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Use of animals in the registration of veterinary medicine products in New Zealand

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Foreword

Many of the animals used each year in New Zealand for research, testing and teaching purposes fall under regulatory requirements to test for potency, food safety, efficacy, target animal safety and toxicology, but animal health product manufacturers also recognise the importance of the Three Rs. Internationally, regulators and industry have come together to find alternative ways of meeting regulatory requirements to ensure product safety, efficacy and purity without the use of animal-based test systems. The International Federation of Animal Health (IFAH) [1], a body representing the animal health companies, described in 2012 their involvement in The European Partnership for Alternative Approaches to Animal Testing - a voluntary collaboration between the European Commission, European trade associations and companies from seven industry sectors.

New Zealand aligns with international regulatory guidelines, e.g. Veterinary International Conference of Harmonisation (VICH; www.vichsec.org [2]) and World Association for the Advancement for Veterinary Parasitology (WAAVP; www.waavp.org [3]). These organisations set international standards aimed at harmonising technical requirements for the registration of veterinary products to minimise the use of testing in animals and the costs of product development. In New Zealand, many products are able to be registered using data generated internationally, reducing the need for animal testing locally.

With this level of co-ordinated international effort and political support, the future looks promising for the replacement, reduction and refinement (3Rs) of animal use in regulatory testing.

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1 International Federation of Animal Health (IFAH). Annual Report 2012. http://www.bft-online.de/fileadmin/bft/publikationen/IFAH-Europe_Annual_Report_2012.pdf

2 Veterinary International Conference of Harmonisation (VICH) www.vichsec.org

3 World Association for the Advancement for Veterinary Parasitology (WAAVP) www.waavp.org

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Use of Animals in the Registration of Veterinary Medicine Products in New Zealand

Dr Karen Booth, National Animal Ethics Advisory Committee

Introduction

In New Zealand, the registration of veterinary medicines is regulated under the Agricultural Compounds and Veterinary Medicines Act 1997. The Act is administered by the Agricultural Compounds and Veterinary Medicines (ACVM) Group of the Ministry for Primary Industries (MPI).

A veterinary medicine is defined under the Act as "any substance, mixture of substances, or biological compound used or intended for use in the direct management of an animal."

In the case of veterinary medicines, this encompasses a wide range of products, including:

- anti-infectives (antibiotics, coccidiostats, anti-fungals);
- vaccines and biopharmaceuticals;
- parasiticides;
- anti-inflammatory agents;
- cardiovascular and respiratory system therapeutic agents;
- anaesthetics, analgesics and sedatives;
- antidotes, anti-toxins and reversal agents;
- euthanasia agents;
- gastrointestinal agents;
- renal and urinary tract modifiers;
- musculoskeletal modifiers;
- nutritional compounds, electrolytes and supplements;
- hormonal growth promotants;
- endocrine agents;
- skin and coat conditioners;
- vertebrate poisons.

Veterinary medicines must have approval from the relevant New Zealand agencies before they can be manufactured, imported, distributed, sold and marketed in New Zealand. In the case of products that are also classified as hazardous substances under the Hazardous Substances and New Organisms Act 1996, an approval is required from the Environmental Protection Authority (EPA). Examples of such products include anthelmintic and ectoparasiticides used for treating parasite infections in livestock. Products containing ingredients of biological origin, such as vaccines, must also have a biosecurity clearance approval from the MPI Animal Imports Group.

What is required to register a veterinary medicine in New Zealand?

The ACVM Act manages veterinary medicines in New Zealand by the regulation of trade name products. In general terms, to register a new product, an applicant is required to provide a registration dossier containing[1]:

- data on the chemistry, manufacture and stability of the product;
- data supporting the efficacy of the product;
- data supporting the safety of the product in the target animal(s);
- data supporting human food safety (i.e. drug residues);
- a proposed label.

In the case of products that are also classified as hazardoussubstances, the following additional information is required:

- toxicology data;
- ecotoxicology data.

The degree of information required depends on a number of factors, such as whether the new product contains known active ingredient(s), is similar to an existing registered product, and/or has an active ingredient/formulation that has already been registered for similar uses in New Zealand.

New Zealand aligns with international regulatory guidelines, e.g. Veterinary International Conference of Harmonisation (VICH; www.vichsec.org [2]) and World Association for the Advancement for Veterinary Parasitology (WAAVP; www.waavp.org [3]). These organisations set international standards aimed at harmonising technical requirements for the registration of veterinary products to minimise the use of testing in animals and the costs of product development. In New Zealand, many products are able to be registered using data generated internationally, reducing the need for animal testing locally.

How are animals used in generating data required to satisfy registration requirements?

This is very dependent on the product being registered, and can include whether it is a novel product or a generic copy of an existing product.

Animal Use Required in the Manufacturing and Stability of the Product

In the case of vaccines, animals may be required for batch release potency testing. These tests are prescribed as national standards (e.g. the USDA's 9CFR), and/or international compendial standards, such as the European Pharmacopeia. Drayer[4] describes how potency tests (assays) help ensure that each consistently manufactured batch of vaccine provides a level of protection as determined in the original efficacy study throughout the products' shelf life. Methods used in currently approved assays range from host animal vaccination and challenge to the quantification of specific protective antigens using *in vitro* technology. The development, maintenance, and update of *in vitro* potency assays continues to be a priority for both the animal health industry and the corresponding regulatory agencies. The development of new assays is emphasised for those that currently involve laboratory animal vaccination/challenge, such as vaccines containing *Leptospira* and *Clostridium* spp. antigens.

The ACVM Group states the following in their Registration Standard and Guideline for Target Animal Safety[5]:

"Similar considerations should be made where an applicant is conducting research to replace use of live animals in quality assurance techniques, e.g. to confirm potency of a vaccine. The development of in vitro techniques to replace routine in vivo safety and potency tests is to be encouraged."

In recent years, regulatory agencies (including New Zealand's), have removed the requirement for target animal batch safety testing[6] in veterinary vaccine manufacture. Previously this test was used to demonstrate absence of toxicity by administering a 2X dose to 2 mammals (or 10 fish or 10 birds, depending on the target species), and observing for a 14 day period for any adverse reactions. With quality controls and testing performed as part of Good Manufacturing Practice (GMP), this test in many cases has become redundant.

Animal Use Required in Demonstrating Human and Food Safety

Human food safety must be demonstrated for veterinary drug products intended to be used in species that produce foodstuffs such as milk, meat, eggs or honey that are intended for human consumption. The ACVM Group specifies the numbers of animals and time points required to generate drug residue depletion data in consumable products.

Number of Animals/Produce Items/Hives per Time Point								
	Ruminants/Deer/ Pre-ruminants	**Ruminants**	**Pigs**	**Horses**	**Birds**		**Fish**	**Bees**
Mode of application	Meat	Milk	Meat	Meat	Meat	Eggs		
Oral Systemic	5	9	5	2	5	3	3	NA
Oral Non Systemic	4	5	3	1	4	3	3	NA
Topical Systemic	5	9	4	2	5	3	3	NA
Topical Non Systemic	4	4	3	1	4	3	3	NA
Parenteral Preparations[2]	5	9	5	2	3	3	0	NA
Intrauterine Preparations	3	5	NA	NA	NA	NA	NA	NA
Intramammary Lactating Animal Preparations	3	9	NA	NA	NA	NA	NA	NA
Intramammary (Dry) Animal Preparations	3	= 7 per week (PNTI) see 8.5	NA	NA	NA	NA	NA	NA
Gaseous Anaesthetics	1	1	1	NA	NA	NA	NA	NA
Hives Application	NA	NA	NA	NA	NA	NA	NA	1

Source: ACVM Registration Standard and Guideline for Determination of a Residue Withholding Period for Veterinary Medicines[7]

Number of Time Points								
	Ruminants/Deer/ Pre-ruminants	**Ruminants**	**Pigs**	**Horses**	**Birds**		**Fish**	**Bees**
Mode of application	Meat	Milk	Meat	Meat	Meat	Eggs		Honey
Oral Systemic	4	4	4	3	4	4	3	NA
Oral Non Systemic	4	4	4	2	3	3	3	NA
Topical Systemic	4	4	4	3	4	4	3	NA
Topical Non Systemic	3	3	3	2	3	3	3	NA
Parenteral Preparations[2]	4	4	4	3	3	3	0	NA
Intrauterine Preparations	2	3	NA	NA	NA	NA	NA	NA
Intramammary Lactating Animal Preparations	3	3	NA	NA	0NA	NA	NA	NA
Intramammary (Dry) Animal Preparations	3	See 8.5. (PNTI)	NA	NA	NA	NA	NA	NA
Gaseous Anaesthetics	1	1	1	*	0	0	0	NA
Hives Application	NA	NA	NA	NA	NA	NA	NA	2

Source: ACVM Registration Standard and Guideline for Determination of a Residue Withholding Period for Veterinary Medicines

Studies to determine a meat withholding period (WHP) require animals to be slaughtered, whereas milk residue studies do not. These studies are conducted to Good Laboratory Practice (GLP) standard, the 'gold' regulatory standard for registration studies. As such, the ACVM Group will accept GLP residue studies conducted 'off-shore' to set WHPs in New Zealand, which removes the need for duplication of effort and unnecessary sacrifice of animals.

Animal Use Required in Demonstrating Efficacy

Most animal use for registration of veterinary products occurs in the generation of efficacy data. The number of animals required depends on the type of product being tested. We enjoy a sensible regulatory approach in New Zealand, in that a significant number of studies conducted to support registration of products overseas do not need to be repeated here. This avoids duplication of effort, cost, and reduces the need for animal use in research and testing.

For companion animal (cat, dog and equine) products, this usually means an international (EU/US/Australian) dossier will satisfy New Zealand registration requirements.

One notable exception is production animal (sheep, cattle, goats and deer) anthelmintics. Due to the uniqueness of our pastoral farming system and parasite spectrum, applicants are required to provide at least one New Zealand dose confirmation study per labelled parasite.

For some product types, the numbers of animals required is prescribed in international regulatory guidelines (e.g. for anthelmintics, the WAAVP/VICH Guidelines).

For example, the VICH Guideline for Bovine Anthelmintics[8] states "the minimum number of animals required per experimental group is a critical point. Although the number of animals will depend on the possibility to process the data statistically according to the adequate statistical analysis, it has been recommended by WAAVP, to achieve harmonisation, that the inclusion of at least 6 animals in each experimental group is a minimum. This applies for dose determination, dose confirmation and persistency trials."

For most products, the number of animals required for demonstration of efficacy is driven by the scientific requirement to show that the product does what the label says it will do. In most situations this is determined statistically. Animal numbers in treatment groups must be adequate to detect differences between treatment groups with a statistical power of at least 80%. This provides confidence that the treatment effect seen is not due to chance, but is due to the product.

The ACVM Group has a number of efficacy Registration Standards and Guidelines that outline the requirements for these studies: http://www.foodsafety.govt.nz/industry/acvm/documents/manuals-guidelines.htm.

For "MeToo" products (i.e. generics that are very similar to a pioneer registered product), efficacy may be demonstrated by provision of a bioequivalence study that will involve animals. Once again, a regulatory standard study must be conducted[9]. Two trade name products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same quantitative dose, are similar to such a degree that their effects can be demonstrated to be essentially 'the same'. These studies may investigate blood levels, and/or pharmacological endpoints, and/or clinical endpoints.

Bioequivalence cannot be used in New Zealand to obtain registration of trade name products that are ectoparasiticides (e.g. pour-ons), intramammary formulations or teat dips. Therapeutic equivalence cannot be used to obtain registration for vaccines and other immunobiologicals.

Animal Use Required to Demonstrate Target Animal Safety

The ACVM Registration Standard and Guideline for Target Animal Safety specifies the New Zealand minimum requirements to demonstrate safety of the product. The overarching principle however, is that the registrant fully understands the safety profile of their product.

The numbers of animals required are specified as follows.

At least ten animals from each target animal group must be used for each different use pattern being proposed. It is recommended that at least five untreated control animals are required as comparison for each treated group of animals. If controls are not included, deviations from normal will be regarded as a product effect.

Results obtained from pilot studies should be used by the applicant to provide an indication of the number of study animals that will be used in the full safety study, in discussion with a biometrician and other scientific experts.

The principles of the 3Rs (replace, reduce and refine) are clearly upheld by the New Zealand regulator. The following is an excerpt from the standard:

"Information can be generated about the impact of a trade name product on the health of animals using a range of techniques, particularly:

- *in vivo* experiments, where behavioural responses, physiological factors and/or pharmacological properties are monitored in conscious or anaesthetised animals;
- *in vitro* experiments, where animal tissues are isolated prior to experimentation and/or monitoring;
- chemical techniques, where no animals or animal tissues are utilised;
- a selection of a variety of the above techniques.

One of the major principles employed to minimise the animal welfare implications associated with the use of animals in scientific procedures is that of replacement, where use of alternatives to live animal techniques is encouraged. The ACVM Group strongly supports this philosophy.

If *in vitro* work will yield information that adequately satisfies the safety registration requirements of a product, it may suffice without proceeding with *in vivo* studies.

However, it must be proven that the *in vitro* results can be extrapolated accurately to the *in vivo* situation in New Zealand. In cases of doubt, small pilot projects involving a few animals to confirm findings and to validate the extrapolation should be considered.

Similar considerations should be made where an applicant is conducting research to replace use of live animals in quality assurance techniques, e.g. to confirm potency of a vaccine. The development of *in vitro* techniques to replace routine *in vivo* safety and potency tests is to be encouraged. A recent example of this is the development of an *in vitro* assay to determine the potency of leptospirosis veterinary vaccines, to replace the existing animal challenge model[10].

If alternatives to whole animal experiments are employed, their validity must be proven.

Applicants should remember that eggs, foetuses and embryos, where development of an integrated nervous system is evident, must be treated in a humane manner. Development of an integrated nervous system must be assumed for all foetuses in the second half of gestation."

Animal Use Required for Toxicology Studies

Arguably, generation of toxicology data results in the greatest welfare impact on animals.

The Organisation for Economic Co-operation and Development (OECD; www.oecd.org) specifies the studies required, and their conduct. These tests are usually conducted on the active ingredient, or (less commonly) finished product formulation in laboratory animal species (e.g. rats), and are used to determine:

- acute toxicity – oral, dermal, inhalation, dermal, eye, skin sensitisation;
- chronic toxicity – oral, dermal, inhalation;
- reproductive & developmental toxicity;
- carcinogenicity;
- genetic toxicity – usually by *in vitro* testing;
- ecotoxicology – including water flea, fish.

This data provides information regarding the potential human and environmental health effects resulting from use of the product – i.e. end user safety, target animal safety, human food safety and environmental safety.

These studies carry both a high financial and animal welfare cost, so usually only one package is generated by the applicant company for use in multiple jurisdictions. These packages are not required to be repeated for known active ingredients or formulations.

Summary

The principles of the 3Rs have permeated the modern regulatory environment since first introduced by Russell and Burch in 1959. In New Zealand, the ACVM Group considers the replacement, reduction and refinement of animal use in research, regulatory trials and manufacturing to be important. The conscious alignment with internationally accepted guidance has resulted in a reduced requirement for animal use in New Zealand, particularly for companion animal species. There is still a requirement to generate New Zealand data on veterinary products for use in animals in the livestock space – reflecting our unique pastoral agricultural system and parasite/microbial spectrum.

Animal health product manufacturers also recognise the importance of the 3Rs. Internationally, regulators and industry have come together to find alternative ways of meeting regulatory requirements to ensure product safety, efficacy and purity without the use of animal-based test systems. The International Federation of Animal Health (IFAH) [11], a body representing the animal health companies, described in 2012 their involvement in The European Partnership for Alternative Approaches to Animal Testing - a voluntary collaboration between the European Commission, European trade associations and companies from seven industry sectors.

With this level of co-ordinated international effort and political support, the future looks promising for the replacement, reduction and refinement (3Rs) of animal use in regulatory testing.

References

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