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Guideline on environmental risk assessment for immunological veterinary medicinal products

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*This guideline replaces the Note for guidance: environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95). The current revision consists of administrative changes made in order to align the guideline to definitions and terminology of Regulation (EU) 2019/6. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary.

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Guideline on environmental risk assessment for immunological veterinary medicinal products

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Executive summary

The main aim of this guideline is to advise on the approach for assessing the potential risk to the environment from the use of immunological veterinary medicinal products before they are authorised for market use in the EU. The guidance is based on Regulation (EU) 2019/6 and aims to ensure that such products do not pose unacceptable risks to the environment.

1. Introduction (background)

This guidance concerns the environmental risk assessment needed to comply with the requirements Article 8 of Regulation (EU) 2019/6. This requires an assessment to be undertaken of the potential risk to the environment from use of the immunological veterinary medicinal product, before it may be placed on the market. This assessment must address the risks arising from each of the components of the product, not just the risk from live organisms invaccines. The assessment need not, however, address the possible outcome of misuse or accidents.

Annex II to Regulation (EU) 2019/6 describes the process of assessment as consisting of two phases. The first phase is compulsory and should indicate the potential exposure of the environment to the product and thelevel 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 the secondphase and no further investigations will be required.

In the majority of cases, the nature of immunological veterinary medicinal products is such that they will have a very low environmental risk potential. It can be expected that only in exceptional circumstances a Phase II assessment will be necessary.

The following guidance should be used for the Phase I assessment and to reach a conclusion onthe risks. If further investigations and a Phase II assessment is required, the same assessment procedure and format should also be used.

The level of detail to be considered in a risk assessment will depend on certain circumstances. It will be lower, for example, where it is immediately obvious that the hazards and hence the risks are low or that the proposed control measures are clearly adequate to limit the 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.

The risk assessment is intended to be an overall statement reflecting all the information contained in the dossier.

Although, wherever possible, the risk assessment should be based on quantifiable outcomes, it is recognised that many of the judgements must necessarily be qualitative.

How much information is needed on any particular point will depend on its importance in the assessment and the extent to which it is generally accepted material. Much of the information that is required should have already been addressed in the rest of the section on safety, particularly with respect to live organisms in the product, through studies of excretion and spread, and in the considerations of the risk to unvaccinated animals of the same or other species. There is no need to spell out in great detail what is mentioned elsewhere in the dossier or in textbooks or literature, but a clear cross reference to this information should be provided. In addition, within this section, sufficient information should be provided for the logic of the argument to be clear, and enough

justification should be included on any unusual or particularly important points for the assessment to be transparent.

Note that it is always permissible for the applicant to assume the worst and act accordingly, if the cost of gathering the information (by experimentation or review) for a more precise assessment is disproportionate.

2. Legal basis

The legal basis for the authorisation of a veterinary medicinal product is laid down in Regulation (EU) 2019/6. The present document should be read in particular in conjunction with the introduction and general principles and Section IIIb.3D (requirements for immunological veterinary medicinal products: environmental risk assessment) of Annex II to Regulation (EU) 2019/6, as amended.

For vaccines within the scope of this guideline containing GMOs, the additional legal requirements as outlined in Article 8.5 of Regulation (EU) 2019/6 will apply.

3. Framework for risk assessment

The aim of the risk assessment is to identify hazards, to estimate the likelihood that the hazardswill lead to actual harm and to take decisions regarding the appropriate control measures. The main elements of a risk assessment are therefore:

(i) hazard identification;

(ii) assessment of exposure to the hazard and the likelihood that the hazard will occur;

(iii) assessment of the consequences of that exposure;

(iv) assessment of the level of risk (by consideration of the severity of any adverse consequences and the likelihood that they will occur);

(v) selection and assignment of appropriate control measures (risk management), as far aspossible.

4. Assessment of risk

4.1 Hazard identification

In the context of this guidance, hazards are defined as those features of the substance which have the potential to cause harm to the environment, either directly (such as infection of a non-target-species by vaccine virus) or through some form of possible event (such as the infection from organisms excreted by the vaccinated animal). It is important to be exhaustive in the identification of possible hazards and not to discount, at this stage, any of the hazards given below on the basis that they are unlikely to occur. The assessment of possible exposure and likelihood are separate stages of the assessment process.

This stage of the assessment should aim to identify all possible factors contributing to adverse effects and should include the following:

4.1.1. Capacity of live organisms to transmit to non-target species

The specificity of the host range is very important for veterinary products. Any likely changes as a result of the attenuation should be taken into account.

4.1.2. Shedding of live product organisms (route, numbers, duration)

The extent to which the product organisms in live vaccines multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication-defective organisms, and the likelihood of exposure may be less than that associated with the wild type organisms. However, the potential for organisms passaged from animal to animal to become less attenuated and more likely to be excreted and spread must be taken into consideration.

4.1.3. Capacity to survive, establish and disseminate

This is also a key consideration: if an organism is not capable of surviving, then other hazards are likely to be minimised. The risk assessment associated with live vaccinal organisms could be completed at this stage if the risks to the environment are low or effectively zero. However, if it is likely that the organism could survive for a sufficiently long period for it to cause harm, and possibly establish and disseminate in the environment, then not only this hazard but also other hazardous characteristics need to be considered.

4.1.4. Pathogenicity to other organisms

The pathogenic properties of many organisms are well documented, and these should be identified, if appropriate. It should be considered whether a change in host range could occur as a result of the attenuation which has been undertaken.

4.1.5. Potential for other effects of live product organisms

Consideration should be given to whether the organism might have the potential to exert other effects such as the transmission and replication of viruses in other organisms as a result of the effects of recombination.

It should be considered whether the organisms have the capacity to transmit potentially harmful characteristics to other organisms for instance via plasmids.

4.1.6. Toxic effects of the product components

The potential of each of the components in the product to exert a toxic effect must be considered. 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 of form part of the animal's normal diet. For other pharmacologically active excipients, some information may be available from the data gathered or generated in support of the application in accordance with Regulation (EC) No 470/2009.

In the case of products administered other than by injection, the assessment should include assessment of the total quantity of each substance that is released into the environment.

4.1.7. Toxic effects of excreted metabolites

It should be considered whether excreted metabolites of the product components administered to the target species could present a hazard.

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. For other pharmacologically active excipients, some information may be available from the data gathered or generated in support of the application in accordance with Regulation (EC) No 470/2009.

4.2 Assessment of the likelihood

The next step is to estimate the likelihood (probability and frequency) of hazard(s) being manifested. 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 manifestation of the hazard should be identified and assessed. Climatic, geographical and soil conditions, demographic considerations, the types of fauna and flora in the potential receiving environment are some of the important ones.

Consideration should be given to any potential exposure of the environment to the product and the magnitude and duration of such exposure.

When estimating probabilities and frequencies for live vaccinal organisms, consideration should be given to the number of organisms that might reach the environment, since the probability that a hazard will translate to adverse effects will often be influenced by the number of viable organisms in the environment. This could be due, for example, to excretion, as well as being influenced by the number of organisms per dose and whether many doses will be given at one time (e.g., in mass vaccination), or a single or small number of doses will be administered.

For toxic components in the product and hazardous metabolites, the quantities and concentrations of these that might reach the environment should be considered.

The following should be taken into account:

(i) Type of packaging and procedures before and after administration

(ii) The packaging should allow any initial preparatory steps (e.g. reconstituting freeze-dried preparations) to be undertaken in a safe and aseptic manner. However, the proposed method of preparation and administration will have a bearing on the degree of exposure of the environment to the product and need to be considered. For example, single-dose preparations for administration to a companion animal in the surgery is likely to result in less exposure than mass medication of farm animals including poultry and fish. It may be appropriate to consider who is likely to administer the product (veterinary surgeon or farmer), and the likelihood of any necessary instructions for safe use of products being achievable. It will also be necessary to consider whether or not unused product can be readily disposed of in a reliably safe manner.

(iii) Route of administration (parenteral vs. oral vs. oculonasal vs. spray)

(iv) It may be expected that there is more opportunity for exposure to the product when the product is administered by spray, orally or oculonasally than by injection. Oral, bath or dip vaccination of fish may result in considerable exposure.

(v) 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, including taking into consideration, the likelihood of the organism to spread to or reach these species.

Similar considerations need to be applied to all toxic components of the product and hazardous metabolites, for instance, whether the chemical preservative may reach susceptible non-target animal species or susceptible plants.

It is recommended that the possibility of exposure and the likelihood of hazards occurring is expressed as 'high', 'medium', 'low' or negligible', although it is recognised that this requires subjective judgement

4.3 Assessment of the consequence of a hazard occurring

For each hazard of the product identified, 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 be realised. Thus, again, the characteristics of the potential receiving environment need to be considered.

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

An assessment of the magnitude of harm is based on the assumption that the hazard will translate into an adverse effect. Inevitably there will be a degree of judgement in making the assessment, but the consequences should be described as 'severe', 'medium', 'low', or 'negligible'. A 'severe' consequence might be a major change in the numbers of one or more species leading to negative effects on the functioning of the ecosystem and/or other connected ecosystems. It is unlikely that such changes would be reversible. A 'low' consequence might be if any change in population densities is such that it has no negative effects on ecosystem function and no impact on endangered or beneficial animal or plant species.

The above illustrations reflect the potential effect of the product on populations. In some cases, however, it may be more appropriate to consider the likely effects on individual organisms, for example endangered mammals. In most cases it should be possible to use the guidelines to assess in qualitative terms the degree of harm which a particular product might cause.

4.4 Assessment of level of risk

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 understood to be the product of exposure/likelihood and consequence. It is inevitably always going to be difficult to 'multiply' qualitative statements such as 'high' and 'low', but the table in

Annex 1 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. Therefore, there will 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.

4.5 Selection and assignment of appropriate control measures

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to that hazard should be repeated to ascertain whether the application of additional risk management measures/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, further studies and a Phase II assessment should be undertaken.

5. Format for presentation of conclusions of the risk assessment

Applicants may find the following structure useful to record their risk assessment.

1. Summary

Summary of the overall risk of damage to the environment from the proposed marketing of the product.

2. Assessment of the risks to the environment

2.a Hazard identification. Hazardous characteristics of the product that could, in certain circumstances, lead to harm to the environment.

2.b Assessment of likelihood.

2.c Assessment of the consequence.

2.d Assessment of level of risk.

2.3 Assessment of the overall risk to the environment (the total risk after consideration of the risk of each of the hazards occurring): High, medium, low, effectively zero.

Annex I

ESTIMATION OF RISK

Consequence of hazard	**Likelihood of hazard occurring**			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively zero
Medium	High	High	Medium/low	Effectively zero
Low	Medium/low	Low	Low	Effectively zero
Negligible	Effectively zero	Effectively zero	Effectively zero	Effectively zero