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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON USER SAFETY FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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1. INTRODUCTION (background)

Applications for marketing authorisations of veterinary medicinal products, including immunological veterinary medicinal products (IVMPs) in the European Union are issued in accordance with Directive 2001/82/EC of the European Parliament and of the Council dated 6 November 2001 (as amended by Directive 2004/28/EC). This legislation requires that the applicant provides documentation on the reasons for any precautionary and safety 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 veterinary medicinal product might pose to the environment, to human and animal health and to plants (Article 12 (3) (g)). For medicinal products that imply such risks, the legislation allows for the definition of special precautions to be taken by the person administering the medicinal product to animals, in order to reduce the risks to an acceptable level. Those precautions are to be stated in the Summary of Products Characteristics (SPC) and package insert (Articles 14.5.12 and 61).
In the Notice to Applicants for veterinary medicinal products: Presentation and content of the dossiers (Vol. 6B, Update 2004) it is stated in the Immunological Section that it is preferable for the toxicology, user safety, environmental and residues aspects of the expert report to be presented separately.

In the Guideline for an assessor preparing assessment reports for veterinary medicinal products (EMEA/CVMP/115769/2005) in the assessor's conclusion on safety it should be indicated "what if any suitable warnings need to be added to the SPC and product literature to reflect side effects observed, risk to non-target species including the operator and other human and ecotoxicity risks".
In the Guideline on Summary of Product Characteristics (SPC) for IVMPs (Update 2005) it is required that in section 4.5 of the SPC (Special precautions for use, including special precautions to be taken by the person administering the medicinal product to animals) "the risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user should be stated. If applicable, information should also be given for persons in close contact to the treated animal e.g. animal owner, children, immunocompromised persons, and pregnant women. Where necessary, recommendations to minimise exposure of the product user during administration and, where relevant, during preparation of the product for administration, should also be given. Guidance on remedial action to be taken following accidental contact should also be given, when necessary. It might be helpful to describe the expected outcome of a self-injection.

The legislation does not give specific guidance on exact data requirements and assessment methods to be used to identify the risks, or on the measures for risk reduction. This guideline is presented to provide this guidance for user safety related to IVMPs.

2. SCOPE

This guideline applies to new applications and renewals of marketing authorisation for IVMPs and does not require the generation of specific or additional data.

The assessment of the user safety of a product should address only the exposure situations resulting from the normal conditions of use and from the foreseeable accidents (including accidental self injection, oral ingestion, inhalation). It does not include exposure situations resulting from deliberate misuse.

For the assessment of user safety, the user is regarded as any person administering the IVMP or that may come into contact with the IVMP or components of the product before its application to the animal (e.g. during storage or preparation of the product to be administered), during its application, and 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 used to assist in restraining the animals during vaccination or living in the same environment. Consumers of products derived from vaccinated food producing animals (meat, milk etc) are excluded from this definition. This guideline does not cover occupational safety during the production of IVMPs.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part 7 Safety Testing of the Annex I to Directive 2001/82/EC as amended.

4. PRINCIPLES OF ASSESSMENT

The assessment of the user safety will comprise the following steps:

- hazard identification and characterisation
- exposure assessment
- assessment of the consequence of a hazard occurring
- risk characterisation
- risk management (selection and assignment of appropriate control measures)
- risk communication.

All relevant exposure scenarios should be considered. To allow the characterisation of risks for each scenario, the hazards should be identified and characterised, taking into account the route and frequency of anticipated exposure. When there is a predicted risk for the user, appropriate measures for risk management should be proposed and evaluated.
Special attention should be paid to categories of potential users, such as immunocompromised persons (due to disease or immunosuppressive treatment) and pregnant women who may be more susceptible and should therefore avoid exposure to infectious challenges.
Following the risk assessment, and on a case-by-case basis, the appropriate warnings, if any, are incorporated in the SPC.

5. HAZARD IDENTIFICATION AND CHARACTERISATION

From data collected during the research and development phases of a specific IVMP and without requiring extra experimental workload, it is important to know if and what a specific hazard exists for the user of that product.
Effects have to be assessed primarily for the active ingredients of the IVMPs. However, when there is a specific concern it may be necessary to assess the effects of one or more excipients, especially adjuvants.
For live vaccines the human pathogenicity of the strain contained in the IVMP is the main concern (e.g. zoonotic agents, such as brucella, rabiesvirus, salmonella, Newcastle disease virus).
Pathogenicity for humans should be based on scientific assessment. For certain vaccine strains it has been documented by human cases caused by the same strain (e.g. Brucella melitensis Rev.1). Probable pathogenicity of the strain could be assessed from published information for related modified strains or field strains (e.g. rabies). Agents 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 certain live vaccines, side effects of adjuvants, such as local or systemic reactions as a result of accidental injection, are of main concern (e.g. oil adjuvants). Reactions, including allergic reactions, to different components (e.g. preservatives and other excipients) should also be considered.

6. EXPOSURE ASSESSMENT

The way of preparation of a vaccine (e.g. recovery from liquid nitrogen, rehydration, dilution of ingredients, loading in application apparatus or system, etc.); the type of users; the route of administration of the vaccine (e.g. injection by syringe or mechanical device, coarse spray, oral, etc.); the rate, the extent, the duration and the frequency of exposure to the vaccine (e.g. single dose, repeated dose, booster or seasonal/occasional vaccination), the number, the species and category of animals to be vaccinated (e.g. individual or mass vaccination, companion or food producing animals, young or pregnant animals, etc.); and the time period of excretion from vaccinated animals, should be considered.
The risk of exposure to the IVMP is equally shared between the person who administers the vaccine and persons assisting in restraining the animal(s). Furthermore, in cases when the vaccine strain is excreted by the vaccinated animal(s), the animal owners or caretakers may be exposed to an additional risk after vaccination.

7. RISK CHARACTERISATION

The information obtained from exposure assessment should allow a qualitative characterization of the risk by taking into account the likelihood that an effect will occur. By contrast, in cases where no information on dose response relationship is available, a quantitative risk assessment cannot 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. Whenever possible, available information on the severity of an effect at the anticipated exposure levels should be taken into account as well.

8. RISK MANAGEMENT

When the outcome of the assessment identified a specific risk for the user recommendations for the risk management should be proposed, including:

- Prevention or minimising exposure of the product user during administration and, where relevant, during preparation and/or following administration, taking into account that for live agents no quantitative assessment was possible and that the effects may occur at any exposure level. These recommendations may include use of personal protective equipment according the route of administration (e.g. gloves, masks).
- Identification of highly susceptible categories of users (e.g. immunocompromised persons, pregnant women).
- Remedial action to be taken following accidental contact, when necessary. It might be helpful to describe the expected outcome of any exposure, including self-injection. This is particularly important in respect of live zoonotic agents and oil-adjuvants. If the advice of physician is deemed necessary adequate information should be given on the nature of the risk identified.

9. RISK COMMUNICATION

On a case-by-case basis, the outcome of the risk assessment for the user should be summarised and, in the case of any risk identified, appropriate warnings incorporated in the SPC and the package insert.
Specific risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user should be stated.
If applicable, information should also be given for persons in close contact to the treated animal e.g. animal owner, children, immuno-compromised persons, and pregnant women. In some cases recommendations for appropriate action will be linked with particular characteristics of the user, such as risk for compromise of the immune system.
Where advisable, special recommendations related to the identified specific risk, like “wearing gloves and/or covering clothing, protecting faces by masks, or goggles” etc; “avoiding the handling by pregnant women or immunocompromised people”, should be included.
Guidance on remedial action to be taken following accidental contact should also be given, when necessary. It might be helpful to describe the expected outcome of any exposure, including self-injection. This is particularly important in respect of live zoonotic agents and oil-adjuvants. If the advice of physician is deemed necessary, adequate information should be given on the nature of the risk identified, taking into account that it is not always possible for the physician in an emergency situation to identify the risk from the composition of the product.
Statements, like “seek medical advice immediately and show the package insert or the label to the physician”, should be included only when the specific risk has been identified in the SPC.
In the case that the result of the assessment is inconclusive, for example due to absence of specific scientific information, a statement could be included on a case-by-case basis.
The absence of any specific identified risk shall be stated in the SPC (e.g. "none"). However, even in this case, seeking medical advice could be envisaged, provided the non-specific risks are mentioned (e.g. injury from a mechanical device, etc).

APPENDIX I - EXAMPLES

In the case of identified risk, the following statements, which do not cover all possible cases, should be used:

"In case of accidental self-injection / ingestion / spillage onto the skin, seek medical advice immediately and show the package insert or the label to the physician". This warning is valid only when a risk has been identified and the package insert and label contain clear indication of the risk for the information of the physician.

"People with known hypersensitivity to XXX should <avoid contact with the product> <should administer the product with caution>.

"Personal protective equipment consisting of XXX should be worn when handling the products".

The product should not be administered by pregnant women.

The vaccine can be pathogenic for humans. Since this vaccine has been prepared with live, attenuated microorganisms, appropriate measures should be taken to prevent contamination of the handler and other people that collaborate in the process.

Vaccinated /species denomination / may excrete the vaccine strain up to <x days/weeks> following vaccination.

Immunocompromised persons are advised to avoid contact with the vaccine and vaccinated animals during < period>.

The vaccine strain can be found in the environment for up to <x days/weeks>. Personnel involved in attending vaccinated /species denomination / should follow general hygiene principles (changing clothes, wearing gloves, cleaning and disinfection of boots) and take particular care in handling litter from recently vaccinated /species denomination /.

Operators should not handle vaccine if known to suffering from immunosuppressive disease.

Care should be taken to wash and disinfect hands after handling poultry faeces, particularly in the first /xx/ days after vaccination of birds.

Open vial under water to avoid aerosols.

Special attention should be paid to products containing mineral oil and the following statements are recommended:

<u>To the user:</u>

"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".

<u>To the physician:</u>

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".

For the immediate packaging and for the outer carton the following working is suggested: "Accidental injection is dangerous – See package insert before use".