

The role of veterinary medicine regulatory agencies

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Summary

An effective animal medicine regulatory programme includes a systematic, evidence-based means of documenting the safety and effectiveness of products before they are produced, marketed or used in a particular country or region. The programme must also include adequate monitoring and controls over the use of these substances. It is clear that such programmes provide veterinarians, farmers and other animal medicine users with greater assurance that veterinary drugs and biologicals will be safe and effective in preventing and mitigating disease. It is important that these regulatory controls include programmes to ensure that human food obtained from treated animals is safe and that all potential toxicological and microbiological hazards that may be associated with the use of veterinary medicines have been adequately evaluated.

There is a great need worldwide for veterinary medicines that provide needed therapies for vast numbers of animals and animal species and, in the case of food-producing animals, for medicinal products that enhance the productivity and efficiency of food production and ensure food safety when they are used in accordance with their approval specifications. The public health mission of regulatory agencies succeeds when they are able to put into the hands of the user an approved, safe and effective, well-manufactured and appropriately labelled medicine, and when there are adequate controls in place to assure proper compliance.

Keywords

Adverse event reporting – Antimicrobial resistance – Codex Alimentarius – Compliance programmes – Drug residue safety – Food-producing animals – Human food safety – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products – OIE Focal Points for Veterinary Products – Pre-market approval – Veterinary medicines (drugs and biologicals) – VICH.

Introduction

Safe and nutritious food products derived from animals are more likely to come from healthy animals than from those that are compromised by disease. Veterinary medicines help to prevent animal disease and maintain animal health. Veterinary medicine regulatory programmes that effectively monitor and control every step in the development, production and use of these products help to ensure the availability and usefulness of these important substances.

While the effective control of veterinary medicines is the responsibility of many individuals and organisations, the primary purpose of this article is to provide information about the appropriate role of governmental veterinary medicine regulatory agencies in ensuring animal health and food safety. The regulation and control of veterinary medicines by governments often involve several different agencies and even different Ministries or Cabinet departments. This is especially true for the regulation of veterinary medicines used in food-producing animals. Many countries have separate agencies responsible for animal

health and for human health. But, increasingly, recognition is being given to the fact that healthy animals are more likely to produce safe food for humans and less likely to be reservoirs and vectors of zoonoses. This is resulting in much closer collaboration between those in government who are responsible for animal health and those responsible for human health.

In those nations where such organisational complexities exist, good coordination and communication among all relevant governmental bodies are essential for ensuring the effectiveness of veterinary medicine regulatory controls. The objective of any veterinary medicine regulatory programme should be to help make available safe, effective and high-quality veterinary drugs and biologicals. This includes providing an assurance that human foods derived from animals are harmless. Thus, an effective programme must embrace the compatible goals of protecting both animal health and human health.

It should be noted that the regulatory agencies responsible for drugs and biologicals used on the farm or ranch are also often the organisations that control medicinal products that are administered to companion animals/pets. It is important to ensure the quality of life for these animals, through safe and effective medical interventions. Pets in many countries are closely bonded to their human owners, and the close interactions between these animals and their owners can present an ideal opportunity for disease transmission. Therefore, many therapeutic medicines for companion animals also serve the important human public health purpose of preventing the development of zoonotic diseases.

Veterinary medicines

Veterinary medicines are generally defined as products that are intended for use in animals for specific purposes. These purposes include the diagnosis, cure, mitigation, management, treatment or prevention of disease in animals. They can also include the modification of any structure or function of an animal's body, such as enhancing reproductive capabilities or other production uses, such as feed efficiency or growth promotion. Substances used as veterinary drugs and biologicals can include chemicals, viruses, sera, toxins, vaccines, bacterins, allergens, antibiotics, antitoxins, toxoids, immunostimulants, cytokines, antigens, diagnostic components of natural or synthetic origin, genes or genetic sequences, carbohydrates, proteins, and other substances. Such substances could be injected, ingested, inhaled, absorbed, or in some other way exposed to the animal, including through water and feed.

Because veterinary medicines are intended to produce specific biological effects in animals, they are inherently risky and their approval and use must be closely controlled and

monitored by regulatory agencies, farmers, veterinarians, food manufacturers, drug and biological manufacturers, and others involved in the 'farm to fork' food chain. The inherent risks associated with the use of these products, as well as the potential for fraudulent or deceptive practices, should be balanced against the benefits provided. In other words, there must be an adequate demonstration of effectiveness or efficacy for every claimed use of a product before approval is granted. As with other consumer products that have the potential to harm people or animals, those individuals and companies involved in this chain have a unique responsibility to act with a very high degree of care and to do all that is necessary to ensure product safety. In some ways, the regulation of animal medicines is more complex than the control programmes for similar products in humans. Veterinary medicines are designed to meet the therapeutic and production needs of a large and diverse number of animal species with considerable variations in indications for use.

Legal structures and principles that support regulatory controls

A governmental regulatory programme must have the political support of national leaders and the legal authority to operate effectively. There are many forms and structures of government throughout the world, reflecting the historical, cultural and philosophical differences among nations. The aim of this paper is not to advocate any particular governmental or economic system. The veterinary medicine controls described in this paper reflect broad principles and programme elements that can be accommodated by most governmental infrastructures, regardless of national political beliefs. In general, the legal basis as well as the substantive requirements for product regulation should express the particular priorities and circumstances unique to each country or region. Some of the factors relevant to the regulation of veterinary medicines, and which may also vary from country to country or region to region, include the following:

- differing views about the appropriate roles and responsibilities of government agencies *versus* those of industry or professional organisations
- different levels of resources available for regulation
- regional differences in the epidemiology of animal diseases
- differences in the practice of veterinary medicine
- differences in agricultural conditions and climates
- differences in on-farm practices.

Based on national or regional circumstances, programmes that are very different from one another can still provide appropriate regulatory controls over the approval, monitoring, compliance and enforcement activities involved in the development and use of veterinary medicines. The purpose of this paper is to describe the key principles and core elements of efficient and effective regulation of veterinary medicines that are applicable to all countries.

The legal basis that underlies most regulatory programmes includes laws, regulations, guidance and policy. Laws describe binding rules of conduct or product standards that have been formally adopted by a government authority, such as a national legislature or parliament. Typically, laws do not include many of the specific details needed to explain how an individual, business, state or local government, or any other body might operate or ensure compliance. Because the legislative process is usually very difficult and time-consuming to amend, the use of regulations, guidance and/or policies is often a more practical way of providing detailed specific information and of being able to revise existing requirements relatively quickly. Regulatory adjustments are often necessary, as knowledge is gained through experience in the use of specific regulatory controls or as a result of changes in the scientific basis for the controls.

Rules or regulations that implement laws should be issued by an administrative agency through formal procedures that are transparent and permit input from all relevant interest groups and individuals. In most countries, for regulations to be binding, there is a specific delegation of authority from the legislature to the administrative agency. In the United States, this delegation of authority is based on the Administrative Procedure Act, passed by Congress and signed by the President in 1946 (www.archives.gov/federal-register/laws/administrative-procedure).

Guidance provides advice and reflects the administrative agency's 'current thinking' but is usually not binding. This means that alternative approaches could be used if they satisfy the statutory or regulatory requirements. Guidance documents are statements of policy on a particular regulatory issue or an interpretation of a law or regulation, and may relate to the design, production, labelling, promotion, manufacturing and testing of regulated products. Guidance provides the industry or other interested parties with specific recommendations on how to comply with laws and regulations and avoid enforcement actions. Policies are formal opinions about regulatory matters and are also usually not binding.

Specific regulatory requirements should be published and made available to all interested parties. The most effective legal structures are usually fully transparent and open to scrutiny by all interested parties, often through 'notice and comment' procedures, which take into consideration any legal requirements to protect confidential or proprietary

information. Proposed and final rules, guidance documents and policy statements are typically published in the official journal of each nation. (For example, in the United States, this publication is the *Federal Register*, available at www.federalregister.gov; in the Commonwealth of Australia it is the *Chemical Gazette*; and in the Republic of South Africa it is the *Government Gazette of South Africa*.)

Other procedures to develop appropriate regulations, guidance documents and policies include opportunities for interested parties to directly request agencies to draft guidelines or rules (e.g. citizen petitions). When regulators are considering the development of new, complex or controversial regulations or policies, they may find it useful to convene a formal advisory committee of outside experts to make recommendations to their agency.

Effective regulatory programmes should contain control measures that serve both to prevent unacceptable risks and to intervene or respond when problems occur. They should also enable continuous improvements to take place by using mechanisms or measurements to evaluate whether each programme is achieving its objectives.

Shared responsibilities

Many individuals and organisations share some responsibility for the use of veterinary medicines, i.e.: regional, national, state and/or local regulatory agencies; drug and biological manufacturers; farmers and ranchers; veterinarians; veterinary professional organisations; trade associations; international standard-setting organisations; abattoirs and food processors; consumer organisations and others. All of these individuals or groups should have specific roles and responsibilities that are clearly defined. In many countries, veterinary medicine companies serve the crucial role of undertaking research and developing the information and data that support the safety, efficacy, quality and accurate labelling of the products for which they are seeking approval. This information must be provided to the appropriate approval or licensing agency in a transparent and ethical manner. Academic and scientific institutions may also have a role as they are a source of expertise and knowledge to support a risk-based, scientific foundation for effective regulation. Regulatory agencies have the responsibility of establishing and maintaining up-to-date legal requirements and of ensuring the effective operation of the national veterinary medicines control system. These regulatory officials must apply the controls under their authority in a consistent and impartial manner, free from improper or undue influence or conflict of interest. Regulatory authorities also have the responsibility of making their decisions based on information derived from objective, science-based evidence and the principles of risk analysis. Farmers, ranchers and veterinarians have the important role

of controlling and managing the risks involved in selecting, administering and using these products.

All of these stakeholders share the common interest of ensuring that only approved products that are safe and effective are put in the hands of the user. Government regulatory agencies have the crucial responsibility of ensuring that only safe, effective, high-quality, well-manufactured and properly labelled animal drugs and biologicals are available in the marketplace for use, and that unsafe and ineffective products, such as counterfeit and illegally compounded medicines, are not available.

Use of international and other standards

Laws, regulations, guidance and/or policies relevant to the control of veterinary medicines may also make reference to, or be based on, product standards or conformity assessment procedures that have been developed and/or harmonised by international or multilateral organisations, such as the Codex Alimentarius Commission (Codex), the World Organisation for Animal Health (OIE), the World Health Organization (WHO), or the International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH). The World Trade Organization's (WTO's) Agreement on the Application of Sanitary and Phytosanitary Measures (the 'SPS Agreement') states that risk analysis frameworks that are adopted by national governments should be consistent with the relevant risk analysis guidelines and policies developed by Codex or the OIE.

Codex and OIE standards are often adopted as guidelines or even requirements by many countries. If a WTO trade dispute occurs, involving an SPS measure, a country that relies on Codex and/or OIE standards does not have to demonstrate that its measures are based on sound science and on public health or animal health protection principles. On the other hand, if a dispute arises over a standard that was not established by Codex and/or the OIE, then the country maintaining that standard may have the legal burden of demonstrating that it is based on an acceptable risk analysis framework.

The VICH programme is a trilateral one, aimed at harmonising technical requirements for veterinary product registration. Its Member Countries are the European Union, Japan and the United States, while Canada, New Zealand and Australia participate as Observer Countries. Experts who represent each country are drawn from both the government regulatory and industry sectors. Since 1996, VICH has established and implemented a large number of

harmonised regulatory guidelines that describe appropriate testing protocols, standards and procedures for studies designed to demonstrate the safety, efficacy and quality of veterinary medicinal products. The Member Countries have committed themselves to accept and use all finalised VICH guidelines, whereas Observer Countries accept and use many of these guidelines but have not made the commitment to adopt all of them. (Details of all VICH guidelines can be found on the organisation's website: www.vichsec.org/en/guidelines2.htm.) In 2012, VICH convened the first VICH Global Outreach Forum for the purpose of raising awareness of VICH guidelines among non-VICH countries involved in developing veterinary medicines. Countries and organisations attending these forums now include: South Africa, China, Brazil, Argentina, Russia, India, the West African Economic and Monetary Union, the Veterinary Medicines Committee of the Americas, and a number of others.

In addition to taking into account guidelines developed by international organisations, regulatory authorities should consider the value of using elements of other countries' programmes that are designed to meet the same or similar objectives. Building on the information obtained from other national or international organisations can help to make limited regulatory resources go a lot further. Some work must be carried out first to enable confidence in, or to determine the degree of equivalence or comparability of, the data and information provided by the other country.

Pre-market approval requirements and procedures

As a result of the inherent risks involved with the use of veterinary medicines, most countries have preventive controls in place, in the form of well-established procedures for pre-market approval or licensing of these products. The regulatory structure for approving new animal drugs and biologicals that meet the legal standards of safety and effectiveness typically uses a decision-making process that weighs the benefits against the risks of each product. In general, before a new animal medicine is approved for commercial use, four vital 'pillars' should be established. First, the product must be safe: safe for the animal, safe for the humans consuming food derived from the treated animal, safe for the user or the person administering the product, and safe for the environment. Secondly, an animal medicine must be effective for its intended uses. These uses are those prescribed, recommended or suggested in the labelling of the product. Thirdly, the animal medicine must be a quality manufactured product, i.e. the result of a validated manufacturing process conducted in accordance with current good manufacturing practices (GMPs) or other processes that ensure quality and reliability. Fourthly,

the product must be properly labelled to inform the user not only of how to use the product, but also of any safety considerations, drug and vaccine withdrawal times, and storage and handling procedures. Once in the marketplace, an animal medicine should be monitored to ensure that these characteristics are maintained and that the product is used appropriately.

In many countries, new animal medicines may be exempt from pre-approval requirements if they are intended solely for investigational use; for example, if they are undergoing studies designed to demonstrate their safety and effectiveness. These investigational studies, while limited, nevertheless should be followed carefully by regulatory authorities to ensure that the animals being used in these experiments are properly and humanely handled and that any human food products derived from these animals do not enter the marketplace. In many countries, such investigational studies must be notified to the appropriate regulatory authorities to help ensure that these requirements are being met.

For food-producing animals, regulatory agencies need to ensure that the use of therapeutic or production animal drugs and biologicals helps to maintain animal health and improve animal welfare. By improving animal health and production, these products can, in turn, help to increase the availability of an affordable, abundant and wholesome food supply to meet the needs of a growing worldwide human population. One of the important challenges facing veterinary medicine regulators is to engage in the development and evaluation of new animal drugs and biologicals, especially new innovative technologies, to assist in meeting the ever-increasing demand for safe, affordable and abundant food production.

In most countries, the studies that are conducted to demonstrate safety, effectiveness and quality are undertaken by the drug and biological industry. Many of these studies may also be conducted by government laboratories or academic institutions. But, whatever the source for supporting data, the government regulator who reviews the information must be able to rely on the data presented by the product's sponsor. The reviewer must have a very high level of confidence in the data that support safety and effectiveness. For example, when sponsors are new and less experienced, or if only one or a very few studies are submitted, the required levels of data integrity and quality may often be set higher. Alternatively, if the reviewer can rely on a broad array of data from numerous studies that corroborate each other, the reviewer's confidence in the weight of evidence creates some flexibility in the type of data that can be accepted. As a general rule, all safety studies must be conducted in accordance with the set of regulations or standards known as current good laboratory practices (GLPs). Different GLP standards are used around the world; however, sponsors

and authorities in many countries employ the harmonised standards developed by the Organisation for Economic Co-operation and Development (OECD) (2). Effectiveness studies are expected to meet current good clinical practice (GCP) standards. The representatives participating in VICH have developed a guideline on GCP (12), which is used by many sponsors and authorities.

Specific technical requirements covered in pre-market reviews and assessments

There are a number of important technical elements that must be covered by any product review as part of an approval or licensing process. These technical requirements make up the supporting evidence, drawn from both data and other information, needed to conclude that the product is safe and effective for its intended use. Each of these technical sections is described briefly below, with particular detail on the information that supports the assessment of human food safety risks.

Human food safety

Evidence supporting the human food safety section of the review should be required for applications covering animal drugs and biologicals intended for use in species used for human food. This information must include a description of practicable methods for determining the quantity, if any, of the new animal medicine left in or on human food, and any substance formed in or on food because of its use. It must also describe the proposed tolerance or withdrawal period or any other restrictions on use to ensure that the proposed use of the product will be safe. This information should also contain any data on residue toxicology, microbial food safety if the animal drug has anti-infective properties, and residue chemistry.

Human food safety assessment is primarily focused on drug residues. Residues can include the parent compound, its metabolites, and any other substance formed in or on the animal's edible tissues as a result of using a veterinary medicine. Evaluating the safety of veterinary medicine residues should be based on risk assessment principles, where risk is a function of the particular hazard and exposure to that hazard. These risks involve human exposure to medicines or related factors through the consumption of edible animal tissues. In general, two key possible human health hazards from the use of veterinary medicines include the potential toxicity of the residue and/or effects on microorganisms.

Human food safety technical requirements may be divided into three categories:

- toxicology
- microbiology
- residue chemistry.

Toxicology

The purpose of toxicology studies is to obtain data to establish safety parameters, such as acceptable daily intake (ADI), safe concentration, tolerance or maximum residue limit (MRL), and withdrawal time. Such human food safety data may include short- and long-term toxicology studies to measure acute and chronic effects, as well as other results.

The toxicological endpoints which are studied to evaluate the safety of medicines used in food-producing animals for humans may include: hepatic toxicity, nephrotoxicity, genotoxicity, carcinogenicity, reproductive toxicity, developmental toxicity, neurotoxicity, respiratory tract toxicity, immunotoxicity, and dermal sensitisation and irritation. Studies involving oral exposure in surrogate laboratory animals are typically used to determine a safe level of exposure by identifying the 'no observable effect' level from dose-response curves and applying appropriate uncertainty factors to extrapolate the results from animal studies to predicted effects in humans. Among the human studies sometimes used are: epidemiological studies, human clinical studies and human case reports. Based on the results of these studies, a human toxicological ADI level for total drug residues in edible tissues is established. The ADI represents the amount of drug residue that can safely be consumed per day over a human's lifetime without adverse effects. Typically, for drugs used in dairy cows and/or in laying hens, the ADI is divided among the edible tissues (muscle, liver, kidneys and fat), milk and eggs. If the drug is not used in dairy cows and laying hens, the full ADI is allocated to muscle, liver, kidneys and fat. Through this process, a safe concentration value for total drug residues in each edible tissue can be calculated.

Considerable success has been achieved in harmonising the testing protocols and methodologies for most toxicological studies typically used to assess the human food safety of animal drug residues present in edible animal tissues. This agreement has been gained through the work done by countries participating in VICH. At present, there are seven finalised VICH guidelines covering studies of human food safety (26, 27, 30, 31, 33, 34, 44).

Microbiology

The development of resistance to antimicrobial therapies by pathogenic aetiological microorganisms is a major concern in both veterinary and human medicine. In veterinary medicine, these concerns extend beyond resistance in

pathogens of the target animal. As part of the pre-approval evaluation of antimicrobial drugs in food-producing animals, a great deal of effort has been made to address the potential development of resistance in foodborne, zoonotic pathogens that may infect humans.

In treated food-producing animals, the emergence, selection and dissemination of antimicrobial resistance is a complex ecological phenomenon involving genetic changes and exchanges, microbial selection and dissemination of resistance, and the persistence of resistant phenotypes. Veterinary medicine regulators should adopt the principles of judicious use of antimicrobials to help combat this problem in food-producing animals. For example, the United States Food and Drug Administration (FDA) has produced guidelines describing its commitment to reduce, eliminate or prevent the unnecessary use of antimicrobial drugs important to human medicine and public health in food-producing animals (5).

For antimicrobial animal drugs or compounds with antimicrobial activity, sponsors should address microbial food safety concerns, by assessing whether antimicrobial-resistant, foodborne bacteria of public health concern in or on food products from animals treated with antimicrobials have any clinically relevant effects on humans.

The FDA's Center for Veterinary Medicine (CVM) has experience in implementing a risk-based approach to evaluating, during the pre-approval process, the potential for resistance to develop from the use of an antimicrobial drug in food-producing animals. While much information has been gained through this experience, challenges remain. For these pre-approval assessments, a quantitative approach (i.e. data-rich) is well suited for assessing risk and recommending appropriate risk mitigation steps to minimise resistance associated with the proposed uses of the drug. However, to date there are very few instances where quantitative risk assessments have actually been carried out to evaluate antimicrobial resistance (e.g. some uses of the drugs enrofloxacin and virginiamycin have been evaluated using quantitative risk assessments). Quantitative data are not available for many antimicrobial compounds, especially in the context of a specific drug for treating a specific bacterium under specific conditions of use. Such 'drug/bug/use' information is ideally needed to undertake a pre-approval evaluation of a particular antimicrobial drug. Thus, CVM has been using a non-binding, qualitative risk assessment approach (3), while encouraging sponsors to use as much quantitative information as possible to address specific elements in their risk assessment, including any data available from antimicrobial resistance monitoring programmes (see additional details in the section entitled, 'Monitoring of antimicrobial resistance in foodborne microorganisms', below). A guideline has been developed by VICH that outlines the types of studies and data that are

recommended to characterise the potential development of resistance as it might occur in the animal under the proposed conditions of drug use (32).

The studies for establishing a human toxicological ADI level for total drug residues in edible tissues were described in the "Toxicology section, above. However, one should note that if the drug being evaluated is an antimicrobial drug, the ADI may be based on a microbiological ADI rather than a toxicological ADI, depending on whichever value is smaller. Microbiological ADIs present two endpoints of concern: the disruption of the colonisation barrier and a change of resistance in the bacterial population of human intestinal flora. Normal intestinal microflora function as a barrier to limit the colonisation of the colon by pathogenic bacteria. The potential for disrupting this function must be assessed when reviewing the safety of antimicrobial residues that may be in food. Such residues may also contribute to the development of resistance in human intestinal bacteria. Thus, VICH has developed a relevant guideline for designing appropriate studies to determine if there is a need to address these two microbial human food safety endpoints (54).

Residue chemistry

Residue chemistry studies may be undertaken to control the level of exposure to any hazard that has been identified in the toxicological or microbial food safety studies described above. These studies may include total residue and metabolism studies, comparative metabolism studies, analytical method validation studies, and tissue residue depletion studies. The representatives of the countries which take part in VICH have reached agreement on four protocols for residue chemistry studies (49, 50, 51, 52).

Target animal safety

Information submitted by the medicine's sponsor should permit an evaluation of the cumulative effect of the medicine on the animal, so that it does not adversely affect the treated animal. Target animal safety studies must contain full reports of all studies that show whether or not the animal medicine is safe for the target species. The target animal safety data may include studies which identify the toxic syndrome(s) associated with the medicine and the margin of safety for using the product in the treated animal. Three guidelines covering target animal safety studies have been developed by VICH (42, 43, 46).

User safety

Information should be considered that covers hazards associated with administering the medicine to animals, i.e. risks to the veterinarian or farmer. User safety concerns

also include hazards associated with the manufacturing of the product, both direct occupational exposure at the production site and indirect exposure from manufacturing emissions. It is also important to consider hazards associated with air, water and wastes, all of which may be contaminated because of the manufacture, use and/or disposal of the medicine.

Effectiveness

Information on the effectiveness of the medicine should contain full reports of all studies that show whether or not the animal medicine is useful for its intended purpose. The sponsor should demonstrate, through substantial evidence, that the product does have the effect it claims or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labelling. The sponsor should also provide information to assist in selecting the dosage (i.e. dosage characterisation). A sponsor might provide a logical scientific rationale or use a variety of studies to present this effectiveness information, including:

- studies conducted in the target species
- studies conducted in laboratory animals
- field investigations
- bio-equivalence studies
- *in-vitro* studies.

Pharmacokinetic and pharmacodynamic studies may further document the medicine's effectiveness. Sponsors may derive dosage characterisations from many data sources, including dose-titration studies, pilot studies, foreign studies, published literature, *in-vitro* studies, inter-species dose extrapolations and pharmacokinetic and pharmacodynamic studies. Member Countries of VICH have agreed to nine harmonised guidelines covering effectiveness studies (15, 18, 19, 20, 21, 22, 23, 24, 25).

Chemistry and manufacturing controls

Information supporting the chemistry, manufacturing and related controls sections of an application should contain complete data on the manufacture of the animal medicine, including manufacturing methods and controls, stability data, and GMP compliance or related information. This is important to ensure that the medicine that is sold to the public will be of a quality similar to that of the medicine that was demonstrated to be safe and effective and has similar attributes. In other words, it is vital to make sure that the quality of the product meets the appropriate standards, and that the product itself is manufactured in a manner that ensures its consistency and is the same substance that is described on the label.

Questions that the sponsor must answer include:

- how and where is the medicine made?
- how are the raw materials tested and monitored?
- what control procedures are in place to ensure product consistency and quality?
- are the attributes and characteristics of the product adequately identified and characterised?
- are the test methods used to monitor the product's quality appropriate?
- for how long does the product maintain its quality after it is made?

Many countries require that on-site inspections take place before a medicine is approved to verify that the chemistry and manufacturing controls described in the application or dossier are actually being employed in the manufacturing facility. It is crucial to provide the reviewing authority with full access to manufacturing and distribution sites at all times (including access to quality assurance and other relevant records). Periodic inspections to monitor GMPs, batch-release controls, and distribution practices, such as cold-chain and transportation controls, should continue to be carried out after a product has been licensed or approved. Member Countries of VICH have developed (or, in some cases, are developing) 19 harmonised guidelines covering various product quality issues (6, 7, 8, 9, 10, 11, 13, 16, 17, 28, 29, 37, 38, 39, 40, 47, 48, 55, 56).

Environmental impact

Environmental impact data should demonstrate that the use, manufacture and disposal of the medicine do not pose a significant risk to, or have a significant impact on, the environment. These data should contain either an environmental impact assessment (EIA) or evidence that provides the basis for an exemption from an EIA. Before approving a new animal medicine, the regulatory agency should consider the potential effects of the use of the product on the environment. In many cases, including drugs intended for many uses in minor species, a categorical exclusion from the need to provide an EIA might be possible. In other cases, such as new chemical entities (and almost always in the case of a drug for an aquatic species), some type of EIA will be necessary to support a finding of no significant impact on the environment. Harmonised guidelines have been established by VICH, describing the data requirements and basic risk assessment process for evaluating potential environmental effects caused by veterinary medicines and their use. These VICH guidelines include exposure-based screening and quantitative risk assessment procedures (14, 35).

Labelling

The sponsor should provide the regulatory agency with the proposed product labelling, including what will appear on the immediate container (e.g. vial, syringe, packet) or feed-bag label, the package insert, and the packaging (outer box or carton). Labelling can include the indications for use and the target animal, the dosage and route of administration, adverse reactions reported in field studies, the treatment period, and any recommendations for successful use. It may also contain results from target animal safety studies and appropriate warnings and contra-indication statements. Withdrawal times for edible tissues may be included. Storage conditions and formulation information should also be included.

The labelling must indicate whether the product should be made available only under a prescription or may be sold over the counter. Prescription medicines are products that only an individual with professional expertise (i.e. a veterinarian) can properly dispense or administer, provide adequate instructions for post-treatment care, monitor the safe use of the product, or treat any adverse reactions. A decision on whether the use of this medicine would be effective should consider whether an accurate diagnosis can be made with a reasonable degree of certainty, whether the product can be properly administered, and whether the course of the disease can be followed so that the success or lack of success of the product can be observed and managed. The regulatory agency may also review the label to ensure that the trade or proprietary name of the product cannot be interpreted to be inappropriately promotional or false or misleading.

Other information

Other information may include all data pertinent to the safety and effectiveness of the drug, which have been received or otherwise obtained by the applicant from any source. It should contain information from any investigations, reports of pilot studies, foreign marketing experience, scientific literature reports, and any other data that have not already been submitted by the sponsor as part of a major technical section. This information should be comprehensive and balanced and include favourable and any unfavourable literature. It is the sponsor's responsibility to be transparent and to provide the regulator with any information, of which the sponsor is aware, that pertains to the safety or efficacy of the product in question, even if this information was not developed by the sponsor.

Additional considerations for generic animal medicines

Some products are generic copies of animal medicines that have been previously approved and shown to be safe and

effective when used in accordance with their labelling. Generic products may be approved through an evaluation process that requires the manufacturer to show that their drug has the same active ingredient as the previously approved 'pioneer' product; that the active ingredients are in the same concentrations; and that the product is bio-equivalent.

Member Countries of VICH are developing agreement on a guideline that describes the study protocols and data requirements associated with *in-vivo*, blood-level bio-equivalence studies for veterinary drug products. This guideline is currently in draft form and addresses the following topics: a harmonised definition of bio-equivalence; factors/variables that need to be considered when developing scientifically sound, blood-level, bio-equivalence study designs; and information that should be included in a blood-level, bio-equivalence study report.

In many countries, generic applications may require a lower burden of evidence to show safety and effectiveness than innovator products. However, they should still require the identity of the generic product and the previously approved product; the proposed labelling for the generic product and the approved labelling for the innovator product; the identities of all the active and inactive ingredients and any other components used in the manufacturing process, and their concentrations in the final product; the same active ingredients and the same strength, dosage and route of administration as the approved product; possibly a tissue residue depletion study for the proposed generic product, if it is intended for use in food-producing animals; and details of the manufacturing process, including manufacturing facilities, key personnel, analytical methods, specifications, quality control procedures, etc. Generic applications should also include an assessment of environmental impact.

Special incentives for some veterinary medicinal products

Some categories of veterinary drugs and biologicals pose special challenges when ensuring the availability of safe and effective products. This is especially true for medicines used in non-major species or for minor indications. In this context, 'major species' refers to an animal species which has a relatively large population of potential users. 'Minor uses' are uses in major species for indications that occur infrequently and only in a small number of animals or limited geographic areas. Most countries face problems in ensuring the availability of products for minor species or minor uses. Sponsors are reluctant to invest in the expensive studies needed for approval if the potential market for their product is small.

Some countries have developed special programmes to meet these challenges. For example, in the United States, 'The Minor Use and Minor Species Animal Health Act' was passed in 2004 (4). This law was intended to make more medications legally available to veterinarians and animal-owners to treat minor animal species and uncommon diseases in major animal species. The Act provides innovative ways to bring these kinds of products to market and is designed to help pharmaceutical companies overcome the financial roadblocks involved in providing limited-demand animal medicines, by, for instance, allowing 'conditional approval' and making a drug available before collecting all the necessary effectiveness data (but only if there is a reasonable expectation that the drug will be effective, and after proving that the drug is safe). Another incentive under United States law makes some of these new drugs eligible for grants to support safety and effectiveness testing or gives their sponsors exclusive marketing rights for certain periods of time.

Permitting 'extra-label uses' or 'off-label uses' is another way of making medicines available when marketplace disincentives exist. 'Off-label use' refers to the use by a veterinarian (or, in some cases, other health professionals and even lay people) of an approved product in a way that is not in accordance with the label or package insert. This practice can also involve the use of human medicines in animals, when there is no corresponding product licensed for veterinary use. Off-label use can be an important part of practising veterinary medicine. Many off-label uses are both effective and safe, often evidenced by subsequent approvals of such uses for numerous veterinary medicinal products.

Product regulatory agencies sometimes take the position that off-label use by a veterinarian relates to the practice of veterinary medicine and may therefore be outside their authority. This is particularly true when a clear veterinarian/patient relationship exists. The regulation of off-label uses may be justified, however, where special concerns arise over such uses in food-producing animals. The safety of drug use in food-producing animals involves not only the veterinarian and the patient, but also the potential consumer of the food. In such cases there is a need for the regulatory agency to ensure that 'off-label uses' do not compromise the safety of food derived from the treated animal. For this reason, regulatory agencies often place restrictions on off-label uses when they involve food-producing animals (Box 1).

Post-market monitoring of adverse events

It is important that the veterinary medicine regulatory agency monitors the use of products after they have been

Box 1**Restrictions on off-label use of veterinary medicinal products in food-producing animals in North America**

Canadian Food and Drug Regulations C.01.610.1: No person shall sell a drug for administration to animals that produce food or that are intended for consumption as food if that drug contains: chloramphenicol or its salts or derivatives; a 5-nitrofuranyl compound; clenbuterol or its salts or derivatives; a 5-nitroimidazole compound; or diethylstilbestrol or other stilbene compounds.

U.S. Food and Drug Regulations Sec. 530.41: Drugs prohibited for extra label use in animals. The following drugs, families of drugs, and substances are prohibited for extra label animal and human drug uses in food-producing animals: chloramphenicol; clenbuterol; diethylstilbestrol; dimetridazole; ipronidazole; other nitroimidazoles; furazolidone; nitrofurazone; sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypridazine); fluoroquinolones; glycopeptides; and phenylbutazone in female dairy cattle 20 months of age or older. The following drugs, or classes of drugs, that are approved for treating or preventing influenza A, are prohibited from extra label use in chickens, turkeys, and ducks: adamantanes; and neuraminidase inhibitors.

approved and placed on the market. Studies that support pre-market approval requirements are based on a limited number of test animals. When these products are marketed, the number of animals exposed to them often increases by a hundred or a thousand times. The primary purpose of a reporting programme for adverse events is to provide early warnings of harmful effects and/or evidence of a lack of effectiveness that were not detected or predicted during the pre-market product testing. In addition, such programmes can be used to monitor the performance of products that have not been legally approved or have not been approved for particular uses in animals. Information from adverse events can be used to make decisions about product safety which may include changes to the label or other regulatory actions, including withdrawal of approval or product seizures. These reports should take into consideration several confounding factors, such as:

- dosage
- concomitant use of medicines
- the medical and physical condition of the animals at the time of treatment
- environmental and management variables
- product defects
- extra-label uses.

The countries participating in VICH have worked for a number of years to develop harmonised guidelines for

pharmacovigilance reporting of adverse events. At present, these countries are very close to implementing national reporting schemes that will be consistent with VICH guidelines (36, 41, 45, 53).

Monitoring antimicrobial resistance in foodborne microorganisms

Programmes to monitor the prevalence of antimicrobial-resistant pathogens and other foodborne microorganisms should be carried out by the drug-approving regulatory agency to assist in identifying and tracking resistance patterns, as well as to collect data on the levels of resistance in animals, humans and retail meats. This information can help to target regulatory interventions to minimise the development of resistance. Evidence of increased rates of resistance developing in bacterial populations associated with human food, which has been derived from animals treated with antimicrobials that are also important in human medicine, may raise public health concerns. If these concerns are significant, regulatory actions should be considered, such as amending label indications for use or retracting approval of the antimicrobial.

Monitoring to ensure compliance

In every country, there is a crucial need to adequately monitor compliance with veterinary medicine regulatory programmes. Regulatory programmes often have detailed written requirements for post-market monitoring. Upon closer examination, however, some countries have very few resources dedicated to the implementation of these programmes. Adequately trained, experienced and technically competent personnel are needed to undertake these important tasks. There are several particularly important areas that need to be monitored to assure compliance:

- data quality
- veterinary drug residues.

Monitoring data quality

Effective veterinary medicine regulatory programmes should include the authority to conduct on-site inspections of study facilities, clinical investigators or contracted research organisations. These compliance programmes help to ensure the integrity of scientific testing and the

reliability of the test data submitted to regulatory agencies. Such inspections permit the agency to assess, through audit procedures and real-time inspections, whether the data submitted are reliable enough for the agency to be able to pass sound judgements on the safety and effectiveness of medicinal products.

These monitoring programmes should assure compliance with the following standards: GLPs (particularly for safety studies and pharmacokinetic studies) and GCPs (most typically for effectiveness studies, including laboratory effectiveness studies). In general, these kinds of inspections are recommended by the technical experts who review application data and results (e.g. reviews of human food safety or manufacturing technologies).

Usually, in the United States, these types of inspections are scheduled to take place at the time the study is being conducted (real-time or in-life inspections) or after the study has been completed (data audits). A real-time inspection allows the regulator to observe certain aspects of the study as they are being conducted or to look for particular issues of concern to the application reviewer. A data audit inspection allows for a full accounting of the study and may be conducted before or after the data are submitted to the regulatory agency for review.

Monitoring veterinary drug residues

It is crucial that regulatory agencies charged with controlling veterinary medicines should adequately monitor animal-derived food products, to ensure that those products contain no drug residues that violate established tolerance levels or MRLs. Illegal drug residues in a country's food supply can cause serious public health problems. The residues of greatest public health concern should be given the highest priority for enforcement or remedial action. If necessary, action should be taken against the food, against the food retail market, against the slaughterhouse, and/or against the veterinarian or farmer responsible, in order to prevent future violations. Most countries have lists of MRLs or tolerances that represent safe levels. Since 1985, much cooperative international work has been done by countries participating in the Codex Committee on Residues of Veterinary Drugs in Foods. As a result of these efforts, consensus has been reached on MRLs for more than 100 veterinary drug compounds. Many Codex veterinary drug MRLs have been adopted as guidelines or requirements by countries around the world. Codex has also published a 'Compendium of methods of analysis identified as suitable to support Codex veterinary drug MRLs' (1).

Enforcement

Effective regulatory programmes must have the legal authority to impose penalties, sanctions and other methods

of enforcement. These methods should include procedures to rapidly remove products that violate regulatory requirements from the marketplace, as well as processes to prohibit or close down manufacturers, practitioners and any others involved in the chain of distribution and use of an illegal or unsafe product. All enforcement information and the basis for these actions should be made available to the public, serving as an effective message to all about the importance of complying with regulatory requirements.

Making the best use of scarce health protection resources

Every public health and animal health protection agency has limited resources, including money, personnel and time. It is vital that every opportunity to effectively utilise the resources that are available should be identified and made use of. As mentioned above, there are diverse approaches to regulating veterinary medicines worldwide. Some authorities review some or all of the safety, efficacy and quality data before products can be registered or licensed. Other authorities may pool their regulatory knowledge and resources to review and monitor products with other national agencies that have comparable regulatory programmes, if they have confidence in how those programmes are implemented. Finally, some authorities perform few or none of the veterinary medicine control functions described in this paper. But, however limited a country's resources may be, all national regulatory authorities must work to ensure that animal medicines used in their country are safe and effective, whether that be through comprehensive review and monitoring programmes or through an in-depth understanding of the scientific basis for medicine approvals in other countries, or from any other relevant information upon which they may rely. This is part of each government's sovereign duty to protect the health and safety of the animals and people within its nation. Every country's regulatory programme must work to put in place a core set of scientific competencies and expertise to make necessary public health and animal health decisions. Standards and procedures must be available and able to be implemented when undertaking data assessments and/or in gaining a thorough understanding of assessments conducted by others. Those countries where there are few or no safety and efficacy control programmes are probably serving, or will serve in the future, as attractive markets for purveyors of unsafe or ineffective veterinary medicines.

Veterinary medicine safety information needs to be shared across geographic and political boundaries to synergise vital regulatory efforts and to make the best use of limited resources. Sharing data between agencies in real time is more practical today than ever before, through the use of

information technologies such as the Internet, e-mail, and video-conferencing capabilities. With special precautions taken to protect certain non-public or proprietary information, the kinds of information that can be shared include: pre-market product reviews, regulatory standards such as assessment criteria and procedures, warnings of adverse events, GMP/GLP/GCP inspection results, and information about product recalls and other enforcement actions.

Developing and sharing information within and among international and regional standard-setting organisations, such as the OIE, Codex, WHO, the Pharmaceutical Inspection Convention Scheme (www.picscheme.org/) and VICH are particularly effective ways of consolidating the common efforts of veterinary medicine regulatory agencies. Formal and informal bilateral arrangements between two agencies or among a number of agencies are also very effective ways to communicate important information.

The OIE has undertaken much of this crucial information-sharing work, first by identifying a National Focal Point within each OIE Member State who is responsible for controlling veterinary products, and then by supporting the work of the OIE Collaborating Centres, which have competence in strengthening national veterinary medicinal product regulatory infrastructures. Both the OIE and these Collaborating Centres continue to hold meetings with appropriate officials and technical experts around the world, to cooperate and share crucial information, with the goal of ensuring the global availability of safe and effective medicines to combat animal disease.

Challenges

For the animal medicine industry to produce an adequate and diverse supply of drugs and biologicals to meet the therapeutic and production needs of animals, regulatory processes must be constructed not only to fulfil statutory requirements but also to be efficient and conducive to the development of new products. At first glance, these statements may seem contradictory. Responsible regulatory agencies must first and foremost ensure that new animal medicines are safe and effective for their intended uses. They must also prevent the introduction of unsafe and ineffective products into the marketplace, as well as remove those that may already be present in the marketplace. But, at the same time, regulatory agencies must have efficient processes that are responsive to their stakeholders' needs. These include timely review decisions, effective and timely

communications and effective management of dossier or application reviews.

Regulators of animal drugs and biologicals are seeing an increase in non-traditional products, derived from techniques employing biotechnology, nanotechnology and immunology. For food-producing animals, regulators are seeing more products with production-enhancing and environmental sustainability claims. For non-food-producing animals, regulators are assessing more chronic disease treatments, cancer therapies and claims of life-enhancing treatments. There are also special concerns related to drug approval: for instance, issues of antimicrobial resistance, the limited development of new antimicrobials, the increase in novel substances as alternatives to antimicrobials, and concerns over resistance to antiparasitic drugs.

Without a doubt, the development and marketing of a new animal medicine is, in many countries, a complex and onerous undertaking. To meet the growing demand for safe and effective products, future regulators must become even more actively engaged with sponsors at the early stages of the development and evaluation of new animal medicines, especially when innovative technologies are being used. Animal products of the future will not necessarily fit the current review models. These products will probably use new technologies that regulators have not yet considered and for which vital safety and effectiveness standards have yet to be developed. Meeting rigorous standards for safety and effectiveness and maintaining the high quality of the manufactured product represent substantial challenges. As products change, regulatory agencies must employ new science-based approaches to prove safety and effectiveness but must also avoid the lure of increasing scientific rigor that goes beyond that which is necessary.

The availability of approved veterinary medicines ensures protection for animals, the public and product manufacturers. The presence of consistent and equitable standards around the world assures sponsors that their competitors will have to meet essentially the same regulatory requirements. Moreover, providing a seal of approval that distinguishes the approved product from competing unapproved, illegal, counterfeit or illegally compounded animal medicinal products means that farmers and veterinarians have the assurance of a reliable and high-quality product. ■

Le rôle des autorités chargées de la réglementation des médicaments vétérinaires

M.V. Smith

Résumé

Tout programme réglementaire en médecine vétérinaire qui se veut efficace doit disposer de moyens factuels permettant de vérifier systématiquement l'innocuité et l'efficacité des produits avant qu'ils ne soient produits, commercialisés ou utilisés dans un pays ou une région en particulier. Un tel programme doit également prévoir un suivi et un contrôle adéquats de l'usage qui est fait de ces substances. Il est évident que de tels programmes offrent une meilleure garantie aux vétérinaires, aux éleveurs et aux autres utilisateurs de médicaments vétérinaires quant à l'innocuité et l'efficacité des produits vétérinaires et biologiques utilisés dans le cadre de la prévention et de la lutte contre les maladies. Il est important que ces contrôles réglementaires comportent des programmes permettant de garantir l'innocuité des aliments destinés à la consommation humaine provenant d'animaux ayant fait l'objet d'un traitement médical et de s'assurer que tous les risques toxicologiques et microbiologiques potentiels susceptibles d'être associés à l'utilisation de médicaments vétérinaires ont été correctement évalués.

On a grand besoin de disposer partout dans le monde, de médicaments vétérinaires permettant de traiter un grand nombre d'animaux et d'espèces animales et, dans le cas des animaux destinés à l'alimentation, de médicaments susceptibles d'accroître la productivité et l'efficacité de la production alimentaire et de garantir la sécurité sanitaire des aliments lorsqu'ils sont utilisés conformément aux caractéristiques pour lesquelles ils ont été approuvés. Les autorités réglementaires remplissent leur mission de santé publique lorsqu'elles sont capables de mettre à la disposition des utilisateurs des médicaments autorisés, sûrs, efficaces, de qualité et convenablement étiquetés, en s'assurant au moyen des contrôles appropriés du bon respect des règles édictées en la matière.

Mots-clés

Animal destiné à l'alimentation – Antibiorésistance – Autorisation de mise sur le marché – Codex Alimentarius – Coopération internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments vétérinaires – Contrôle sanitaire des résidus de médicaments – Médecine vétérinaire – Médicament vétérinaire – Notification d'un événement indésirable – Points focaux de l'OIE pour les produits vétérinaires – Produits biologiques vétérinaires – Programme de mise en conformité – Sécurité des aliments destinés à la consommation humaine – VICH.



Función de los organismos de reglamentación de los medicamentos veterinarios

M.V. Smith

Resumen

Para que un programa de reglamentación de la medicina animal sea eficaz debe prever un mecanismo sistemático y científicamente fundamentado para certificar la inocuidad y eficacia de los productos antes de su fabricación, comercialización o utilización en determinado país o región. Semejante programa debe contemplar

asimismo los sistemas adecuados de seguimiento y control del uso que se hace de dichas sustancias. Resulta obvio que los programas de este tipo ofrecen a los veterinarios, productores y demás usuarios de la medicina veterinaria mayores garantías de que los medicamentos y productos biológicos de uso veterinario serán inocuos y eficaces para prevenir o atenuar enfermedades. Es importante que esos controles reglamentarios incluyan programas que garanticen la inocuidad de los alimentos obtenidos a partir de los animales tratados, así como la debida evaluación de todo eventual peligro toxicológico o microbiológico ligado al uso de fármacos veterinarios.

En todo el mundo hay gran necesidad de medicamentos veterinarios que sirvan para dispensar los tratamientos requeridos a un gran número de ejemplares y especies animales y, en el caso de los animales destinados al consumo humano, de productos medicinales que mejoren la productividad y eficacia en la obtención de alimentos y garanticen su inocuidad cuando los productos se empleen con arreglo a las especificaciones aprobadas. Un organismo de reglamentación tendrá éxito en su misión de salud pública cuando consiga poner en manos del usuario un medicamento aprobado, inocuo, seguro y eficaz, bien fabricado y debidamente etiquetado, y tenga instituidos los controles adecuados para asegurarse del debido cumplimiento de las normas.

Palabras clave

Animal de producción alimentaria – Aprobación previa a la comercialización – Codex Alimentarius – Cooperación Internacional para la Armonización de los Requisitos Técnicos relativos al Registro de Medicamentos Veterinarios – Inocuidad de los alimentos humanos – Inocuidad de los residuos medicamentosos – Medicamento veterinario – Medicina veterinaria – Notificación de eventos adversos – Productos biológicos de uso veterinario – Programa de observancia de normas – Puntos focales de la OIE para los productos veterinarios – Resistencia a los agentes antimicrobianos – VICH.



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