

Safe use of vaccines and vaccine compliance with food safety requirements

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Summary

Advanced technologies and regulatory regimes have contributed to the availability of veterinary vaccines that have high quality and favourable safety profiles in terms of potential risks posed to the target animals, the persons who come into contact with the vaccine, the consumers of food derived from vaccinated animals and the environment. The authorisation process requires that a range of safety studies are provided to evaluate the products. The design and production of vaccines, and their safe use, are primarily assessed by using data gathered from extensive pre-marketing studies performed on target animals and specific quality tests. The current post-marketing safeguards include good manufacturing practices, batch safety testing, inspections and pharmacovigilance. In addition to hazard identification, a full benefit/risk evaluation needs to be undertaken. The outcome of that evaluation will determine options for risk management and affect regulatory decisions on the safety of the vaccine; options might, for example, include special warnings on package inserts and labels.

Keywords

Animal – Assessment – Benefit – Consumer – Environment – Health – Pharmacovigilance – Risk – Safety – User – Vaccine.

Introduction

Historically, vaccination of animals has been a strategic component of policies, designed to prevent and control infectious diseases. In this respect, vaccination has had evident benefits for animal welfare and health. As well as the quality, safety and efficacy of the vaccine in relation to the target animal, the impact on public health and the environment must also be considered. By improving animal health, veterinary vaccines can reduce the circulation of animal pathogens and waste and may result in a reduction in the use of disinfectants and antimicrobials.

As a matter of principle, veterinary vaccines must be safe not only for the target animal species but also for the vaccine users, consumers of foodstuffs of animal origin and the environment. The risks associated with the use of vaccines are primarily related to the properties of the vaccine, care in handling and administration, and recipient host factors. Side effects may be local or systemic; they may occur at, or shortly after vaccination, or be delayed. In order to establish that a vaccine is safe, a risk assessment, followed by a benefit/risk analysis, must be undertaken for each vaccine before it can be authorised.

Criteria and requirements for risk assessment have been designed to ensure that vaccine producers gather a package

of safety data on the product through studies of both target animals and non-target animals, as well as quality data. Extensive testing is required as part of the vaccine development in order to obtain marketing authorisation. After development, testing is also routinely performed as a part of the batch release procedure on every batch of vaccine. New technologies have improved the safety and the efficacy of vaccines, thus ensuring satisfactory levels of immunity and reducing, or even eliminating, harmful and/or unexpected side effects in vaccinated animals.

In some cases, a risk assessment may indicate that a vaccine poses a potential risk to the target animals, public health or the environment; if so, the benefit/risk analysis, weighing the benefits of the vaccine against its risks, will determine whether the vaccine can still be used. If the vaccine offers considerable advantages in preventing illness, but presents potential risks to the target animals or human beings or the environment, the benefits would need to outweigh the risks. If the vaccine is authorised for release despite the risks, its use should be accompanied by adequate risk management measures that would minimise or eliminate the risk.

Marketing authorisation depends upon the risk assessment and benefit/risk analysis, which are based on the intended use and claimed benefits of a vaccine. The use and claim will be included in the summary of product characteristics (SPC), the package insert and the labelling, which should provide instructions for use, storage and waste disposal, as well as any appropriate safety warnings. These documents must make clear to the user that 'off-label' use (use not specified by the manufacturers) can be extremely dangerous; such off-label use could include administering the vaccine to non-target animal species or by a route different from the recommended ones. Users should also be aware that the use of contaminated vaccines can cause the spread of extraneous or exotic microorganisms in specific agent-free farms or geographical areas (10).

In recent years, and particularly in developed countries, public debate over the benefits of vaccination has increasingly been fuelled by fears that some risks have been underestimated. The suspected link between vaccination of cats and the development of sarcomas at the injection site of vaccines is an example (2, 12). Some cat owners are often so worried that they prefer to take the risk of not vaccinating their animals, instead of having them exposed to the potential risk of sarcoma development following vaccination.

Another case for concern is the use of multiple simultaneous vaccinations for different diseases, the validity and benefits of which are being questioned by several research groups. There are currently investigations into the possibility that such multiple vaccinations could lead to harmful side reactions such as interference with and

overloading of the immune system of animals, particularly companion animals. Similarly, early life immunisation programmes are increasingly criticised due to the unpredictable outcome of vaccinating very young animals and the fear of inducing tolerance or autoimmunity mechanisms (11, 15). Vaccination of animals is sometimes undertaken to mitigate the effects of poor management systems; this can result in serious risks of disease and should be avoided.

In general, there is no need to establish a maximum residue limit (MRL) for the active principles contained in specific vaccines, and a withdrawal period is not necessary after vaccination in most cases, because in general vaccination does not result in harmful residues of the active principles or immunological responses distinguishable from those that arise naturally (4). However, with certain live vaccines with zoonotic agents, withdrawal periods may be necessary. Furthermore, excipients and adjuvants as primary components of vaccines need to be considered when evaluating the safety of vaccines (16).

The present paper will give an overview of the regulatory requirements for vaccines. It will also address the main outcomes of the risk/safety assessment of the use of vaccines in target animal species, and in relation to vaccine users, consumers of food derived from vaccinated animals, and the environment.

Regulatory requirements

Most countries have a range of legislation to ensure at least minimum standards for the quality, safety and efficacy of veterinary medicinal products. 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 for pharmaceutical veterinary medicines as well as vaccines.

In order to obtain a marketing authorisation (or registration or licence, as appropriate) the company that intends to bring the product on the market must submit an application to the authority concerned, accompanied by a comprehensive package of data on the quality, safety and efficacy of the vaccine. The application should also address 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. Following the initial assessment of the application, additional questions usually arise ('list of questions') that the applicant (or sponsor) of the veterinary medicinal product will have to answer. Once all questions have been satisfactorily addressed and it is established that there are no risks that would prevent the

licensing of the vaccines, a marketing authorisation will be issued, imposing specific conditions of use, storage and waste disposal. Standards of manufacturing safety, including the design and production of vaccines, will often be regulated under different legislation and separate regulating authorities (e.g. workplace safety and environmental safety at the manufacturing plant are not usually covered by legislation governing veterinary medicines).

Harmonisation of rules and testing among individual countries and regions is carried out by international organisations concerned with animal health on a worldwide scale, such as the World Organisation for Animal Health (OIE) and the World Trade Organization (WTO). There is an ongoing programme to harmonise data requirements for veterinary medicinal products (including vaccines) in a number of areas, e.g. quality monitoring and target animal safety studies, within the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

To give an example, in the European Union (EU) and the countries of the European Economic Area, the requirements for obtaining a marketing authorisation are laid down in Directive 2001/82/EC, and subsequent amendments (7). Appendix 1 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. Further guidance is given in specific guidelines issued by the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA) (6) and the European Commission (3). For vaccines which are the subject of a European Pharmacopoeia monograph, specific requirements may be included in the relevant monograph (9).

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. Different procedures exist in the EU to obtain a marketing authorisation: in the centralised procedure, which is optional for new chemical entities and innovative products, and mandatory for products derived by biotechnological processes, the application is assessed by the CVMP. This procedure leads to a marketing authorisation binding in all EU Member States. In the mutual recognition procedure and the decentralised procedure the Member States, in which the product is

intended to be marketed, carry out the assessment aiming for consistent marketing authorisations. National marketing authorisations issued by individual Member States exist for veterinary medicinal products, which were on the market in the EU before 1995, and can be issued today, if a product is intended for one single EU Member State only. Depending on the process of the marketing authorisation chosen, the procedure is defined by Regulation (EC) No. 726/2004 (8) or described in Directive 2001/82/EC (7).

Principles of risk assessment/risk analysis

In order to ensure the safety of vaccines a risk assessment is necessary. The aim of the risk assessment is to identify hazards, to estimate the likelihood that the hazards will lead to actual harm, and to take decisions about appropriate measures for prevention and control. Risk assessment is a science-based process involving the following stages:

- hazard identification
- hazard characterisation
- exposure assessment
- risk characterisation.

In the first steps the potential hazards associated with the vaccine are comprehensively identified and characterised. In parallel, the exposure scenarios for the different protection goals for the vaccine under consideration are identified and described. A risk characterisation then estimates the probability of the identified hazards occurring. If any risks are not as low as reasonably practicable, the process of risk assessment should be repeated to ascertain whether additional management techniques and risk mitigation measures could reduce the level of risk.

Although, wherever possible, the risk assessment should be based on quantifiable outcomes, it is recognised that many of the judgments must necessarily be qualitative only. The risk can often be judged on a rating scale ranging from negligible through low and medium to severe or unacceptable.

Once all risks have been assessed – and if possible reduced – the residual risks are weighed against the benefits of the vaccine, in order to decide whether to grant a marketing authorisation, and to consider possible risk mitigation measures, if appropriate. The approved conditions of use of a veterinary medicinal product should be described in a clear and unambiguous manner. The identified risks and risk mitigation measures must be communicated to the users of the vaccines.

Safety of the target animals

Problem statement

Errors in the manufacturing process or incorrect use of vaccines are the two main causes of potential risks for target animal species. Unsafe live or poorly inactivated vaccines may harm the animal to which they are administered, and the causative agent may also spread and harm other animals or have serious ecological effects. Apart from the threat of potentially serious consequences related to contamination of vaccines by extraneous agents, which in extreme cases could lead to disease outbreaks and death of animals (10, 17), it is the likelihood of local toxicity and long-lasting side effects that generates the greatest concern for animal health and welfare (13). Adverse events can vary from carcass damage, as in the case of particularly aggressive adjuvants, to death of animals.

Scope of the assessment

The purpose of the evaluation during the development phase is to determine whether the vaccine is safe if used at the proposed dose level. The evaluation is limited to the health and welfare of the target animals.

Safety testing in target animal species must show the potential risks that may occur under the proposed conditions of use of vaccines. Laboratory safety studies have been designed to meet necessary basic requirements before initiating field trials. For the final assessment, safety data produced under controlled experimental conditions will be supported by results obtained during field trials. These trials are carried out with a statistically significant number of animals and designed to reflect, as accurately as possible, the practical conditions of use of the products being tested.

Risk assessment

Hazard identification and characterisation

The specific information that needs to be provided depends upon various factors, including:

- the type of vaccine (inactivated or live, bacterial or viral)
- the nature of the adjuvants that will be used
- the use history of similar products
- dose
- claims
- proposed usage regimen
- animal species, class and breed.

As a general rule, the 'worst case' or most severe potential harm should be assessed, even if it is highly unlikely (e.g.

a once in a lifetime probability), using a dose corresponding to the quantity of the product to be recommended and of the maximum titre or potency.

One dose, repeated doses and overdose tests are normally required for each of the target species, testing animals of the most sensitive class, age and sex identified on the label, and using all recommended routes and methods of administration. Essential parameters to be evaluated for the safety of a vaccine are local and systemic reactions to vaccination, including application site reactions and their resolution, and clinical observation of the animals. Other objective criteria, such as rectal temperature and performance measurements, are also recorded. Examination of the reproductive performance of breeding animals as well as of immunological functions must be considered when data suggest that the initial material from which the product is derived may be a risk factor.

For live vaccines specific additional tests are required, e.g. testing the potential that different levels of pathogenicity may be retained in the case of specific animal species, or of a certain age or class of animal, or specific routes of administration (induction of clinical signs or lesions of disease, or persistency/latency of the microorganism in the body of a vaccinated animal). Special requirements for live vaccines include the definition of the biological characteristics of the vaccine strain (e.g. animal tissue tropism) and the exclusion of any potential for the vaccine strains to revert to virulence.

The nature and severity of adverse reactions following the administration of a veterinary vaccine can be dependent either on the antigen that is used (e.g. crude bacterial antigen compared to well-purified viral antigens) or on the susceptibility of the different animal species. The depth, length and width of local reaction as well as any histological change in the tissue structure have to be measured. Local reactions can vary from granulomas of limited or larger extent, to abscesses; from inflammation to necrosis and fibrosis of tissues. In recent years, some excipients (e.g. as part of stabilisers) or adjuvants (particularly oil/emulsion adjuvants) and vaccine administration (in terms of both route and timing) have frequently been implicated as the cause of adverse reactions, both at injection sites and systemic (including fever, arthritis, anorexia, soreness and lethargy). Moreover, recent reports have raised concerns among professionals in relation to vaccination and delayed adverse events, particularly in companion animals and specifically in relation to vaccine-associated fibrosarcomas in cats and immune-mediated disease in dogs. Although their role is still debated, adjuvants have been associated with a local tissue irritation which in very extreme circumstances may result in metaplasia of fibrocytes and tumour formation (14).

Most of the common systemic reactions – such as pain, fever and anorexia, but also vomiting, reduction in milk yield, anaemia, arthritis, epilepsy, thyroid disease, liver failure, diabetes and allergies – have been associated with the use of vaccines in animals. Residual endotoxins and pyrogenic effects of antigens and adjuvants (oil, saponin) may be responsible for adverse events which can more commonly be expected as a consequence of the use of vaccines. Anaphylactic and delayed allergic reactions can also occur but are more insidious and in most cases are not controllable. The risk of allergic reactions has been reported to increase after repeated injection of vaccines (13). Other risks may be posed by the immunosuppressive effects of modified live viruses, such as bovine herpesvirus 1 (BHV-1), bovine viral diarrhoea virus (BVDV), and the SG33 strain of myxomatosis virus used in specific vaccines. Parvovirus and canine distemper vaccines have been reported to be responsible for many diseases of the immune system in dogs (1, 15). Among the most deleterious and suspected effects on the immune system are tolerance and autoimmunity, overloading of the immune system by multiple and simultaneous administration of vaccines, interaction with other vaccines or reciprocal interference with the immune response against antigens.

Exposure assessment

In principle, adverse events may potentially occur at any exposure level to vaccines, whether administered once in a lifetime or repeatedly, and with products containing minimum or larger combinations of antigens. In particular, risks may increase when vaccines are administered to pregnant or lactating animals, or are used for early life immunisation of animals, such as *in ovo* or day-old vaccination of birds. Concern has been expressed about this; some practitioners argue that the youngest recommended age for vaccinating various species should be increased, because early vaccination may interfere with persistent maternally derived antibodies, and may therefore affect both the safety and efficacy of vaccination. It is necessary to ensure a wide spectrum of protection against major infectious diseases early in the life of animals; consequently, in most cases animals have to be vaccinated repeatedly in a relatively short time period, which increases the risks of adverse reactions. In order to avoid unnecessary vaccination of animals, data generated by studies on the duration of immunity should be used when preparing vaccination schemes.

Risk characterisation

Once hazards have been identified as likely, the risks associated with those hazards should be characterised in

terms of the harm they might cause. Two broad categories with qualitatively different risk profiles are commonly recognised. Inactivated and subunit vaccines, as well as conventionally designed and produced live vaccines, are generally considered to be low-risk products in respect to target animal safety. Live genetically modified organisms (GMO) or vectored vaccines are usually considered to have high-risk profiles. In order to balance the greater risks of such GMO or vectored vaccines, higher levels of efficacy and benefits are normally required from them than from conventional vaccines. Nevertheless, even low-risk products may entail higher risks for the target animals, e.g. if injected intramuscularly.

Risk management and risk communication

Improved manufacturing processes (e.g. targeted use of only protective epitopes from specific proteins, or reduced use of sensitising agents such as residues of bovine serum, cell debris, egg proteins, preservatives) and new generation adjuvants are key issues for the prevention of side effects in target animal species. In particular, adjuvants may be tailored for specific needs of the antigen or species and to enhance the type (e.g. humoral, mucosal, cell-mediated), timing and magnitude of protective immunoresponse. The use of routes and methods of administration known to cause less adverse reactions should be preferred. Vaccination schemes should be developed taking into account which vaccines are more appropriate for animals of different ages and categories, and provide long-lasting immunity following a single immunisation, thus reducing the risks of potential immunosuppression or immunomediated diseases.

Recommendations for the appropriate use of 'core' vaccines in companion animals should be based on the severity of disease caused by the agent, the risk of the agent being transmitted to susceptible animals, and the potential for a particular infection to be zoonotic. Antibody titre testing before vaccination could be useful to determine if a vaccination is really needed. 'Non-core' vaccines should be used when a known or likely risk of exposure is anticipated or when an individual animal's lifestyle represents a significant risk of infection. Warnings about possible side effects should realistically reflect the data obtained in safety studies. The outcome of the risk assessment must be summarised within the characteristics of each product, and the label should include warnings about potential over-dosage, contra-indications, and undesirable side effects for each target species and category of animal (e.g. pregnant or lactating animals). If the product is incompatible with other vaccines or medicines that might be administered, that must also be reported, as must any special precautions for use. In the case of any identified risk, appropriate warnings must be incorporated in the package insert and/or label.

User safety

Problem statement

Vaccines should be safe not only for the target species, but also for the user, i.e. the person administering the vaccine or any other person assisting or involved in the administration of the vaccine or likely to come into contact with it.

The user must be informed of any specific hazard through the label and the package insert. This warning must identify any risk, and give advice on ways to prevent it occurring, as well as the measures to be taken in the case of exposure. The hazard could occur during normal use or through an accidental exposure during or following the administration.

It is evident that user safety is a critical factor for vaccines containing well-known live zoonotic agents or certain adjuvants. However, for the majority of vaccines the situation is not so clear. Risk assessments need to be performed, considering the specific properties of vaccines and their intended use on a case-by-case basis.

Scope of the assessment

An assessment of the user safety of a product addresses only situations resulting from the normal conditions of use and from foreseeable accidents (including accidental self-injection, oral ingestion or inhalation). It does not consider exposure resulting from deliberate misuse.

For the assessment, the user is regarded as any person who:

- administers the vaccine
- comes into contact with the vaccine or components before its application to the animal (e.g. during storage or preparation of the product to be administered)
- comes into contact during its application
- may be exposed to the vaccine after its application (e.g. through contact with disposed of, unused or waste product, or with treated animals).

This implies that the user can be, for example, a veterinarian, a farmer, a breeder, a pet-owner or any person who assists in restraining an animal during vaccination or who lives in the same environment. Consumers of products derived from vaccinated food-producing animals (such as meat and milk) are excluded from this definition (see 'Consumer safety'). This discussion does not cover occupational safety during the manufacturing of vaccines or other risks, for example, due to injury from a mechanical vaccination device or from a contaminated needle.

Risk assessment

Hazard identification and characterisation

Risk assessment is primarily concerned with examining the effects of the active ingredients, but also, if necessary, of excipients and, especially, adjuvants. For live vaccines the human pathogenicity of the vaccine strain is the main concern. For certain vaccine strains, pathogenicity has been documented by study of human cases caused by the same strain (e.g. *Brucella melitensis* Rev.1). The probable pathogenicity of a strain could also be assessed from published information for related modified strains or field strains (e.g. rabies) or from pharmacovigilance data. Agents that are rarely pathogenic for humans may be of special interest in the case of immunocompromised individuals or pregnant women (e.g. toxoplasma). For inactivated, but also for some live vaccines, effects of adjuvants, such as local or systemic reactions as a result of accidental injection, are of most concern (e.g. oil adjuvants).

Exposure assessment

Factors to consider include:

- the method of preparation of a vaccine (e.g. recovery from liquid nitrogen, rehydration, dilution of ingredients, loading in application apparatus or system)
- the route of administration of the vaccine (e.g. injection by syringe or mechanical device, coarse spray, oral)
- the duration and frequency of exposure to the vaccine
- the number, species and category of animals to be vaccinated (e.g. individual or mass vaccination, companion or food-producing animals)
- the time period of excretion from vaccinated animals.

The risk of exposure to the vaccine is shared equally between both the person who administers the vaccine and people who assist in restraining the animal(s). In cases where the vaccine strain is excreted by the vaccinated animal(s), the animal owners or caretakers may in addition be exposed to the strain after vaccination.

Risk characterisation

In contrast to pharmaceuticals, where information on dose–response relationships is available, in vaccines no quantitative risk assessment can be made. As an example, if hazards are identified for live vaccines, it must be assumed that the effects will occur at any exposure level.

Risk management and risk communication

Recommendations for managing risk include implementing appropriate precautionary measures such as

the use of personal protective equipment. When the vaccine strain may be excreted, the period during which this is liable to occur should be stated on the package insert or label. In some cases, recommendations for appropriate action will be linked with particular characteristics of the user, such as immunocompromised persons and pregnant women. Guidance on remedial action to be taken following accidental contact is also given when necessary. If the advice of a physician is considered necessary, adequate information should be given on the nature of the identified risk, taking into account that it is not always possible for the physician in an emergency situation to identify the risk and take the full responsibility for risk assessment without proper information. Statements such as 'seek medical advice immediately and show the package insert or the label to the physician' should be included only when a specific risk has been identified. When the assessment does not identify any specific risk, an appropriate statement could be included on a case-by-case basis (e.g. 'none', 'no specific risk identified').

Guidance on standard warnings to be used in the EU has been published (3). A typical example is the following warning for vaccines containing oil adjuvants: To the user: 'This product contains mineral oil. Accidental injection/self injection may result in severe pain and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given. If you are accidentally injected with this product, seek prompt medical advice even if only a very small amount is injected and take the package insert with you. If pain persists for more than 12 hours after medical examination, seek medical advice again.' To the physician: 'This product contains mineral oil. Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even in a loss of a digit. Expert and prompt surgical attention is required and may necessitate early incision and irrigation of the injected area, especially when there is involvement of finger pulp or tendon.'

Consumer safety

Problem statement

The use of a veterinary medicinal product in food-producing animals may result in the presence of residues of the medicine in the animal body and in animal-derived foodstuffs such as meat, milk and eggs. This applies to pharmaceutical veterinary medicines as well as to immunological products. While medicinally induced immunological responses are usually indistinguishable

from those which arise naturally, and are considered not to affect consumers, consideration must be given to other substances contained in the vaccine, in particular excipients and adjuvants.

Scope of the assessment

The purpose of the assessment is to evaluate the known or potential adverse effects on human health of exposure to food-borne hazards or, more specifically, of exposure to residues of the chemical components of the immunological veterinary medicinal products used in food-producing animals. In the EU, such a safety-of-residue evaluation is required for all pharmacologically active substances which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered. Active principles of biological origin used in an immunological veterinary medicinal product intended to produce active or passive immunity or to diagnose a state of immunity are excluded.

In the EU the risk assessment of any chemical components of vaccines that may affect consumer safety is considered in a separate procedure prior to the marketing authorisation process. Council Regulation (EEC) 2377/90 lays down the procedure and lists all substances that are allowed to be used in veterinary medicinal products for food-producing animals. Appendix I lists all substances for which final MRLs have been established, Appendix II lists all substances for which the specification of MRLs was not considered necessary to protect consumer health, and Appendix III contains all substances with provisional MRLs (5).

Adjuvants in vaccines, due to their very nature, are usually pharmacologically active and require a safety-of-residue evaluation. Depending on the nature of the excipient, these may be exempted following a case-by-case consideration based on appropriate data that has shown the absence of such activity at the dose at which the adjuvant is included in the veterinary medicinal product.

Substances used in the manufacturing process of the active ingredients, which are not intended to be present in the final product but of which traces might be present, are not considered to require a safety-of-residue assessment.

As mentioned before, medicinally induced immunological responses are usually indistinguishable from those which arise naturally, and are considered not to affect consumers. However, on a case-by-case basis, depending on the nature of the vaccine, e.g. in the case of live vaccines containing zoonotic organisms, a precautionary withdrawal period will be required to exclude risks to the consumer of food derived from the vaccinated animal.

Risk assessment

Hazard identification and characterisation

The purpose of hazard identification is to identify residues of a vaccine that may cause adverse effects on health and that may be present in any particular food derived from animals. In the hazard characterisation stage, the nature of the adverse effects associated with these residues is evaluated qualitatively and/or quantitatively on the basis of toxicological and pharmacological studies in laboratory animal species. Where available, observations in humans are taken into account. At this stage, where appropriate, the acceptable daily intake (ADI) for the substance under consideration is established.

Exposure assessment

The exposure assessment concerns vaccines intended for use in food-producing animals, and evaluates the likely intake of residues of a vaccine through food of animal origin. Data on absorption, pharmacokinetics, metabolism and residue depletion are usually necessary for the exposure assessment.

Risk characterisation

In a risk characterisation, an estimate is made of the risks to the consumer from any residues from vaccines that may be present in animal products. Regarding the chemical components identified as potential hazards for the consumer, the risk characterisation will decide whether MRLs would need to be established. Consideration is given to whether a withdrawal period would be necessary before food can be derived from the vaccinated animal.

Risk management and risk communication

The outcome of the assessment of risks to the consumer should be summarised and, where any risk is identified, appropriate advice should be given on mitigation measures. Such measures, e.g. a withdrawal period, should be incorporated in the SPC, package insert and label.

Environmental safety

Problem statement

A veterinary medicinal product may have undesirable effects on the environment and therefore, before any veterinary medicinal product can be authorised, any risk of harm it may pose to the environment should be assessed. On the basis of the assessment, specific risk mitigation measures may be considered.

Scope of the assessment

In the EU the environmental assessment is undertaken in two phases. Phase I is compulsory and should indicate the

potential exposure of the environment to the product, and the level of risk associated with any such exposure. Where it is concluded that the risk is low, there will generally be no need to proceed to Phase II and no further investigations will be required. In the majority of cases, the nature of vaccines is such that they will have a very low environmental risk potential. It can be expected that a Phase II assessment will be necessary only in exceptional circumstances, e.g. in vaccines containing live GMOs (3).

The level of detail to be considered in a risk assessment will depend on the characteristics of the vaccine. Little detail will be required, for example, where it is immediately obvious that the hazards and hence the consequent risks are low, or that the proposed control measures are clearly adequate to limit contact between the product and the environment. For example, for inactivated vaccines to be administered by injection, the hazards and risks from the active ingredients are likely to be negligible.

Risk assessment

Hazard identification and characterisation

In the context of the environmental risk assessment for vaccines, hazards are defined as those features of the substance which have the potential to cause harm to the environment either directly (as in the case of infection of a non-target-species by a vaccine virus) or through some form of possible event (such as infection by organisms excreted by the vaccinated animal). It is important to be exhaustive in the identification of possible hazards, which should aim to identify all possible factors contributing to adverse effects and should include the following:

- the capacity of live organisms to transmit to non-target species
- the shedding of live vaccine organisms from vaccinated animals (route, numbers, duration)
- the capacity to survive, establish and disseminate
- pathogenicity to other organisms
- potential for other effects of live product organisms
- the toxic effects of the product components
- the toxic effects of excreted metabolites.

Regarding the two latter effects, in the case of products which are administered by injection, no detailed assessment of the potential risk of the excipients is likely to be required when the substances are of biological origin or form part of the animal's normal diet.

Exposure assessment

In the first step, the likelihood (probability and frequency) of the hazard(s) is estimated. A key factor in determining

this is the potential receiving environment. This includes the wider as well as the local environment in which the product is intended or likely to be used.

Particular characteristics of the local environment that could contribute to the likelihood of the hazard – e.g. climatic, geographical and soil conditions, demographic considerations, the types of fauna and flora in the potential receiving environment – should be identified and assessed. Consideration should be given to any potential exposure of the environment to the product and the magnitude and duration of such exposure. The exposure assessment should consider:

- the type of packaging and procedures before and after administration
- the route of administration (parenteral vs. oral vs. ocular vs. spray)
- shedding of live product organisms (route, numbers, duration).

For the ‘hazard-survival capacity’ of living organisms, it is appropriate to assess the proportion of the organisms that are likely to survive. If the organism has pathogenic characteristics, the proportion of target species in the environment likely to be affected should be assessed, taking into consideration the likelihood that the organism will spread to or reach these species. It is recommended that the possibility of exposure and the likelihood of hazards occurring are expressed as ‘high’, ‘medium’, ‘low’ or ‘negligible’, although it is recognised that this requires subjective judgment.

Subsequently the consequences of possible hazards are assessed. This must be done for each identified hazard of the product being assessed. Whenever it is possible or probable that the components in the product will reach the environment, it must be considered whether that environment would cause or allow the hazard to happen. Thus, again, the characteristics of the potential receiving environment need to be considered.

For vaccinal organisms or excreted passage organisms, the main consideration will be the likely presence or absence of susceptible non-target species in the potentially affected environment.

Risk characterisation

Having identified any hazards and assessed the degree and likelihood of exposure and the consequences of that exposure, it is necessary to evaluate the risk associated with each hazard. Risk is generally held to be the product of exposure/likelihood and consequence. It is inevitably going to be difficult to ‘multiply’ qualitative statements such as ‘high’ and ‘low’, but **Table I** should help this process. The risk matrix is not definitive and there will always be some scope for flexible, case-by-case evaluation. In many cases, it will be necessary to decide between one of two outcomes and, as in the earlier parts of the process, some justification for the choice should be provided. In addition, a range of risks may be apparent if more than one hazard is being evaluated. There will therefore be a need to make an overall assessment of the risk, taking all factors into consideration. Once an overall assessment of the risk associated with each hazard has been produced, it will be necessary to evaluate the significance of the risk.

Risk management and risk communication

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to the hazard should be repeated to ascertain whether the use of additional management techniques could reduce the level of risk; consideration might be given, for example, to limiting the proposed routes of administration to those likely to lead to a lower level of risk. If it is considered that there is insufficient knowledge to come to a satisfactory conclusion, other studies and a Phase II assessment should be undertaken, addressing the specific issues that give rise to concern on a case-by-case basis.

The outcome of the environmental risk assessment should be summarised and, where any risk is identified, appropriate warnings and advice on mitigation measures

Table I
Environmental risk assessment: characterising the nature of a risk (high, medium, low, zero) by evaluating the likelihood of its occurrence and the severity of its consequences

| | High likelihood of hazard occurring | Moderate likelihood of hazard occurring | Low likelihood of hazard occurring | Negligible likelihood of hazard occurring |
|--------------------------------|-------------------------------------|---|------------------------------------|---|
| Severe consequences | High | High | Medium | Effectively zero |
| Moderate consequences | High | High | Medium/low | Effectively zero |
| Minor consequences | Medium/low | Low | Low | Effectively zero |
| Negligible consequences | Effectively zero | Effectively zero | Effectively zero | Effectively Zero |

should be incorporated in the SPC, package insert and label.

Pharmacovigilance

Veterinary pharmacovigilance monitors the safety of veterinary medicines, including vaccines, used for the prophylaxis, diagnosis or treatment of disease in animals once they have reached the market after authorisation. The aim is to ensure that veterinary medicines are safe for the animals, for persons who come into contact with veterinary medicines, for the environment and, in the case of medicines used in food-producing animals, for consumers of the food derived from these animals.

Under the EU pharmacovigilance scheme, suspected adverse reactions in animals and in human beings relating to the use of veterinary medicinal products under normal conditions are recorded. The EU system also takes into account any available information related to:

- lack of expected efficacy
- off-label use
- investigations into the validity of the withdrawal period
- potential environmental problems arising from the use of the product, which may have an impact on the benefit/risk balance of the product.

The responsibility for pharmacovigilance reporting lies with the marketing authorisation holders, who are required to collect and evaluate all reports of suspected adverse reactions to their veterinary medicinal products, and report to the responsible authority for the veterinary medicinal product concerned. The adverse reaction reports are submitted mainly by veterinarians, but also by animal owners. All suspected serious adverse reactions and human adverse reactions relating to the use of the veterinary medicinal product must be reported promptly by the company, usually within 15 or 30 days after it receives the report (e.g. 15 days for the EU), depending on the specific legislation of the country where the product is authorised. All adverse reports received, serious and non-serious, must be compiled in a so-called Periodic Safety Update Report (PSUR) or Periodic Summary Update (PSU), which includes a benefit/risk analysis of the product. The PSUR or PSU is to be submitted to the responsible authority at specified intervals. In the light of any adverse reports received, the benefit/risk analysis of the product is reviewed. If necessary, the conditions for the authorisation may be amended, e.g. by amending the claim or by adding new or revised warnings to the SPC, package insert and label. If the risks identified through pharmacovigilance cannot be overcome by risk management measures and the risk/benefit balance is no longer positive, the marketing authorisation of the product may even be suspended or withdrawn.



Utilisation sans risques de la vaccination et conformité des vaccins avec les exigences de la sécurité sanitaire des aliments

K. Grein, O. Papadopoulos & M. Tollis

Résumé

Grâce aux évolutions technologiques et réglementaires, les vaccins vétérinaires actuellement disponibles sont de grande qualité et présentent un profil de sécurité favorable en termes de risques potentiels pour les espèces cibles, pour les personnes qui manipulent les vaccins, pour les consommateurs de produits alimentaires issus d'animaux vaccinés et pour l'environnement. Le processus d'autorisation exige qu'une série d'études soient réalisées afin d'évaluer l'innocuité des produits. L'évaluation des vaccins au stade du développement, de la production et de l'utilisation sans risque se fait principalement au moyen

d'études approfondies conduites avant la commercialisation chez les espèces cibles, ainsi que de tests de qualité spécifiques. Les garanties postérieures à la commercialisation sont fournies par les bonnes pratiques de fabrication, par les essais de sécurité par lots, par les inspections et par la pharmacovigilance. Après avoir identifié les dangers, une évaluation exhaustive du rapport bénéfice/risque doit être réalisée. Les résultats de l'évaluation mettent en avant certaines options de gestion du risque et déterminent les mesures réglementaires à prendre en matière de sécurité ; par exemple, des mises en garde spéciales pourront être exigées sur les emballages et les étiquettes des produits.

Mots-clés

Animal – Bénéfice – Consommateur – Environnement – Évaluation – Pharmacovigilance – Risque – Santé – Sécurité – Utilisateur – Vaccin.



Utilización segura de vacunas y observancia de las normas sobre higiene de los alimentos en el uso de vacunas

K. Grein, O. Papadopoulos & M. Tollis

Resumen

Los adelantos tecnológicos y los regímenes reglamentarios han ayudado a disponer de vacunas veterinarias que aúnan gran calidad y características de seguridad favorables desde el punto de vista de los posibles riesgos que presentan para los animales diana, las personas que entren en contacto con la vacuna, los consumidores de alimentos procedentes de animales vacunados y el medio ambiente. El proceso de autorización requiere que se presenten diversos estudios de seguridad para evaluar cada producto. Al evaluar la concepción y fabricación de vacunas y determinar el grado de seguridad que ofrece su empleo, se utilizan sobre todo datos procedentes de vastos estudios con animales diana, previos a la comercialización, y de controles de calidad específicos. Una vez que un producto ha obtenido licencia de comercialización también existen medidas de salvaguarda, que hoy en día consisten en aplicar buenas prácticas de fabricación y pruebas de seguridad de los lotes, realizar inspecciones e instaurar un dispositivo de farmacovigilancia. Además de determinar los peligros, es necesario proceder a una evaluación completa de la relación entre beneficios y riesgos. Los resultados de tal evaluación determinarán la línea que se adopte en cuanto a la gestión de riesgos e influirán en las decisiones normativas sobre el grado de seguridad que ofrece la vacuna. Cabría obligar al fabricante, por ejemplo, a incorporar un aviso especial en las etiquetas o encartes al embalar el producto.

Palabras clave

Animal – Beneficio – Consumidor – Evaluación – Farmacovigilancia – Medio ambiente – Riesgo – Salud – Seguridad – Usuario – Vacuna.



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