile additional data requested by VDD.

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<sup>20</sup> Labour costs have been estimated at \$37,500, the midpoint of the range of losses (\$25,000-\$50,000) provided by Company 4 during the interview.

Company 5 incurred direct costs totalling \$19.8 million, which were the result of lost potential sales and an additional clinical study requested by VDD.

- Direct costs incurred by Company 5 include the additional clinical study requested by VDD when clinical data was available from research completed in another country. This cost totalled \$66,911 (\$57,800 (study cost) compounded over three years).
- Company 5 estimated potential sales for this product at \$1 million, \$1.7 million and \$2.5 million for the first three years on the market, followed by approximately \$6.75 million in sales every year after. The net present value of their estimated market losses is \$19,777,219.

## DOWNSTREAM LOSSES

The costs to the agricultural industry for the five cases analyzed stem from the losses in efficiency and productivity resulting from not having the drugs available for use.

Company 1 conducted studies that illustrate a decreased incidence of a livestock disease in calves treated with Product 1 compared to drugs that are currently available. These studies show that there is a substantial loss in cost savings of not having this drug on the market. The cost savings per calf equals approximately \$12.50 (changes with yearly exchange rates). If all Canadian farmers were to treat cattle that become infected with this disease, and if Company 1 captures 15% of the market as it has estimated, the net present value of the lost cost savings since 2000 equals \$7,832,002.

Product 2 enhances the productivity of food animals. The estimated per year loss to the industry of not having access to this product was calculated by determining the value of the increase in efficiency and multiplying these savings by the gross margin per unit. Given Company 2's estimated market share of 45%, savings were calculated at \$19.3 million. The net present value of this loss in efficiency gain (during the period Company 2 has been waiting approval) to the industry equates to \$83.2 million.

Product 3 is an antibiotic for the livestock industry that can be used to treat a number of common ailments. This type of drug is not new to the industry; in fact there are numerous other drugs that treat the same ailments. For these reasons, it was not possible to estimate the impact to the agricultural industry of not having Product 3 available. The true benefit of Product 3 is qualitative in that it causes minimal reaction to the animal around the injection site.

Because Product 4 is intended for use outside of livestock agriculture, it is difficult to estimate a dollar value of the cost to the industry of not having the drug available. As a result, impacts to industry can only be described qualitatively.

Product 4 is a treatment drug and there are no similar drugs available on the market. However, a black market for this type of medication has developed which consists of

'compounds' of active ingredients found in human medications that have been altered for animal use. Due to the inconsistency of these compounded drugs, there is little uniformity in treatment length and dosage. The primary advantage of Product 4 will be cost savings from fewer veterinarian visits and a faster return to training/performance due to the availability of a consistent and reliable drug.

Because Product 5 is a drug intended for companion animals, it is difficult to estimate a dollar value from the impacts of not having the drug available. As a result, impacts to industry can only be described qualitatively.

The costs to pet owners of not having this drug available include increased veterinarian visits and the monetary and mental costs of the possible death of companion animals.

### LOSSES TO THE ECONOMY

Company 1 downsized its labour force<sup>21</sup> by two account managers and two sales representatives, for an opportunity loss to the economy of \$191,570. In addition, Company 1 had originally planned to hire other new staff as a result of Product 1.

No attempt was made to assess the impact of the loss of time under the patent for the compound.

If Company 2 had received approval for Product 2, it was expected that they would do further research. Their research expectations were in the range of \$500-1,000,000, and have been estimated at a loss to the economy of \$868,219 (\$750,000 compounded from 1999).

Company 4 expected to hire two senior level staff (salaries of \$150,000) and eight junior level staff (\$60,000 per year) that would have been required with the approval of this product.

### 3.3.3 Case Study Summary

Table 3.1 summarizes the economic impacts of VDD not approving these five products in a timely fashion in Canada. These impacts include direct losses to companies, downstream losses to the agriculture industry and losses to the economy.

Recall from the discussion of methods that the columns in the table cannot be added together to determine a total economic impact resulting from the five cases analysed. Individual categories (direct, downstream and economy) have been added across the cases to demonstrate the total direct losses (to companies) of \$75.9 million, downstream losses to the agriculture industry of \$91 million and losses to the Canadian economy of \$1.8 million resulting from the five cases.

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<sup>21</sup> There were also additional direct losses that could not be quantified (for confidentiality reasons) that pertained to the severance packages provided to those employees that lost their jobs.

We note again, that in the cases of the products for companion animals, the injury cannot be measured in economic terms. Thus our estimates are conservative.

**Table 3.1 Summary of Total Economic Impacts**

<b>CASE</b>	<b>Direct Costs</b>	<b>Downstream Impacts</b>	<b>Impacts to Economy</b>
Case 1	\$21,617,257	\$7,832,002	\$191,570
Case 2	\$11,858,200	\$83,158,474	\$868,219
Case 3	\$19,493,313	N/A	N/A
Case 4	\$3,038,750	N/A	\$780,000
Case 5	\$19,844,130	N/A	N/A
<b>Total Economic Losses</b>	<b>\$75,851,650</b>	<b>\$90,990,476</b>	<b>\$1,839,789</b>

Throughout the case studies there were consistent problems identified by several of the case study companies. The following is a list of the common observations (Note that these are the opinions from the case companies, not the authors of this report):

- The divisions within VDD did not communicate.
- Reviewers bear no accountability for questions asked or research requested:
  - Do not have to justify on a scientific basis for additional tests.
  - There is no third party appeal mechanism that industry can use to question review requests for additional data that industry thinks unwarranted from a safety and efficacy standpoint (This comment was noted prior to the December 2003 blueprint for appeal mechanisms in Canada).
- VDD consistently “changes their mind” on requirements, i.e., data or information requests.
- VDD specifies a requirement for research but also approves the research design at a fee.
  - This is a conflict of interest
  - The Canadian regulator has become the “judge and jury” with a cost at each stage
  - Cost recovery, as it is carried out in Canada conveys a perverse incentive to the regulatory body
- Canadian product approvals are often considered a last resort after all other country approvals have been obtained.
  - Approval process in Canada is thought of as cumbersome, expensive, time consuming and represents only one tenth of the product market.
  - Canada’s questions can delay approvals for larger markets elsewhere.
- VDD is inconsistent as to when they will use product trial data from other countries in reviews.
- There has been a significant reduction in research and development within the Canadian divisions of the companies.



- Canada's product approval process and personnel are risk adverse to product approval and technological advancement.
  - Young reviewers in Canada are passing off regulatory responsibility (i.e., indecisive about making a decision) to academics.
- Canada is not spending enough time updating their Maximum Residue Limits. Since this statement was identified, VDD has established 17 more MRLs/AMRLs, for a total of 67 in 2003. VDD projects a total of 180 MRL's/AMRL's by mid 2004 (VDD, 2003).

## **4.0 Designing an Optimal System**

Section 4.0 describes the methods used to obtain information for the development of an optimal product approval system. Specifically, section 4.1 describes the focus group process and section 4.2 describes the results from the day. Section 4.3 puts the information into perspective and identifies potential solutions for a 'tough but fast' Canadian system.

### **4.1 The Focus Group**

One of the intentions of the study was to provide direction on how to improve the current procedures so they are aligned with an optimum 'tough but fast' policy. This was accomplished through a facilitated focus group session.

On Thursday, April 10, 2003 the George Morris Centre facilitated a focus group discussion in Toronto to develop an 'optimal' regulatory system for Canada's animal drug product approval. The focus group brought together key members of the industry (industry personnel, producers, veterinarians and government) to help identify and develop the basic requirements for an optimum 'tough but fast' system in Canada. The following is a list of the organizations that attended the focus group session:

#### *Industry*

- Canadian Animal Health Institute
- Elanco Animal Health
- Novartis Animal Health Canada Inc.
- Bayer Inc
- Boehringer Ingelheim (Canada) Ltd.

#### *Producers*

- Canadian Cattlemen's Association
- Canadian Poultry and Egg Processors Council

#### *Veterinarians*

- Linwood Veterinary Clinic
- Feedlot Health Management Services

#### *Government*

- Canadian Food Inspection Agency
- Unfortunately Health Canada declined the invitation after repeated requests.

#### *Facilitation*

- George Morris Centre

The day began with a background presentation to provide participants with information on the regulatory approval systems in the United States, European Union, Australia and

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Canada. Discussion surrounding the perceived problems with the Canadian system and a Canadian product submission case study were also presented.

Following the presentations, the participants were asked to separate into groups to brainstorm and provide ideas for an optimal Canadian system. A workbook was provided that contained questions with respect to the Canadian product approval system. Participants were also given a matrix of information of the key points from the regulatory systems of each of the countries discussed in the opening presentation (see Appendix B).

There were six areas that the George Morris Centre identified as discussion areas. The questions were developed to determine if the objectives of the Canadian legislation were appropriate, whether the procedures for market approval, applicant tasks and costs and incentives were appropriate, and whether the Canadian system was transparent and consistent. The following are the specific questions used in the focus group discussion:

1. Objectives of the Legislation

Are the current objectives of Canada's legislation appropriate? Does the legislation require adjustment? If so, what should be added or removed?

2. Procedures for Market Approval - What the government requires for product approval, for example, efficacy, food safety, manufacturing and compliance. The 'procedure' is the submission containing details on manufacturing, quality control, residue and clinical studies.

Are the procedures for market approval appropriate? What, if anything, should be added or removed?

3. Applicant Tasks – The specific tasks required for approval. For example, submitting application, fees, and data from clinical studies.

Are applicant tasks clear and consistent? If not, how can the tasks be improved?

4. Costs and Incentives

Is the cost structure appropriate? If not, how can the government be made accountable for industry expense? What incentives can be put in place to make the Canadian system more efficient?

5. Transparency

Would you say the current system lacks transparency? Why? Can it be transparent with the variety of science that must be addressed for approvals? What is required for a transparent Canadian system?

6. Consistency

Would you say the current system lacks consistency? Why? Can it be consistent with the variety of science that must be addressed for approvals? What is required to ensure regulatory consistency?

7. What are the perceived costs and benefits of the system you designed?

Dr. Larry Martin (CEO) and Cher Brethour (Research Associate) from the George Morris Centre facilitated the 'optimal' product approval discussion. The next section describes the results from the focus group discussion.

#### **4.2 Results of the Focus Group Discussion**

The following is a synopsis of the brainstorming from the focus group session for each of the questions identified above.

##### 1. Objectives of the Legislation

When asked if the objectives of the Canadian legislation were appropriate, the consensus from the group was that they were, but the real problems were with the regulations, not the legislation specifically. However, it was agreed that if the following were included in the legislation, the system would function more efficiently.

- Establish/publish Maximum Residue Limits at Notice of Compliance
  - Without Maximum Residue Limits set by Health Canada, any amount of residue from a drug can be identified as a problem or cause for concern. As technology improves, more and more residues can be detected, i.e., it is now possible to detect residues at levels that could previously not be detected. If there is no MRL established at notice of compliance, any residue is considered a problem. This will hinder trade.
  - Establishing MRL's will protect and facilitate trade.
- Separate the companion animal and food animals in the legislation

##### 2. Procedures for Market Approval

The following processes were identified as being fundamental for an optimal, efficient and fair system in Canada.

- Pre-submission meetings.
  - To determine specific requirements for the application in advance. The meetings may also serve as an opportunity to discuss the types of data required and testing or laboratory procedures to be used.
  - Being able to identify as an applicant what will be usable in the submission when designing trials.
  - The intent is to involve the reviewer at an early stage of the process.
- Independent appeal process for all stages of the review.

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- The applicant has the ability to appeal scientific decisions made at any stage of the submission through a tiered process that would include independent arbitrators.
  - Politics or the precautionary principle should not be a part of the approval process.
  - Human Resource management.
    - Ensuring that there is enough qualified staff at Health Canada (specifically Veterinary Drugs Directorate) whose primary function is reviewing submissions.
    - Minimize how often review staff are pulled from their jobs to work on other projects.
  - Harmonization of approval process.
    - At a minimum accept reviewed studies from referenced jurisdictions.
    - Share comment notes from reviewers in other jurisdictions – onus would be on the sponsor.
      - May require a Memorandum of Understanding.

### 3. Applicant Tasks

The following suggestions were made to improve the application process for Canadian submissions to make them more clear and consistent.

- The approval systems should be based strictly on evidence based science.
  - Develop a decision tree to make scientific decisions.
- Industry training on regulatory issues, and regulatory training on industry issues.
  - Better understanding and trust for users of products and industry.
- Current guidelines and policies.
  - Joint consultations --- consistency for both industry and reviewers.
  - Since the focus group in April 2003, VDD has developed four “Guidance for Industry” documents published on the VDD website January 13<sup>th</sup>:
    - Preparation of Veterinary New Drug Submissions.
    - Preparation of Veterinary New Drug Submissions: Clinical Safety and Efficacy Requirements.
    - Preparation of Veterinary New Drug Submissions: Human Safety Requirements.
    - Preparation of Veterinary New Drug Submissions: Manufacturing and Quality Control Requirements.

(VDD Guidance for Industry, 2003)

#### 4. Costs and Incentives

The following points were identified to make the cost structure for product approval more efficient.

- Fees should be consistent with VDD performance delivery, industry market size and competitive with regulatory programs in developed countries that Canada competes with.
- Health Canada reviewers performance should be measured against the objectives of the Business Coalition on Cost of Recovery<sup>22</sup>.
- Phased payment for phased reviews.

The following points were identified to make incentives for product approval more efficient.

- Better connections between government and industry.
  - This includes but is not limited to, pre-submission meetings, annual meetings, global regulators, and corporate reviews to identify new technology.
- Clear performance targets and standards set with objective reviews by Health Canada management staff.
- Performance tracking to monitor adherence to the standards.

#### 5. Transparency

When asked if the Canadian system was transparent, the consensus among the group was that it was not. The following ideas were provided to help improve transparency:

- A submission tracking system similar to the Therapeutic Products Directorate.
  - One spokesperson in each review bureau responds to requests concerning submissions. Manufacturers fax or email their status requests to the contact person who is then obligated to respond within 72 hours.
  - Applicants should have a system to check the status of their submission by using a login and password on the Internet.
- Develop standard operating procedures for regulators and reviewers.
- Performance targets and regular reporting.
  - Develop a set of clear performance targets and standards with objective reviews by management.
- Performance information on products made accessible.
  - Generate report cards on products that are made public.

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<sup>22</sup> The Business Coalition on Cost Recovery (BCCR) was founded in 1998 to address user fees as part of the government Cost Recovery Program. The BCCR includes over 20 of Canada's leading business organizations representing large, medium and small businesses in a diverse range of sectors of the Canadian economy. The combined membership of the Coalition employs over 2.2 million Canadians and is directly responsible for over \$330 billion in economic activity annually.

- Access by users to data and information about products, e.g., veterinarians can obtain information on products.

## 6. Consistency

When the group was asked if the Canadian regulatory system for product approvals was consistent, the group felt it was not. The following ideas were provided to help improve consistency:

- Have consistency across regulatory agencies. The same type of information and standards should be used in all jurisdictions, for e.g. Canada could become part of the international harmonization effort of VICH.
  - VICH – International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products. It is a trilateral programme (EU-US-Japan) aimed at harmonizing technical requirements for veterinary product registration. The program was officially launched in 1996 and Canada's current status is as an 'observer'.
    - Since the focus group in April 2003, VDD has adopted and made effective (on November 1, 2003) 27 VICH guidelines for Canada (VDD VICH Website, 2004).
- Knowing what will be usable in the submission when they are designing trials.

## 7. Perceived Costs and Benefits

The following is a list of the perceived costs and benefits of the 'optimal system' designed by the focus group participants:

- Less costs from the increase in throughputs of products.
- Trade issues would be avoided with resulting user benefits.
- Overall increase in food safety.
- With more assurance and availability of products animal welfare would improve from healthier livestock and reduced mortality.
- Predictability in investment and staffing decisions for industry submitting applications for approval.
- Research and Development incentives for Canada if the system is tough but fast, an example might include a tax credit system amenable to Research and Development.
- Develop image of Canada as a great place to do research. The industry is small enough to evoke change and there is already the skill set and facilities in place.

### **4.3 Summary of Focus Group**

The purpose of the focus group was to bring together key members of the industry (industry personnel, producers, veterinarians and government) to brainstorm and develop improvements to the current approval procedures so they are aligned with an optimum 'tough but fast' product approval system in Canada.

The focus group session and questions drew out several recurring concerns about the Canadian regulatory system. The most noticeable was the need for pre-submission meetings and an appeal process or dispute mechanism. It is believed that pre-submission meetings will allow applicants to ask questions, prepare more appropriately for the submission (which could speed up the process) and help to make budgeting decisions as a business. It was also expressed that a third party appeal that is applicable throughout the decision process, would allow applicants the opportunity to express their concerns with decisions.

Participants also felt strongly that harmonization of regulatory approval processes in Canada (e.g., VICH) would prevent applicants from having to 'reinvent the wheel' for Canadian submissions. This would also increase the likelihood of research and development in Canada. Another suggestion to speed the review process was to share the regulatory review comments that were already generated by countries that had already approved the product.

The final suggestions all related to the submission review. Participants felt strongly that decisions should be based on evidence-based science and that the influence of politics and the precautionary principle should be left out of the review process. It is understood that in some circumstances politics may be a factor in the final approval, however, politics should never impact the *reviewer's* recommendations.

It was also noted that there continues to be staffing concerns within Health Canada. There is concern that there is not enough reviewers and that those that are reviewing are not following a standard operating procedure. The last suggestion was that a submission tracking system be put in place to allow applicants the ability to track the status of their submission. This would enable companies to keep track of their submission and to make business decisions accordingly.

Finally, it was felt that a Maximum Residue Limit should be assigned at the 'Notice of Compliance' stage, to protect Canada's trade position.



## **5.0 Conclusions and Recommendations**

There were two key purposes to this project:

1. Identify the impact of Canada's product registration system on companies operating in the animal health products industry in Canada, and ultimately, determine the economic cost to the agri-food sector and the Canadian economy imposed by this system; and
2. Offer some alternative, potentially "optimum," solutions to the system and identify the costs/benefits of such a system.

The specific objectives are as follows:

1. To describe, compare and contrast the agriculture product approval systems in the United States, Australia, European Union and Canada with respect to the governing authority, structure and responsibility, marketing approval, applicant tasks, fees, time to approval and performance indicators.
2. To estimate the direct loss to companies, downstream losses to the agriculture industry and losses to the Canadian economy resulting from delayed product approval for five case study products submitted to the Veterinary Drugs Directorate for approval in Canada.
3. To develop recommendations based on the above analysis for improvements to the Canadian system.

Below are the summary and conclusions from this study.

### **5.1 Summary and Conclusions**

Regulatory systems, almost by definition, impose costs on the private sector. Their major intent is to require people to do things in the public interest that might not be done absent the regulation. As a result, they may be viewed as extra costs imposed by society, that society is willing to pay to manage risks.<sup>23</sup>

Thus, the economic impacts about which society should be concerned in a regulatory system are inherently "comparative" or "relative" – i.e., one always asks, compared to what or whose regulatory system? Underneath this is the fundamental question, is this regulatory system doing an efficient and effective job of managing the risks to society? It is not possible to answer this question in absolute terms because to do so would require knowledge of the "perfect" system, against whose costs we could compare the Canadian system. The perfect system for product registration is not known.

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<sup>23</sup> Of course, if the regulatory system prevents poor products or practices from occurring, then the "costs" may be short term in nature, compared to the long-term costs that would have arisen absent the regulatory system.

However, by attempting to understand the structure and performance of product registration systems in other countries, our intent in this project was to provide a general comparison. Many Canadians tend to compare our systems with the US. This is quite relevant in this case because of the close links in products and in the markets of the downstream livestock and meat industries. In this study, we undertook a rather detailed description and comparison of performance of the animal product registration systems in the US and Canada. We also examined the systems in the European Union (EU) and Australia. The EU was chosen because it is one with which many companies deal who are also involved in the Canadian market, and one that provides access to a potentially large market for animal health products.

Australia was chosen because, like Canada, that country represents a relatively small market. In addition, preliminary research indicated it made major structural changes to its product registration system a few years ago. Therefore, it seemed a likely candidate to provide some lessons.

Examining the structure and performance of the alternative systems, which is done in section 2.0 and responds to objective one, provides a number of interesting insights:

- There are substantial structural differences in the systems among the countries. For example, in some the intent of the legislation that creates them is to protect health. In others, it includes a health protection component, but also has objectives that relate to trade, thereby requiring regulators to explicitly consider the balance.
- Other structural differences in the systems (among the countries) include internal disciplines designed to facilitate approval processes.
  - For example, until recently there was no appeal mechanism in Canada during the application process or once the drug decisions were made, but they exist in other systems. In December 2003, a blueprint for appeals was published by VDD; however, it is not an *independent* appeal mechanism as requested by industry. There still remains a need for an independent dispute mechanism.
  - For example, there are no mandatory pre-submission meetings (as in the EU) for applicants to get an understanding of what is required prior to submission. It should be noted that these problems refer to the Veterinary Drugs Directorate, not the Veterinary Biologics Section (VBS). The VBS does have set performance standards, generally meets performance standards and tends to be transparent and consistent in delivery of its services.
- At least one country, Australia, has taken a benchmarking approach in one component of its product registration process (pesticide registration) and has been named “world’s best practice” by reviewers. One review of the Australian system indicates that, in addition to superior performance in terms of time to

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make a decision, its openness and transparency have additional advantages:

- There was improved industry compliance with registration requirements due to better information and feedback;
  - Decisions about active constituents and chemical products were made within statutory framework;
  - Registered products in the marketplace meet legislative requirements for performance and safety due to sound decision-making.
- There are substantial differences in fees charged by regulators. Canada's is among the highest, especially per unit of market access that can be gained.
    - Some progress has been made regarding Canadian fees through Bill C-212, a private members bill (passed unanimously through the House of Commons in September 2003 and will likely go to Senate in February 2004 for consideration). The bill would require fee-charging federal departments and agencies to consult with stakeholders prior to establishing a fee; show that a clear private benefit is linked with the fee; establish an independent resolution system; and, set performance standards in exchange for the fee charged. The Bill would also provide fee reductions when performance standards were not met.
  - There appears to be greater unanticipated delays in the approval system in Canada than in the other comparators.
  - Total elapsed time until a decision is made is the slowest in Canada, by a wide margin. It is understood that, since the commission of this report (January 2003), there has been an effort on the part of the VDD to improve this situation but more improvements are needed to make this a world-class regulatory environment.
    - The Canadian system, like the US, makes no commitment about time of approval decision and does not adhere to its internal administrative standards.
      - Canada has an administrative or "provisional" standard of 180 days.
      - US currently have a 180-day provisional standard. However, they have implemented the Animal Drug User Fee Act (ADUFA) in which the legislation will impose performance standards on the CVM that are expected to improve the drug approval process to 180 days, 90% of the time by 2008.
      - Australia aims to finish an approval in 240 days.
      - The EU attempts to complete an approval process in 210 working days, not including "clock stop" days.
    - Actual elapsed time until a decision was made in Canada is not related to the administrative standard.
      - Canada: exceeded its 180-day target 87% of time (2002).
      - US: exceeded its 180-day target 83% of the time (2002).
      - Australia: met its 240-day target 96.2% within timeframe (2001-02).

- EU: limited data, but in the last 3 yrs has generally been within its timeframe.
- It is important to acknowledge that Canada's system has undergone substantial change over the past few years, especially with respect to obtaining more resources, and all the results of those changes have not been manifested. Nevertheless, it is also true the data suggest that the time to make a decision continues to increase, except in some categories where a backlog could be cleaned up relatively quickly.

As one way of gauging the costs of the Canadian animal health product registration system, five case studies submitted to us by animal health companies were analyzed to estimate the costs (Section 3.0, Objective 2) imposed as a result of the additional time required to get to a decision beyond the best performer – i.e., Australia. Costs were categorized into direct impacts to the companies sponsoring the applications, indirect costs to the downstream industries, which are unable to source the product and its health benefits, and finally losses to the economy. The losses range from approximately \$76 million in direct losses to the participating companies, \$91 million in indirect downstream losses to the agriculture industry and \$1.8 million in losses to the economy. Note that the categories cannot be added together to determine a total economic impact, as it would result in double counting. Specifically, part of the direct losses to manufacturers is measured by lost sales, while the losses downstream are measured as lost productivity. If the two values were added together, it would double count the loss because in order for industry to obtain the productivity gains they must purchase the product from the manufacturer. By purchasing the product, the manufacturer no longer experiences the loss in sales.

We make no claim that the cases are a representative sample of what this industry faces in attempting to obtain product approval. Therefore, we know of no way to project the losses to an industry level. On the other hand, 90% of Canadian decisions are not completed within the timeframe set by the Directorate's internal guideline, and over 90% were completed within the time required by the Australian system. Therefore, while we cannot project the cost of the system to the agri-food industry level, it is clear that the losses are large. As indicated at the end of section 3.0, the issues uncovered by the case studies include:

- The divisions within VDD do not appear to communicate.
- Reviewers appear to bear no accountability for questions asked or research requested:
  - Do not have to justify on a scientific basis for additional tests.
  - No third party to appeal nuisance research requirements.
  - There is the need for a tribunal (this comment was noted prior to the December 2003 blueprint for appeal mechanisms in Canada).
- VDD reviewers have consistently "changed their mind" on requirements, i.e., data or information requests.
- VDD specifies a requirement for research but also approves the research design at a fee.

- This is a conflict of interest.
- The Canadian regulator has become the “judge and jury” with a cost at each stage.
- Cost recovery, as it is carried out in Canada conveys a perverse incentive to the regulatory body.
- Canadian product approvals are considered a last resort after all other country approvals have been obtained.
  - Approval process in Canada is thought of as cumbersome, expensive, time consuming and represents only one tenth of the US product market.
  - Canada's questions can delay approvals for larger markets elsewhere.
- There has been a significant reduction in research and development within the Canadian divisions of the companies.
- Canada's product approval process and personnel are risk adverse to product approval and technological advancement.
  - New reviewers in Canada are passing off regulatory responsibility to academics because they are indecisive about making a decision.
- Canada has not been committed to updating their Maximum Residue Limits.

These, the magnitude of losses in the case studies, and Canada's relatively poor performance compared to other jurisdictions suggest that the system imposes very high costs.

With the preliminary results of the foregoing as background, a group of industry, and government met to initiate the design of the characteristics of a stringent, yet timely product registration program for Canada. The group came up with a lengthy and detailed set of characteristics organized around the following headings that are presented in Section 4.1 (Objective 3):

- Objectives of the Legislation
- Procedures for Market Approval
- Applicant Tasks
- Costs and Incentives
- Transparency
- Consistency
- Perceived Costs and Benefits

While the foregoing are discussed in detail in section 4.0, one conclusion arrived at by the assembled group is inappropriate given subsequent information. That conclusion is that the underlying legislation does not need to change. Subsequent work by Rainnie and the Environmental Commissioner (described below) reveals what was already becoming evident to the Centre through a number of anecdotal observations – the problems are not just in approvals of animal health products.

**As Rainnie and the Environmental Commissioners reports show below, the problem is widespread in approval of plant health products, and in approval of consumer (companion animal) products.**

A similar frustration in the pesticide approval and regulatory system was highlighted in the most recent report of the Commissioner of the Environment and Sustainable Development released in October 2003 (Office of the Auditor General, 2003). The report contains a number of criticisms of the Canadian Pest Management Regulatory Agency (PMRA) and its approval processes. A number of these criticisms resemble those that were uncovered in this investigation of the approval processes of VDD within Health Canada. The major findings contained in the section on pesticide regulation focus on the inconsistent framework for registering pesticide approvals, the inability of PMRA to meet its own decision and approval targets for new pesticides as well as minor use pesticides, and the human resources issues that have caused problems within PMRA similar to those within the VDD.

The inconsistency in the framework for registering pesticide approvals is very similar to the inconsistencies in the processes at VDD. The Environmental Commissioner notes that in some cases steps were skipped, but in others a substantial amount of additional information was requested. The conclusions of a comparative study conducted by D.J. Rainnie at the Atlantic Veterinary College agree (Rainnie, 2002). Their study compared the regulatory requirements of the Centre for Veterinary Medicine (CVM) in the United States to VDD with respect to drugs for use in companion animals. Rainnie concluded that although the regulatory requirements for both agencies are essentially the same, the CVM documents that lay out the requirements are more specific, numerous and detailed and therefore are less open to interpretation and resulted in more consistency in CVM reviews. The inconsistency in reviews at VDD found in the case studies during this investigation highlights this finding from Rainnie's report.

Rainnie's report also highlighted that the CVM was more formally standardized and less flexible in all processes throughout the approval process. Therefore, quality control and consistency in the approval process was always higher in CVM when compared to VDD. Rainnie also found that the review process at CVM to be team oriented, but at VDD it was more individualistic. This highlights our finding regarding the human resources issues at VDD and their capacity to prolong the approval process. Finally, Rainnie found that the interpretation of data from the field studies was generally the same in both agencies. This finding should encourage more collaboration between the two agencies thereby reducing any recreation of field data and reducing the amount of time required during approval decision process.

Overall, Rainnie's report (2002), the Report from the Environmental Commissioner (2003), and this study illustrate that the product approval process in Canada, in more than one industry, requires reform so that Canadian industries can continue to remain competitive.

When one views the entire product approval system, one is left with the impression that it is out of the control of Parliament. The legislation and regulations have been developed piecemeal. There is no – or very little - reference to any economic or trade objectives of the legislation. Product reviewers, therefore, do not balance the narrow

concept of risk prevention with the promotion of innovative advancements in health methodologies and products. By the same token, there is very little in the legislation that allows the public, though Parliament and its organizations such as the Auditor General, to hold regulators accountable for the economic consequences of their decisions -or non-decisions. At a time when government says it wants to increase “value adding”, “productivity” or “technology”, it must put regulatory processes in place that are consistent with its intents.

Therefore, our recommendation below goes farther than did the participants (in Section 4.0) in the process for this project.

## **5.2 Recommendations**

This study documents in a systematic way the issues with and improvements made by the animal health product approval system in Canada. Despite the changes made to date (which was well documented in the Director General's presentation to CAHI's annual meeting in June 2003 (Kirkpatrick presentation slides at CAHI Annual Meeting, 2003)), gains in review times have not yet resulted and costs remain high. Anecdotally, we are told that some companies increasingly choose not to bother registering products in Canada, thereby depriving the downstream industries of economically valuable products. It also reduces the animal health industry's investment in Canadian research institutions.

**As a result of our participation in this study, it has clearly come to our attention that the entire agri-food sector is extremely upset with the product registration process in Canada. Work with a group of input supply industries this year resulted in substantial concern with plant product registrations, pesticide registration, vitamin and mineral registration in animal feeds, and even issues in the fertilizer industry. These issues from the “supply side” are echoed by farm organizations that are frustrated with the limited access to products available in competitor countries that are more effective, friendlier to animals and the environment, but are not available to Canadian customers. More recently, we were told by food processors that the issues on registration of inputs is word-for-word interchangeable with their problems in getting food products registered and labels approved.**

If all of this is as true for the other industries as it is for animal health, then the inescapable conclusion is that this is not just a problem with VDD. The attitude and actions that so clearly frustrate the animal health industry, is consistent with a general culture that has developed in the product approval bureaucracy.

Our recommendations come in two areas: first, what should be done to reform the system and what characteristics it should have; and second, what the process should be to make it happen.

### 5.2.1 Changes to the System

1. Parliament needs to change the legislative intent to include a goal of enhancing industry competitiveness as well as protecting animals, people and the environment. They are not in conflict – no company will gain economic advantage for long by abusing animals, people or the environment. In fact, everyone we know is looking for advantages by trying to do the right things, in part because it is perceived to be part of what most consumers want. Therefore, everyone will welcome an approval system that is tough but fast.
2. Parliament needs to extend this change across all product approval legislation, at least in the agri-food sector. The same problems occur for plant health, other input supplies and food labelling.
3. The system should:
  - Be transparent – applicants must be able to understand from the beginning what information is required to obtain an approval. Therefore, the regulatory procedures need to explicitly have clear guidelines for what is required of the applicant and what is required of the regulator.
  - Be consistent – the same things should be expected for a certain type of registration every time. The current system is full of arbitrary decisions by regulators that mean each application is a new adventure.
  - Have well-understood timelines. They should be measurable and enforceable. They should likely include a “stop clock” concept so that both sides are accountable.
  - Have clearly defined gates (e.g., specific issues dealt with separately, i.e. it should be clear what the procedures and decisions are for trade issues separately from efficacy, separately from health, environment, etc.).
  - Function on fact-based processes.
  - Be properly resourced by government, including optimum use of appropriate outside expertise.
  - Include independent appeal mechanism(s).
  - Develop appropriate benchmarks and metrics to measure its performance against objectives and compare to best in class.

### 5.2.2 Process for Change

The process clearly needs to pursue a number of efforts simultaneously:

1. Most fundamentally, CAHI needs to join forces with other segments of the agri-food sector to effect change since all are negatively affected by the larger system. This coalition also needs to get some form of consumer support for the principles. It needs to develop a united front and convince elected government to effect the changes.
2. Our experience is that the case studies are excellent vehicles to make the issues real for people who don't deal with product registrations every day. They clearly show the faults with the system and the frustrations that result. In addition, they



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provide a way to describe the magnitude of cost. A number of them need to be done in the other industries to assist in communication from a consistent framework.

3. In order to move forward, it is likely that the following initiatives need to be taken:
  - a. Contact potential champions among elected representatives to develop a strategy for convincing government of the need for change.
  - b. Contact the people in the “Smart” Regulation process to obtain their understanding and support (this has already started).
  - c. Bring together the affected industries in a series of conferences to establish common ground for the push to get change.

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## **APPENDIX A – Case Study Interview Question Guide**

### **Background on Company and Product**

1. What range of products do you produce/market.
2. Is the product we're discussing marketed or up for approval elsewhere?
3. Was the product we're discussing developed in Canada?

### **Activities in Seeking Approval**

1. At what point, internally, was the decision to seek Canadian registration made and action initiated?
2. At that time, did it appear clear what submissions would be required to obtain a Health Canada approval decision? Did they indicate the likely time period within which an approval decision would be made at the time it was initiated? Did they indicate a likely cost?
3. What materials were provided to Health Canada?
4. What time, effort and direct cost can be associated with the materials submitted to Health Canada?
5. Were other materials requested after the initial submission? How long after the initial submission was the request from Health Canada received? What time, effort and direct cost can be associated with these materials?
6. Was an approval decision made? What reporting was provided by Health Canada during the approval process? What reporting was provided at the time of the approval decision?

### **Product Approval Experience Elsewhere**

1. Where else have regulatory approvals been initiated for this product?
2. Has an approval decision been made in these jurisdictions?
3. Did the regulatory body indicate the likely time period within which an approval decision would be made at the time it was initiated? Did they indicate a likely cost?
4. What materials were provided to the regulatory agency?
5. What time, effort and direct cost can be associated with the materials submitted to the regulatory agency?
6. Were other materials requested after the initial submission? How long after the initial submission was the request from the regulatory agency received? What time, effort and direct cost can be associated with these materials?
7. What reporting was provided by the regulatory agency during the approval process? What reporting was provided at the time of the approval decision?

### **Conclusions**

1. What expectations did you have regarding the regulatory approval process in Canada when the product approval was initiated?
2. Did your expectations influence your decision to seek product approval?

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## **APPENDIX B – Application Assessment Timeline for New Drug Submissions**

## Application Assessment Timeline for New Drug Submissions

\*Days in all cases are business days, except EU where days are actual working days.

### Canada – Veterinary Drugs Directorate

Days



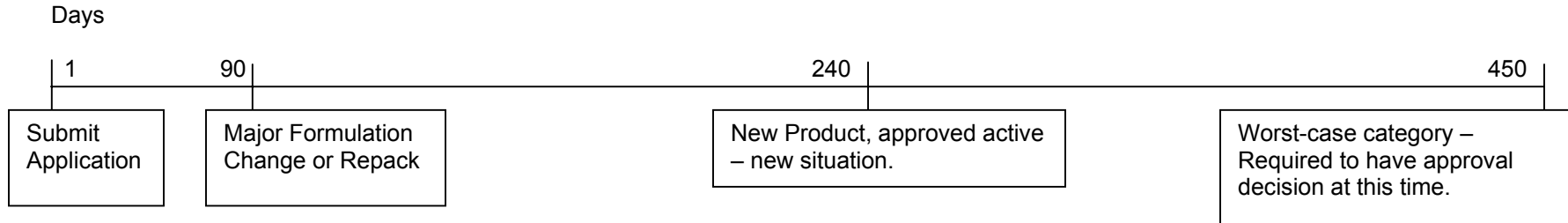
- The 180 days to reach a decision is an administrative standard and is not necessarily adhered to.

### The United States – Center for Veterinary Medicine

Days

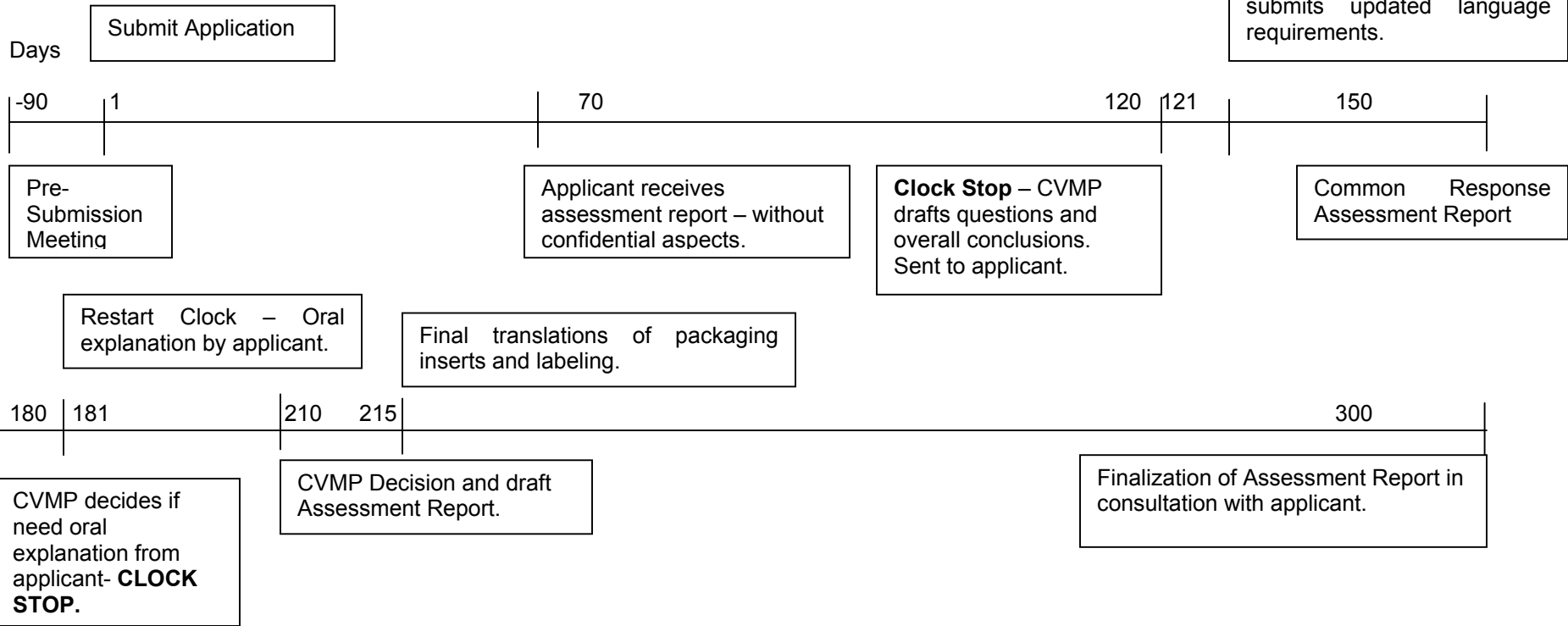


Australia – National Registration Authority for Agricultural and Veterinary Chemicals



The European Union – European Medical Evaluation Agency

Clock restart – (on 11 official days in year). Applicant submits updated language requirements.







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## **APPENDIX C – Regulatory Matrix: Agricultural Product Approvals**

Note: Acronyms are defined at the bottom of the matrix.

<b>REGULATORY MATRIX: Agricultural Product Approvals</b>				
Canada		Australia	US	EU
<b>OBJECTIVES OF THE SYSTEM</b>				
What	<ul style="list-style-type: none"> <li>Ensure drugs sold in Canada are safe and efficacious for animals</li> <li>Ensure safety of food for humans and animals</li> </ul>	<ul style="list-style-type: none"> <li>Establish openness and transparency in decision-making process</li> <li>Evaluate, register and regulate agricultural and veterinary chemicals</li> </ul>	<ul style="list-style-type: none"> <li>Ensure animal drugs are safe and effective for their intended use and that they do not result in unsafe residues in food</li> </ul>	<ul style="list-style-type: none"> <li>Contribute to the protection and promotion of public and animal health</li> </ul>
How	<ul style="list-style-type: none"> <li>Approved for sale if                             <ul style="list-style-type: none"> <li>Safe for animals and effective for purpose</li> <li>No harmful residues</li> <li>Manufactured according to specifications</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Must be satisfied that there is no risk to:                             <ul style="list-style-type: none"> <li>Consumers</li> <li>Administrator of product</li> <li>Environment</li> <li>Target animal/crop</li> <li>Trade in an agricultural commodity</li> </ul> </li> <li>Product must work effectively for specified use</li> </ul>	<ul style="list-style-type: none"> <li>Authorities include:                             <ul style="list-style-type: none"> <li>Approving NADA &amp; INAD applications</li> <li>Issue notices, proposals, orders to refuse to approve applications</li> <li>Approve certain food additives</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>By mobilizing scientific resources to provide high quality evaluation of medicinal products, advice on research and provide useful information to users and health professionals.</li> <li>By developing efficient and transparent procedures to allow timely access by users</li> <li>By controlling the safety of medicines for humans and animals and establish MRLs</li> </ul>
<b>PROCEDURES:</b>				
What	<ul style="list-style-type: none"> <li>Receive approval based on three components:                             <ul style="list-style-type: none"> <li>Efficacy</li> <li>Food Safety</li> <li>Manufacturing and Compliance</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Assess approval based on:                             <ul style="list-style-type: none"> <li>Safety</li> <li>Efficacy</li> <li>Impact on environment and trade</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>FDA approval on basis of:                             <ul style="list-style-type: none"> <li>Quality</li> <li>Safety</li> <li>Efficacy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Decisions should be based on:                             <ul style="list-style-type: none"> <li>Quality</li> <li>Safety</li> <li>Efficacy</li> </ul> </li> <li>Concerned to the exclusion of economic or other considerations</li> </ul>
How	<ul style="list-style-type: none"> <li>Submit 'New Drug Submission'                             <ul style="list-style-type: none"> <li>Contains details on manufacturing, quality control, toxicity, pharmacology, residue and clinical studies.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>4 steps for assessment                             <ul style="list-style-type: none"> <li>Toxicology evaluation</li> <li>MRL and WHP evaluation</li> <li>Dietary exposure evaluation</li> <li>Public consultation and</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Submit NADA or INAD application</li> <li>Review by ONADE to ensure submissions contain adequate and correct information and meet guidelines, i.e.</li> </ul>	<ul style="list-style-type: none"> <li>Scientific evaluation of application by CVMP                             <ul style="list-style-type: none"> <li>Scientific opinion prepared</li> </ul> </li> <li>Opinion sent to EC, draft a decision</li> <li>Consultations by EC with</li> </ul>



**REGULATORY MATRIX: Agricultural Product Approvals**

	Canada	Australia	US	EU
		liaisons	product is safe and effective for intended use	committees
<b>TASKS:</b>				
What	<ul style="list-style-type: none"> <li>Approval given to producers if various criteria are satisfied</li> </ul>	<ul style="list-style-type: none"> <li>Extensive data package must be prepared and must establish that a chemical product is safe and effective</li> <li>Must comply with accepted scientific principles</li> </ul>	<ul style="list-style-type: none"> <li>Applicants apply for approval when they feel that sufficient data has been generated</li> </ul>	<ul style="list-style-type: none"> <li>For Community Marketing Authorizations, must meet criteria as listed in parts A and B of the Annex to (EEC) 2309/93, which include new and innovative products at discretion of applicant, or products derived from biotechnology (compulsory)</li> </ul>
How	<ul style="list-style-type: none"> <li>Producer must provide proof (via data/clinical tests) that:                             <ul style="list-style-type: none"> <li>Evidence to support efficacy, safety &amp; quality.</li> <li>Drug is safe for animals and effective for intended purpose</li> <li>Does not leave potentially harmful residues</li> <li>Drug will be manufactured according to strict specifications</li> <li>Directions on labels that are adequate &amp; include withdrawal periods.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Extensive product development, testing and field trials</li> <li>Consultations with review committees to ensure all data is correct and sufficient</li> <li>Information on the following must be supplied with the application:                             <ul style="list-style-type: none"> <li>Chemistry and manufacturing</li> <li>Toxicology</li> <li>Metabolism and kinetics, residues (incl overseas trade aspects)</li> <li>Occupational health and safety</li> <li>Efficacy and target animal safety</li> <li>Environment</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Sponsors must conduct tests to show that:                             <ul style="list-style-type: none"> <li>Drug is safe for target animal</li> <li>Drug has intended effect</li> <li>Edible products derived from treated products are safe for human consumption</li> </ul> </li> <li>Need authorization from FDA for investigational drugs used on animals for human consumption</li> </ul>	<ul style="list-style-type: none"> <li>Pre-submission meetings are stressed                             <ul style="list-style-type: none"> <li>It is a vital opportunity for applicant to obtain procedural, regulatory and legal advice from the EMEA</li> </ul> </li> <li>Application dossiers must include:                             <ul style="list-style-type: none"> <li>Appropriate fees</li> <li>Expert reports, including required annexes (i.e. Part A or B)</li> <li>Applications for MRL if necessary</li> <li>Manufacturing and batch testing information</li> <li>European Drug Master File, if exists</li> <li>Specimen or mock-up of sales presentation of product</li> <li>Proposed Package Insert</li> </ul> </li> </ul> <p>Submissions must meet</p>

REGULATORY MATRIX: Agricultural Product Approvals				
	Canada	Australia	US	EU
				language requirements
<b>COSTS AND INCENTIVES</b>				
What	<ul style="list-style-type: none"> <li>Fees for a new drug submission range between C\$25,660 – \$70,200</li> <li>Administrative timeframe for VDD is 180 days, 90 days for corporate or brand name changes</li> </ul>	<ul style="list-style-type: none"> <li>Fees for a new active drug submission (primary application) are \$20,060 AUD (~ C\$17,653)</li> <li>Assessment Period for a new active drug is 15 months (450 days).</li> </ul>	<ul style="list-style-type: none"> <li>Fees – November 2003 ADUFA Act passed to collect fees for certain applications.</li> <li>Fees for NADA will range for from C\$40,562 – C\$81,124</li> <li>180 day provisional timeframe. ADUFA Act will impose performance standards</li> </ul>	<ul style="list-style-type: none"> <li>Fees for a new drug submission are ~ 100,000 EUR (~C\$157,000) (under review)</li> <li>Timeframe – 210 day assessment framework, which is on average real time between 550 and 870 business days</li> </ul>
How	<ul style="list-style-type: none"> <li>In December 2003, a blueprint for appeals was published by VDD; however, it is not an <i>independent</i> appeal mechanism as requested by industry. There still remains a need for an independent dispute mechanism.</li> </ul>	<ul style="list-style-type: none"> <li>15 months (450 days) is allowed for in legislation</li> <li>Companies may apply for a partial rebate of application fee if timeframe not met</li> <li>Appeal Process is in place - written request to reconsider decision.</li> </ul>	<ul style="list-style-type: none"> <li>By law, the CVM must notify applicant of status of application after 180 days, regardless if a decision has been made or not</li> <li>Appeal Process is in place – once appeal is received a decision must be rendered within 40 calendar days</li> </ul>	<ul style="list-style-type: none"> <li>No fines for not meeting timeframe, but base performance indicators on legal framework</li> </ul>

Acronyms:

ADUFA: Animal Drug User Fee Act  
 EEC: European Economic Community  
 NADA: New Animal Drug Application (US)  
 INAD(A): Investigational New Animal Drug Application (US)  
 MRL: Maximum Residue Limits  
 WHP: Withholding Period  
 ONADE: Office of New Animal Drug Evaluation (US)  
 CVMP: Committee for Veterinary Medicine Products (EU)  
 EC: European Commission