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VICH and its role for authorisation of veterinary medicinal products

Executive Summary

Many countries have legislation to ensure at least minimum standards to establish the quality, safety and efficacy of veterinary medicinal products.

Work is ongoing through several organisations involved with cooperation between countries to harmonise requirements and to simplify processes regarding veterinary medicinal products. The goal is to allow equal access to safe and efficacious veterinary medicines around the world. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is an ongoing programme to harmonise technical requirements for marketing authorisations for veterinary medicinal products.

This document aims to summarise the principles of a registration/ marketing authorisation system, to describe the VICH role and to explain the process to develop harmonised VICH guidelines.

1. Principles for the registration /authorisation of veterinary medicinal products

What is a marketing authorisation / registration?

As a general rule, before a veterinary medicinal product can be sold or used, it must be authorised by the responsible authority of the country where it will be used. This applies to all types of veterinary medicinal products, i.e. pharmaceutical products as well as vaccines and other immunological products.

A marketing authorisation (also called 'registration' or 'licence') is the approval by the responsible authority in the country concerned that the product can be sold and used, specifying the details of the medicine (e.g. name of active substance, animals for which it can be used, indications for use, dose and duration of treatment), the conditions of use (e.g. storage conditions, shelf life, withdrawal period, instructions for safe use or instructions for safe disposal of waste) and any precautions or warnings for safe use, including possible contraindications. These details and instructions for use of a veterinary medicinal product are part of the labelling and package leaflet of the product, as it is brought on the market.

What is necessary for setting up a marketing authorisation scheme?

It is the responsibility of governments to establish a regulatory system for the authorisation and control of veterinary medicinal products. For this a law or other legal act

setting out the procedure and requirements for marketing authorisations, the process for distribution of the veterinary medicinal products and the system for control is necessary. The governments then need to have the instruments to implement the legislation. Many countries/regions have therefore regulations and published guidance documents that outline the testing requirements and standards for the data required to obtain a marketing authorisation/licence for a veterinary medicinal product in their country/region.

How can a company obtain a marketing authorisation (or 'registration' or 'licence') for a veterinary medicinal product?

In order to obtain a marketing authorisation (or registration or licence, as appropriate) the company that will bring the product on the market (also called sponsor or applicant) must submit an application to the responsible authority in the country concerned. The application should be accompanied by a comprehensive package of data on the quality, safety and efficacy of the veterinary medicinal product, be it either a pharmaceutical product, a vaccine or other immunological product. This data package is often called the 'dossier'.

The data in the application should confirm that the medicine is effective and safe when used in the proposed animal species for the proposed claims. The application should also address any precautionary measures to be taken when storing the veterinary medicinal product, administering it to animals, disposing of waste of the medicine together with an indication of potential risks that the product might pose to human and animal health and to the environment. In the case of medicines used in food-producing animals, information on the time when it is safe for the consumer to eat animal products (such as milk, meat or eggs) following treatment or the end of treatment period (also called "withdrawal period"), should be provided.

Following the initial scientific assessment of the application, additional questions usually arise ('List of questions' or 'Incomplete letter') that the sponsor (or applicant) of the veterinary medicinal product will have to answer. Once all questions have been satisfactorily answered and it is established that there are no risks that would outweigh the efficacy and other benefits of the veterinary medicinal product, the responsible authority can issue a marketing authorisation, imposing specific conditions of use, storage and waste disposal, as appropriate, for the specific product.

As the process of reviewing all scientific data requires a large amount of resources, countries may wish in some instances to rely on assessments already carried out for the same medicine by the authorities in other countries, at least for some parts of the dossier, e.g. the safety and efficacy documentation. It is therefore important to know in which countries marketing authorisations have already been issued. Information and assessments of authorised veterinary medicinal products can be found at the web pages of the regulatory authorities for many countries. Addresses for the web pages of VICH member countries and regions are given in Annex I to this document.

Examples of the legislation and guidance established by the VICH members, the European Union, Japan and the USA are presented in Annex II to this document.

What should be included in an application 'dossier'?

A full application for a marketing authorisation would normally comprise a comprehensive data package with quality documentation, safety data (including target animal safety data), residue data (residue depletion data for products indicated for food producing species) and efficacy (also often called 'pre-clinical and clinical' documentation).

The application dossier should also provide administrative details, e.g. name of the product, name of the active substance(s), pharmaceutical form, name and contact details of the applicant, details on the manufacturer or importer, and a description of how the finished product appears when it is brought onto the market.

Also the composition of the medicine and pharmaceutical details of the product should be provided.

An example of an outline for such a dossier is described in Annex III.

What else is important to ensure that veterinary medicinal products are safe and efficacious?

The active substance(s) and the veterinary medicinal product should be manufactured under conditions that ensure that the resulting medicinal product has the appropriate quality and complies with the required standards. As a second step, systems need to be in place that will ensure continued monitoring once the medicine has been approved and is being manufactured and marketed. Therefore, as example, the legislation in VICH countries requires a manufacturing authorisation certifying that the product is manufactured in compliance with Good Manufacturing Practice (GMP). Following marketing authorisation, products are monitored by a combination of pharmacovigilance (monitoring adverse drug reactions), sampling and testing of products on the market, and regular inspections of manufacturing sites. Also, VICH countries require monitoring systems to assure that compliance with the maximum residue limits for residues from veterinary medicinal products in foodstuffs from animal origin is controlled and surveillance schemes have been set up in the VICH countries as well as many other countries. The residue surveillance concerns both food of animal origin produced by the country / region itself as well as imported foodstuffs.

2. About VICH

What is VICH?

VICH is a multinational (EU-Japan-USA) programme aimed at harmonising the studies and data that are requested by the authorities of the countries and regions that are part of VICH for veterinary product marketing authorisations. The full title is the **I**nternational **C**ooperation on **H**armonisation of Technical Requirements for Registration of **V**eterinary Medicinal Products. VICH was officially launched in April 1996. For more details see the VICH website at: http://www.vichsec.org/

The launching of VICH followed an earlier international harmonisation activity on technical requirements regarding medicinal products for human use, the **I**nternational **C**onference on **H**armonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which held its first meeting in 1991, and other harmonisation activities for veterinary medicines, in particular those coordinated by the World Organisation for Animal Health (OIE), Codex Alimentarius and the Joint FAO/WHO Expert Committee of Food Additives (JECFA).

What are the goals of VICH?

The objectives of VICH are to:

- Establish and implement harmonized regulatory requirements for veterinary medicinal products in the VICH regions, which meet high quality, safety and efficacy standards and minimize the use of test animals and costs of product development.
- Provide a basis for wider international harmonization of registration requirements.
- Monitor and maintain existing VICH guidelines, taking particular note of the ICH work programme and, where necessary, update these VICH Guidelines.
- Ensure efficient processes for maintaining and monitoring consistent interpretation of data requirements following the implementation of VICH guidelines.
- By means of a constructive dialogue between regulatory authorities and industry provide technical guidance enabling response to significant emerging global issues and science that impact on regulatory requirements within the VICH regions.

Thus, the VICH guidelines provide harmonised guidance that describes the data to be provided in an application dossier for a marketing authorisation for a veterinary medicinal product. VICH also establishes guidelines on the pharmacovigilance for veterinary medicinal products, i.e. the requirements for their post-marketing safety monitoring.

However, VICH does not normally develop guidance on how to carry out the assessment of the data or on the assessment approach. Assessments are done by the regulatory authorities of the VICH countries and regions. Only in a few exceptional cases, e.g. the guidelines on environmental impact assessment or the guideline on the establishment of the microbiological ADI, has the VICH produced guidelines covering the assessment approach.

Who is in VICH?

The member countries/regions of VICH are the European Union (EU), Japan and the United States of America. So-called Observer countries are Australia, Canada and New Zealand. VICH works through two main forums: the Steering Committee and specialised Expert Working Groups. The VICH members are represented in both forums, each with equal representation from the country's/region's authorities and the animal health industry. The representatives from observer countries are participating in the working process of the Steering Committee. They may join in Committee discussions and send experts to the

Expert Working Groups, although they have no voting rights. VICH also provides for Interested Parties to attend some meetings. The secretariat functions of VICH are provided by the International Federation for Animal Health (IFAH).

The VICH Organisational Charter (see http://www.vichsec.org/) provides further details.

What is the process to develop VICH guidelines?

The VICH Steering Committee decides on any new topics for which a guideline is to be developed based on a detailed concept paper submitted by a VICH member. The concept paper should address the reasons for the proposed guideline, e.g. need for harmonisation, the feasibility to achieve harmonisation and the expected impact of the proposed guideline. Once the Steering Committee agrees to a new topic, the work is allocated to either an existing Expert Working Group, or a new one is formed.

The Expert Working Group develops a draft guideline in a process involving face-to-face meetings, email exchanges, and/or teleconferences. The process for preparing the draft depends on the complexity of the topic and the existing level of harmonisation. After the Expert Working Group has signed off the draft guideline, it is submitted to the Steering Committee for approval and then published for consultation by the regulatory authorities in the VICH regions and published on the VICH website by the VICH secretariat. A wider dissemination takes place through OIE.

This public consultation is normally 6 months. Following the close of the consultation the Expert Working Group reviews the comments received and finalises the guideline considering these comments. After sign-off by the Expert Working Group the draft final guideline is sent to the Steering Committee for final approval. After approval, the regulatory authorities implement the guideline in the VICH countries/regions, usually within a period of 1 year. This means that the VICH guideline then becomes the official recommended guideline in the member country/region and replaces any previously existing national guidelines. While the VICH observer countries are not bound by the VICH recommendations, they are encouraged to take them into account in due course.

For further details see: http://www.vichsec.org/

Can other countries contribute to the work of VICH?

One of the VICH objectives, as stated in its Organisational Charter, is that the programme should work towards providing a basis for wider international harmonisation of registration requirements.

Countries that are not part of VICH can send comments that respond to draft VICH guidelines during the public consultation. They could also send proposals for new guidelines to VICH for the Steering Committee to consider. Also countries that are not part of VICH are encouraged to use VICH guidelines as national or regional guidelines, if they wish.

VICH is currently working on strengthening its activities on 'global outreach' and to encourage the wider harmonisation of registration requirements and efficient use of resources in regions/countries that are not members of VICH. The aim is to provide support, in close co-operation with OIE, for the governance of veterinary medicinal products globally and to enable broad access to good quality veterinary medicinal products for all livestock producers, veterinarians, and other relevant individuals in other parts of the world, in particular, Africa, Asia and South America.

On which subjects are VICH Guidelines available and where can I find them?

In the period from 1996 to June 2010 VICH has completed in total 41 guidelines, with further 8 guidelines in preparation. The guidelines cover the areas:

For pharmaceuticals: quality, safety (toxicology, target animal safety, antimicrobial safety and environmental impact assessment) and efficacy.

For biologicals: quality and target animal safety.

In addition there is one general guideline on good clinical practice (GCP) and there are VICH pharmacovigilance guidelines.

For further details and to download the guideline texts, see: http://www.vichsec.org/

What is the role of VICH vis-a-vis OIE and Codex/JECFA?

These three global bodies fulfil different roles, which are summarised in the box below in respect to the authorisation and control of veterinary medicinal products. The role of VICH is complementary to OIE or Codex Alimentarius.

- **VICH** develops harmonised data requirements, i.e. standards for the scientific studies on quality, safety and efficacy that are required to obtain a marketing authorisation of a veterinary medicinal product.
- **OIE** develops health standards for international trade in animals and animal products that member countries can use to protect themselves from the introduction of diseases and pathogens, without setting up unjustified sanitary barriers. OIE also is responsible for improving the legal framework and resources of national Veterinary Services.
- The **Codex** Alimentarius Commission develops food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme to protect consumers and ensure fair practices in the food trade. Codex is responsible for establishing food safety standards, i.e. maximum residue limits for residues from veterinary drugs in foodstuffs from animal origin on international level.

Their roles in more detail

The OIE is the intergovernmental organisation responsible for improving animal health worldwide. In 2010 OIE had a total of 175 Member Countries and Territories.

The main OIE roles are:

- to ensure transparency in the global animal disease situation
- to collect, analyse and disseminate veterinary scientific information
- to encourage international solidarity in the control of animal diseases
- to safeguard world trade by publishing health standards for international trade in animals and animal products
- to improve the legal framework and resources of national Veterinary Services
- to provide a better guarantee of food of animal origin and to promote animal welfare through a science-based approach

The OIE develops normative documents relating to rules that member countries can use to protect themselves from the introduction of diseases and pathogens, without setting up unjustified sanitary barriers. The main normative works produced by the OIE are: the *Terrestrial Animal Health Code*, the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, the *Aquatic Animal Health Code* and the *Manual of Diagnostic Tests for Aquatic Animals*.

OIE standards are recognised by the World Trade Organization as reference international sanitary rules.

The OIE has also recommended that each of its Members appoint a focal point to be responsible at the national level for relations with the OIE in the field of veterinary products. The OIE regularly invites these officials throughout the world to take part in training programmes to help them, with the support of its Collaborating Centres to obtain the appropriate international and technical information. The focal points of the 175 OIE Members thus form a worldwide network of experts that can help to bring about the harmonisation of policies in the field of veterinary products with the aim of improving national animal health policies.

The VICH has been established under the auspices of the OIE. Countries not involved in the VICH are kept informed of its progress and are consulted on draft guidelines through the OIE. For further details see: http://www.oie.int/eng/en_index.htm

The Codex Alimentarius Commission is a global body which was established by FAO/WHO to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are protecting health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations. Codex is responsible for establishing maximum residue limits for residues from veterinary drugs in foodstuffs from animal origin on international level primarily based on risk assessments performed by the FAO/WHO Joint Expert Committee on Food Additives (JECFA). .

For further details see: http://www.codexalimentarius.net/web/index_en.jsp

With regard to food safety, the role of VICH is to harmonise technical requirements, not to assess data or establish any safety standards. The VICH has agreed on guidelines on the toxicity data that are required for the food safety assessment of residues from veterinary medicinal products as well as for the establishment of a microbiological ADI, and is working on guidelines on residue kinetics and metabolism. These requirements are applied by VICH countries/regions when setting food safety standards in foodstuffs from animal origin and establishing withdrawal periods for veterinary medicinal products used in food producing animals.

ANNEX I

Links to web pages of regulatory authorities of VICH member countries and regions:

EU

- European Medicines Agency, Veterinary Medicines
  http://www.ema.europa.eu/index/indexv1.htm
- Link to web page addresses for regulatory authorities for veterinary medicines in member States of the European Union:
  http://www.hma.eu/

Japan

- Animal Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries
  http://www.maff.go.jp/j/syouan/tikusui/yakuzi/index.html

- National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries
  http://www.maff.go.jp/nval/english/

USA

- Center for Veterinary Medicine/Food and Drug Administration
  http://www.fda.gov/
  http://www.fda.gov/AnimalVeterinary/default.htm
- Center for Veterinary Biologics
  http://www.aphis.usda.gov/animal_health/vet_biologics/

Australia

- Australian Pesticides and Veterinary Medicines Authority (APVMA)
  www.apvma.gov.au

- Australian Quarantine and Inspection Service (AQIS)
  www.aqis.gov.au

Canada

- Veterinary Drugs Directorate Health Canada
  http://www.hc-sc.gc.ca/dhp-mps/vet/index-eng.php
- Canadian Centre for Veterinary Biologics, Canadian Food Inspection Agency
  http://www.inspection.gc.ca/english/anima/vetbio/vbpbve.shtml

New Zealand

- New Zealand Food Safety Authority (NZFSA)
  http://www.nzfsa.govt.nz/

ANNEX II

Examples for the legislation and guidance established by the European Union, Japan and the USA

EU

In the European Union (EU) and the countries of the European Economic Area, the requirements for obtaining a marketing authorisation for a veterinary medicinal product are laid down in Directive 2001/82/EC, and subsequent amendments. Appendix I to this Directive describes in detail the data – about the quality, safety and efficacy of the product – that must be provided with an application for a marketing authorisation. Directive 2001/82/EC, as amended, also requires the applicant to provide – in addition to the data on quality, safety and efficacy – information on the test methods and any precautionary measures to be taken when storing the veterinary medicinal product, administering it to animals and disposing of waste, together with an indication of potential risks that the product might pose to human and animal health and to the environment.

For veterinary medicinal products intended for food producing animals the safety of residues has to be considered and maximum residue limits (MRLs) must be established for the species and tissues concerned. In the EU the establishment of MRLs is a separate procedure prior to the granting of a marketing authorisation. This requirement applies for the active ingredient for pharmaceutical products but also for excipients or adjuvants, if they have pharmacological activity.

Further guidance is given in specific guidelines issued by the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency and the European Commission. For pharmaceutical products or vaccines which are the subject of a European Pharmacopoeia monograph, specific requirements may be included in the relevant monograph. All data are assessed by the responsible authority, and a risk assessment and a benefit/risk analysis are carried out before a decision on the marketing authorisation is taken.

References:

- European Parliament and Council (2001). Directive 2001/82/EC of the European Parliament and the Council of 6 November 2001. *Off. J. Eur. Comm.* L311: 28.11.2004, pp. 01–66, as amended by Directive 2004/28/EC of the European Parliament and the Council of the 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medical products. *Off. J. Eur. Comm.* L136: 30.04.2004, 58–84. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev5.htm
- European Parliament and Council (2009). Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council. *Off. J. Eur. Comm.* L152:

16.06.2009, 11-22. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:152:0011:0022:EN:PDF

- European Medicines Agency website. Scientific guidelines for veterinary medicinal products. Available at: http://www.ema.europa.eu/htms/vet/vetguidelines/background.htm
- European Commission (2007). Volume 6B of the rules governing medicinal products in the European Union. Available at: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-6/b/vol6b_04_2004_final_en.pdf
- European Pharmacopoeia (2004). – 5th Edition & supplements. European Directorate for the Quality of Medicines and Healthcare (EDQM), Council of Europe, Strasbourg. http://www.edqm.eu/en/Homepage-628.html

Japan

In Japan, medicinal products for human and veterinary use are under the control of Pharmaceutical Affairs Law (Law No. 145, 1960). The law is intended to provide regulations required to ensure the quality, efficacy and safety of the drugs, quasi-drugs, cosmetics and medical devices at each stage of development, manufacturing, importing, marketing, retailing and usage. Subsequent Ministerial Ordinances specifically applied for veterinary medicinal products have been established by the Minister of Agriculture, Forestry and Fisheries (MAFF) and relating regulations and guidelines are also provided in accordance with the Ordinances. A person intending to market release of veterinary medicinal products shall obtain marketing approval for each product from MAFF. Animal Products Safety Division, Food Safety and Consumer Affairs Bureau, is responsible for establishment/amendment of the Ministerial Ordinances and relating Notifications. National Veterinary Assay Laboratory (NVAL) is responsible for examination of application dossier for approval and establishment of guidelines for the applicants.

An application for approval of a new veterinary medicinal product undergoes an investigation by a committee of the Pharmaceutical Affairs Sub-council (PASC) specialized in the category of the product (biologicals, antibiotics, general medicine, etc.). Additionally, the application is subjected to a deliberation by the executive committee of the PASC. Veterinary medicinal products intended for use in food producing animals are also investigated for its residue in food by the "committee on residue of veterinary drugs". Furthermore, veterinary medicinal products for food producing animals shall be assessed for its safety to human health by the Food Safety Commission; and maximum residue limits must be established for the tissues concerned by the Minister of Health, Labour and Welfare, prior to the approval.

The data required for approval varies depending on the status of the products, e.g., in the case of product containing new active ingredient, it is required to submit full set of dossier including: Origin and history of development; Physical, chemical and biological properties; Manufacturing process; Indications, effects, potency; Administration and dosage; Stability; Toxicity; Target animal safety; Pharmacological action; Absorption,

distribution, metabolism and excretion; Clinical trials; and Residue study. Data for toxicity, target animal safety and residue shall meet the Ministerial ordinance of Good Laboratory Practice (GLP) (Ordinance No. 74, 1997), and data of clinical trial shall meet the Ministerial Ordinance of Good Clinical Practice (GCP) (Ordinance No. 75, 1997). Furthermore, it shall be confirmed that the manufacturing control and the quality control in a process complies with Good Manufacturing Practice (GMP) standards specified by the Ministerial Ordinance (Ordinance No. 18, 1994).

References:

- Outline of Regulation System of Veterinary Drugs in Japan". Available at: http://www.maff.go.jp/nval/english/pdf/outline080514.pdf

- "Pharmaceutical Affairs Law[1]" and "Ministerial Ordinances for Veterinary Medicinal Products". Links available at: http://www.maff.go.jp/nval/hourei_tuuti/index.html

- Technical Advices on procedures relating to Pharmaceutical Affairs Law (Notice from the Director General, Food Safety and Consumer Affairs Bureau, MAFF: Notice No. 12-Chiku-A-728; 31, March, 2000). Available at: http://www.maff.go.jp/j/kokuji_tuti/tuti/t0000831.html and http://www.maff.go.jp/j/kokuji_tuti/tuti/pdf/t0000831.pdf

- Procedures relating to Pharmaceutical Affairs Law (Notice from the Director General, Food Safety and Consumer Affairs Bureau, MAFF: Notice No. 12-Chiku-A-729; 31, March, 2000). Available at: http://www.maff.go.jp/j/kokuji_tuti/tuti/t0000832.html and http://www.maff.go.jp/j/kokuji_tuti/tuti/pdf/t0000832_4.pdf

- Procedures relating to Pharmaceutical Affairs Law (Notice from the Director General, National Veterinary Assay Laboratory, MAFF: Notice No. 12-douyaku-A-418; 31, March, 2000). Available at:
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-01.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-02.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-03.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-04.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-05.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-06.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-07.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-08.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-09.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-10.pdf
  http://www.maff.go.jp/nval/hourei_tuuti/pdf/12-418_20-2860-11.pdf

- Standards for Veterinary Biological Products, Notification of the Minister of Agriculture, Forestry and Fisheries (Notification No.1567; October 3, 2002). Available at: http://www.maff.go.jp/nval/kijyun/index.html

USA

In the United States all drugs, including veterinary drugs, are regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FFDCA). There are two main processes involved in regulating the interstate shipment of animal drug products.

- The first process, the Investigational New Animal Drug exemption (INAD), involves the interstate shipment of experimental drugs used for testing in animals. This testing may

[1] *English translation is available from: Yakuji Nippo, Ltd. (http://www.yakuji.co.jp/english_publications#others)

require drugs be given to animals that will later be used to produce human food products. FDA must ensure that the food products derived from these experimental animals will be safe for human consumption.

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

INAD and NADA sponsors usually include university researchers, contract researchers, private practitioners, drug manufacturers, and/or feed or food manufacturers in their protocols. The activities of the investigators are monitored through the bioresearch monitoring program (BIMO). The sponsor's data generation processes are validated through on-site inspections by FDA field personnel. Reports covering laboratory practices relating to toxicology and safety research, and the functions of clinical investigators and sponsors are forwarded to Center for Veterinary Medicine (CVM) for evaluation.

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 for a USDA inspector to monitor the slaughter of research animals intended for human consumption.

Usually, the 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 FFDCA, the sponsor must do the following:

- Assure the proper and safe packaging and labeling 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.
- Request a categorical exclusion from an Environmental Assessment.
- Submit individual completed technical sections (such as target animal safety, effectiveness, human food safety, freedom of information (FOI), and labeling) for "phased review" under the INAD, or, submit the entire requirements for approval 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), and a well-organized summary of the information in the application.

References:

- Food, Drug and Cosmetic Act
  http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm
- Regulations for Animal Drugs
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=514&showFR=1
- Approved Drugs
  http://www.accessdata.fda.gov/scripts/animaldrugsatfda/

- Guidelines
  http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

Australia

- Agricultural and Veterinary Chemicals (Administration) Act 1992
  http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/593357AE6E2C5699CA257308003366D3?OpenDocument
- Agricultural and Veterinary Chemicals Code Act 1994
  http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/current/bytitle/A06DDA96E680781ECA2573120082EBE6?OpenDocument&mostrecent=1
- Agricultural and Veterinary Chemicals Code Regulations 1995
  http://www.comlaw.gov.au/ComLaw/legislation/legislativeinstrumentcompilation1.nsf/current/bytitle/D46CF53F85578946CA25768D0012F0A3?OpenDocument&mostrecent=1

Canada

- Food and Drugs Act and Regulations
  http://laws.justice.gc.ca/en/F-27/index.html
- Health of Animals Act and Regulations
  http://laws.justice.gc.ca/en/H-3.3/

New Zealand

In New Zealand, the requirements for obtaining registration for a veterinary medicinal product are laid down in The Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 and its associated regulations. Guidance information describes in detail the data – in order to be able to assess the product against the risk areas in the ACVM Act – that must be provided with an application for a registration. The ACVM Act manages risks to trade, public health, animal welfare, biosecurity and ensures that any residues in food are at safe levels. Related legislation (the Hazardous Substances and New Organisms Act manages risks to the environment.

For veterinary medicinal products intended for food producing animals the issue of residues is considered and maximum residue limits (MRLs) are established. In New Zealand the establishment of MRLs is a separate procedure usually prior to the granting of a registration. MRLs are set under the Food Act (1981) by way of the New Zealand (Maximum Residue Limits of Agricultural Compounds) Standard.

References:

- Legislation
  http://www.nzfsa.govt.nz/acvm/legislation/index.htm
- Guidance information :

http://www.nzfsa.govt.nz/acvm/publications/information-requirements/index.htm

ANNEX III

Example of outline of the contents of an application for a marketing authorisation with a dossier on quality, safety and efficacy

For medicinal products for human use the content and format of marketing authorisation dossiers has been harmonised within ICH; the agreed standard is called the "Common Technical Dossier" (CTD).

Due to the different resources and needs of the veterinary sector there are no plans to develop a vet CTD within VICH. The list below presents an example of an outline of the application contents based on existing requirements in VICH regions.

A. Pharmaceutical veterinary medicinal products

Administrative details:

- Application form

- Name of product
- Name of the active substance(s)
- Target species
- Strength, pharmaceutical form, route and method of administration

- Description of pack size and type

- Name and address of the applicant/sponsor
- Name and address of the manufacturers and the sites involved in the different stages of the manufacture, testing and release, and where relevant the name and address of the importer

- A proposed labelling text for the immediate and outer packaging
- A package leaflet, if required.
- Examples of proposed packaging

Product profile

- Chemical structure and the physico-chemical properties of the active substance(s)
- Proposed therapeutic indications and target species
- Precautions and warnings, including withdrawal periods, where appropriate
- List of marketing authorisations already issued in other countries, and those applied for

Quality documentation

- Composition of the product
- Method of preparation: manufacturing method, in-process control tests and validation incl. batch analysis
- Active substance(s): specifications, impurities in the starting material, suitability of the manufacturing method, stereoisomerism, where relevant and stability
- Excipients: specifications, suitability and safety data, where appropriate
- Packaging material (immediate packaging): specifications and suitability
- Control tests on intermediate products
- Control tests on finished product
- Stability of the finished product

Safety

Studies on:

- Pharmacodynamics
- Pharmacokinetics
- Toxicology
  - Single dose toxicity
  - Repeated dose toxicity
  - Reproductive toxicity including teratogenicity
  - Genotoxicity
  - Carcinogenicity
  - Other tests, e.g. microbiological effects on human gut flora, sensitisation potential, effects on specific organ systems, where appropriate. This depends on the type of substance and use, e.g. microbiological effects on human gut flora are only required for microbiologically active substances used in food producing animals.
- Target animal safety
- Residue studies (only required for products food producing animals)
  - Metabolism and residue kinetics
  - Pharmacokinetics (absorption, distribution, metabolism, excretion)
  - Depletion of residues
  - Analytical method
- Safety of users
- Environmental impact assessment

Efficacy tests

- Pre-clinical trials (might partly already be included in safety or residues data):
  - Pharmacodynamic mechanisms underlying the therapeutic effect
  - Pharmacokinetics
  - Bioequivalence (if applicable)
  - Dose determination
  - Resistance development (antimicrobials, antiparasitics)

- Results of clinical trials

B. Immunological veterinary medicinal products

Quality documentation

- Composition of the product
- Method of preparation: manufacturing method, in-process control tests and validation incl. batch analysis
- Starting materials listed n the pharmacopoeias and starting materials not listed in the pharmacopoeias
- Adjuvants and excipients: specifications, suitability and safety data, where appropriate
- Packaging material (immediate packaging): specifications and suitability
- Control tests during the manufacturing process
- Control tests on finished product
- Batch-to-batch consistency
- Stability tests

Safety and residues data

Laboratory Studies on:

- Safety of the administration of one dose
- Safety of the administration of an overdose (only for live immunological veterinary medicinal products)
- Safety of the administration of one dose
- Examination of reproductive performance
- Examination of immunological functions
- Special requirements for live vaccines
    - Spread of the vaccine strain
    - Dissemination in the vaccinated animal
    - Reversion to virulence of attenuated vaccines
    - Biological properties of the vaccine strain
    - Recombination or genomic reassortment of strains
- Safety of users
- Study of residues (only required for products food producing animals)
- Interactions

Field Studies

Environmental risk assessment

Assessment required for veterinary medicinal products containing or consisting of Genetically Modified Organisms

Efficacy Tests

General requirements including the choice of antigens or vaccine strains, the efficacy of the IVMP as well as additional data such as diagnostic tests

Laboratory trials (well-controlled laboratory conditions by challenge)

Field trials (using batches representative of the manufacturing process, both safety and efficacy may be investigated in the same field study). Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.