

Guideline on the definition of a potential serious risk to human or animal health or for the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC — March 2006

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1. INTRODUCTION

Based on Article 33(2) of Directive 2001/82/EC as amended ⁽¹⁾ the scope of this guideline is to set out in more detail in which exceptional cases a Member State concerned in a mutual recognition procedure as referred to in Article 32(2) or in a decentralised procedure as referred to in Article 32(3) can refuse to recognise a marketing authorisation or a positive assessment on the basis of a potential serious risk to human or animal health or for the environment.

In the case that at least one of the Member States ⁽²⁾ concerned by the application cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of a potential serious risk to human or animal health or for the environment, as set out in Article 33(1) of Directive 2001/82/EC, when requested to mutually recognise a marketing authorisation granted by another Member State, it shall give a detailed explanation of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant.

As the same pharmaceutical legislation forms the basis for the authorisation process in all Member States and as all Member States have the same legal standards for quality, safety and efficacy, an authorisation granted in one Member State should generally be recognized amongst Member States.

In the **mutual recognition procedure**, according to Article 32(2) of Directive 2001/82/EC, the reference Member State will assess the data in the dossier and issue a national marketing authorisation, provided the risk-benefit balance of the product is considered to be favourable, the quality, safety and efficacy of the product is sufficiently guaranteed and nor other or further reasons for refusal of the marketing authorisation according to Article 30 of Directive 2001/82/EC is given. For the process of mutual recognition the reference Member State has to provide an assessment report that is sufficiently detailed to explain to the Member State concerned why the risk-benefit balance is considered to be favourable, together with the approved summary of product characteristics, labelling and package leaflet.

In the **decentralised procedure**, according to Article 32(3) of Directive 2001/82/EC, no prior national procedure is intended and no existing marketing authorisation is in place at that time. After receipt of a valid application it is the duty of the reference Member State to prepare within 120 days a draft assessment report together with the draft summary of product characteristics, package leaflet and labelling.

Article 33(1) of Directive 2001/82/EC describes the procedure to be followed if a concerned Member State cannot approve the assessment report, summary of product characteristics, package leaflet and labelling as prepared by the reference Member State. In Article 33(1) reference is made to Article 32(4), which in turn refers to Article 32(2) and (3). These Articles concern both mutual recognition procedure and decentralised procedure. Consequently, the grounds for refusal are the same irrespective of whether the concerned Member State evaluates an assessment report, the summary of product characteristics, the package leaflet and labelling from the reference Member State in a mutual recognition procedure or a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet in a decentralised procedure.

The **scope** of this guideline is to define in which exceptional cases a concerned Member State can refuse to recognise a marketing authorisation in a mutual recognition procedure, or a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet from the reference Member State in a decentralised procedure on the basis of a potential serious risk to human or animal health or for the environment. As a consequence this should also limit the variety and number of objections raised by Member States, which has been considered as one of the main obstacles to the attractiveness and efficient functioning of the veterinary mutual recognition procedure.

⁽¹⁾ Amended by Directive 2004/28/EC; OJ L 136 30.4.2004, p. 58.

⁽²⁾ Member States in this context refers to all countries of the European Economic Area

Additionally, a concerned Member State has to provide a detailed and substantiated justification when raising objections based on a potential serious risk to human or animal health or for the environment taking into account the following definitions.

In this context, it should be considered that a Member State plays a different role when it is called upon to approve the evaluation report, the summary of product characteristics, the labelling and package leaflet for a veterinary medicinal product submitted to it by the reference Member State and the role that it plays when it is the only one to issue a national marketing authorisation for a veterinary medicinal product that has not yet been the subject of an application for authorisation in another Member State of the Community, or when it is itself the reference Member State.

In the latter case, the Member State is fully competent to determine the content of the marketing authorisation for the veterinary medicinal product in accordance with Directive 2001/82/EC. In the first case by contrast, the authorisation/evaluation by the reference Member State should normally be recognised, so that the role of the concerned Member States is not to decide whether or not the authorisation/evaluation can be improved, but rather to establish clearly and in a well-argued fashion why the proposed decision on authorisation/evaluation presents a potential serious risk to human or animal health or for the environment.

2. DEFINITION OF POTENTIAL SERIOUS RISK

A **'risk'** is generally defined as the product of the size of a hazard and the probability of the hazard occurring. The term 'risk' relating to the use of a veterinary medicinal product is further defined in Article 1(19) of Directive 2001/82/EC as 'any risk relating to the quality, safety or efficacy of the veterinary medicinal product as regards animal or human health as well as any risk of undesirable effects on the environment'. This definition is complemented by Article 1(20) of that Directive defining a risk/benefit balance as an evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined in Article 1(19).

Directive 2001/82/EC does not provide a definition of a 'potential serious risk to human or animal health or for the environment' but empowers the Commission to do so. Hence, the following definition shall apply:

A **'potential serious risk to human or animal health or for the environment'** is defined as a situation where there is a significant probability that a serious hazard resulting from the use of a veterinary medicinal product will affect human or animal health or the environment and cannot be prevented, reversed or avoided.

'Serious' in this context means a hazard that could result in death, could be life-threatening, could result in significant disability or incapacity, could be a congenital anomaly/birth defect, or which could result in hospitalisation or permanent or prolonged signs in exposed humans or animals, or which could realistically cause these effects where the product enters the environment.

An isolated assessment of a 'potential serious risk to human or animal health or for the environment' cannot be made but has to take into account the positive therapeutic effects of the veterinary medicinal product in question. Consequently, the term 'potential serious risk to human or animal health or for the environment' as used in Article 33(2) of Directive 2001/82/EC has to be interpreted as relating to the overall risk/benefit assessment of the veterinary medicinal product, taking into consideration the nature of the identified risk(s) to human or animal health or for the environment and the potential benefit of the proposed indication(s) for the target species.

To justify a potential serious risk to human or animal health or for the environment, it is not sufficient to only refer to one of the situations mentioned in the following sections. It is necessary to demonstrate for each individual case on the basis of a detailed and scientific justification that a potential serious risk as defined generally is posed.

2.1. Potential serious risk to human health

2.1.1. Potential serious risk for the consumer

The consumer of animal products should not be exposed to an undue and avoidable risk when consuming foodstuffs of animal origin. In order to ensure consumer safety an assessment of the safety of residues of all pharmacologically active substances contained in veterinary medicinal products for food-producing animals in accordance with Council Regulation (EEC) No 2377/90, has to be carried out. This evaluation is based on the determination of the Acceptable Daily Intake ⁽¹⁾ (ADI) on which Maximum Residue Limits ⁽²⁾ (MRLs) are subsequently based.

A potential serious risk to the consumer exists only if the withdrawal period ⁽³⁾, determined from the results of suitable residue depletion studies for a veterinary medicinal product, does not provide a sufficient degree of assurance that the concentrations of residues in foods derived from treated animals (meat, milk, eggs and honey) are not above the permitted concentrations causing a possible exceeding of the Maximum Residue Limits.

2.1.2. Potential serious risk for the user

A potential major hazard to human health (non-professional and professional user) must be regarded as serious and the probability of it occurring in practice, following risk management measures, must be minimal. Major effects (hazards) can only be tolerated if the devices and methods of administration as well as the conditions for use, described in the summary of product characteristics of the veterinary medicinal product, reduce the risk for human health to an acceptable level in relation to the expected beneficial effect for the animal.

A potential serious risk for the user exists only if the extent to which the exposure of the user can be reduced by a precautionary measure, alone or in combination with other protective methods, is not sufficient to reduce the risk to an acceptable level ⁽⁴⁾.

2.2. Potential serious risk to animal health

A potential serious risk to animal health in relation to a specific veterinary medicinal product can mainly be considered to exist under the following circumstances:

- **Efficacy:** the data submitted to support therapeutic efficacy in the proposed indication(s), target species and proposed dosing regimen (as defined by proposed labelling), do not provide a sound scientific justification for the claims for efficacy or if adequate proof for bioequivalence demonstrated by generic veterinary medicinal products to the reference veterinary medicinal product is lacking.
- **Safety:** the evaluation of the preclinical toxicity/safety pharmacology, clinical safety data and post-marketing data does not provide adequate support for the conclusion that all potential safety issues for the target species have been appropriately and adequately addressed in the proposed labelling or the absolute level of risk from the medicinal product, in the context of its proposed use, is considered unacceptable.
- **Quality:** the proposed production and quality control methods cannot guarantee that a major deficiency in the quality of the product will not occur

⁽¹⁾ **Acceptable Daily Intake (ADI):** the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without any appreciable health risk (Volume 8: Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin <http://pharmacos.eudra.org>).

⁽²⁾ **Maximum Residue Limits (MRLs):** the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or µg/kg on a fresh weight basis) which may be accepted by the Community to be legally permitted or recognised as acceptable in or on a food as laid down in Council Regulation (EEC) No 2377/90 (<http://pharmacos.eudra.org>).

⁽³⁾ **Withdrawal period** (as defined in Article 1 point 9 of Directive 2001/82/EC, as amended): the period necessary between the last administration of a veterinary medicinal product to animals, under normal conditions of use and in accordance with the provisions of the Directive, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits for active substances laid down pursuant to Regulation (EEC) No 2377/90 (<http://pharmacos.eudra.org>).

⁽⁴⁾ CVMP Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP/543/03-FINAL <http://www.emea.eu.int>)

- **Overall risk-benefit:** the risk-benefit balance for the product is not considered to be favourable, taking into account the nature of the identified risk(s) and the potential benefit in the proposed indication(s) and target species
- **Product Information:** a potential serious risk exists if information for the professional and non-professional user is insufficient to guarantee a suitable and safe use of the product in the animal

2.3. Potential serious risk for the environment

Applicants are required to submit a complete report which concludes with an Environmental Impact Assessment (EIA) based on the characteristics of the product, its potential environmental exposure, environmental fate and effects as well as risk management strategies as appropriate. The report should take into account the pattern of use, the administration of the product, the excretion of active substance and major active metabolites as well as the disposal of the product.

Following the risk assessment as outlined in international agreed guideline ⁽¹⁾ a potential serious risk for the environment exists if:

- a major risk for one or more of the environmental compartments (e.g. air, water, soil) is identified, taking into account different environmental conditions (e.g. climate, geo-hydrology) in the Member States
- and it (they) cannot be mitigated by any risk management strategies ensuring that no unacceptable risk is associated with the use and disposal of this product

Generally, any major objection must be scientifically justified taking into account the nature and degree of any hazards, the magnitude of the risks involved, the benefits associated with the use of those veterinary medicinal products, and the feasibility and practicability of implementing any measures that mitigate the risks. The Member State intending to refuse the application for marketing authorisation for the veterinary medicinal product should be prepared to support its grounds within the context of a coordination group procedure and if failed in an arbitration procedure. This would also cover any existing knowledge of the substance and specific risks in the concerned Member State which are not outlined in the dossier of the veterinary medicinal product or the assessment report of the reference Member State and which are not included in the summary of product characteristics during the mutual recognition or decentralised procedure.

Member States have accepted common rules and guidelines relating to manufacturing, quality control, evaluation of veterinary medicinal product efficacy, evaluation of its safety and quality assurance and labelling. These scientific guidelines give guidance for the evaluation of an application in general. However, different interpretations cannot be excluded on a specific set of data. It has to be recognised that in these circumstances a lack of compliance with scientific guidelines may not automatically result in a potential serious risk to human or animal health or for the environment unless they fulfil the conditions as described in section 2 of this guideline.

Any objection on the ground of a potential serious risk to human or animal health or for the environment cannot be justified by differences in national administrative or national scientific requirements or internal national policies, unless the conditions of Article 33(1) of Directive 2001/82/EC are fulfilled.

DG Enterprise and Industry will publish a list of examples related to the above definitions of issues which normally would not be considered as grounds for a 'Potential Serious Risk to Human or Animal Health or for the Environment'. This list will be updated based on experience gained with the decentralised and mutual recognition procedures

⁽¹⁾ CVMP Note for Guidance: Environmental Risk Assessment for Veterinary Medicinal Products other than GMO Containing and Immunological Products (EMA/CVMP/055/96-FINAL) Guidelines on environmental impact assessment (EIAS) for veterinary medicinal products – phase I and II (CVMP/VICH/592/98-FINAL; CVMP/VICH/790/03-FINAL <http://www.emea.eu.int>)