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Guideline on the approach to establish a pharmacological ADI

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Executive summary

This guideline gives advice on when to establish a pharmacological ADI and provides guidance on the pharmacological studies and endpoints to be addressed.

1. Introduction (background)

In European legislation it is laid down that foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues of the medicine or its metabolites which might constitute a health hazard for the consumer. In order to ensure this, Maximum Residue Limits (MRLs) have to be determined for all pharmacologically active substances used in veterinary medicinal products.

MRLs are generally derived from toxicologically or microbiologically based Acceptable Daily Intakes (ADI_{tox}/ADI_{micro}). However, certain substances may exert pharmacological effects in humans at exposure levels below those required to produce toxicological / microbiological effects. Pharmacological effects that may be desired in a target animal can be regarded as undesirable in the consumer. Therefore, for these substances, a pharmacological NO(A)EL should be identified and taken into account when setting the ADI.

The guideline can be applied to all pharmacologically active compounds and their active metabolites that may appear as residues in food producing animals when treated with a veterinary medicinal product. It is important to emphasise that setting a pharmacological ADI is not mandatory for all MRL applications and should only be considered where pharmacological effects have been identified.

The overall ADI for the substance should be established as the lowest of the pharmacological, toxicological and microbiological ADIs that have been determined.

2. Scope

The objectives of this guideline are to provide applicants with guidance on when to establish a pharmacological ADI (ADI_{pharm}) and also to provide guidance on the pharmacological endpoints that could be considered when investigating the pharmacodynamic actions of the substance.

3. Legal basis

Article 6(1) of Directive 2001/82/EC requires that a veterinary medicinal product may not be the subject of a marketing authorisation for food producing species unless the pharmacologically active substances which it contains appear in Annex I, II or III of Council Regulation (EEC) No 2377/90. Regulation (EEC) No 2377/90 has been repealed and replaced by Regulation (EC) No 470/2009 and all pharmacologically active substances previously listed in the annexes to Council Regulation (EEC) No 2377/90 are now included in the Annex to Commission Regulation (EU) No 37/2010.

Regulation (EC) No 470/2009 defines "residues of veterinary medicinal products" as "all pharmacologically active substances, expressed in mg/kg or µg/kg on a fresh weight basis, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals" and describes the procedure for the establishment of maximum residue limits for pharmacologically active substances. Article 6 of Regulation (EC) No 470/2009 indicates that the scientific risk assessment shall consider the type and amount of residues of pharmacologically active substances that may be ingested by consumers over a lifetime without an appreciable health risk expressed in terms of the acceptable daily intake (ADI), and notes that alternative approaches to the ADI may be used, if these have been laid down by the Commission as provided for in Article 13(2).

4. Main guideline text

4.1. General principles

Medicines normally exert their effects by a specific mode of action. These effects can be multiple, can be intended or not, and may have different target organs. Such effects are undesirable in consumers of foodstuffs of animal origin. It is therefore necessary to investigate pharmacological endpoints (or a suitable marker) as a basis for the pharmacological NO(A)EL and subsequently pharmacological ADI when this NO(A)EL appears to be the most conservative NO(A)EL.

4.2. When is a pharmacological ADI needed?

A pharmacological ADI needs to be established when pharmacological effects resulting from residues in animal products can be expected at doses in the same range or lower than toxicological effects.

There is NO need for establishing a specific pharmacological ADI:

1. If residues from the pharmacologically active compound are not bioavailable in humans by the oral route, i.e. the pharmacological active compound does not enter systemic circulation after oral ingestion.
2. For substances for which the only expected pharmacological activity is an antimicrobial activity; in such cases a microbiological ADI is set and will cover the relevant pharmacological effects.
3. When there is scientific evidence that the residues (metabolites) in animal derived foodstuffs are devoid of pharmacological activity [ie if there are no residues of the parent compound and the metabolites do not possess the pharmacological activity of the parent substance].
4. If the mode of action is not relevant for humans (differences in pharmacodynamics).
5. The pharmacological endpoint of concern is already included in the standard package of safety (toxicology) studies and hence is covered by the toxicological ADI.

4.3. Studies to be conducted

When the pharmacological endpoint of concern is properly addressed in the standard package of safety studies no special studies need to be conducted. Moreover, many substances also have a history of use in human medicine, therefore human data should be available. These are usually the most useful data to identify a pharmacological NOAEL.

In the absence of human data, laboratory studies should be conducted using appropriate animal or *in vitro* models. Designs of such studies may be available in published literature or may need to be developed depending on the specific mode of action. Because of the differences in pharmacodynamic activity of many groups of substances used in veterinary medicine it is not possible to indicate a precise set of studies.

In general, pharmacologically active compounds can be classified by their mode of action, e.g. NSAIDs, corticosteroids, oestrogens, progestagens, etc. For each class of compound, a most relevant / specific endpoint can be identified. In the annex of this guideline examples are given for substances, their pharmacological endpoints, and possible studies to investigate those endpoints. These examples were derived from previous MRL assessments. Obviously, human relevance and/or sensitivity should be taken into account when selecting these study models and endpoints.

Studies on the pharmacological endpoint of concern should reveal the dose-response relationship at the most relevant time point during or after dose administration. The data should allow the

establishment of a threshold, e.g. a No Observed Effect Level (NOEL) or a Benchmark Dose (BMDL) that can be used as a starting point for the derivation of the pharmacological ADI.

5. Definitions

ADI: Acceptable Daily Intake – 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.

MRL: 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 Union to be legally permitted or recognised as acceptable in or on a food.

NO(A)EL: No Observed (Adverse) Effect Level - the highest administered dose in a study at which no (adverse) effects are observed.

Pharmacological Activity: in CVMP position paper [EMEA/CVMP/072/97-Rev.1 (Revised July 2004)] it is reported that "*substances capable of pharmacological action are substances which are pharmacodynamically active at the dose at which they are administered to the target animal by means of the veterinary medicinal product in which they are included".*

6. References

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, as amended. Available from Commission Webpage: http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council. Available from Commission Webpage: http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm

Revised CVMP position paper on the definition of substances capable of pharmacological action in the context of Council Directive 2001/82/EC, as amended, with particular reference to excipients and manufacturing materials. Available at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004525

Annex

Table 1. Some examples of studies to investigate pharmacological endpoints of substances used in veterinary medicine

Intended mechanism of action	Proposed indication	Pharmacological Endpoint used to determine ADI
Cyclooxygenase inhibition	Treatment of inflammatory musculo-skeletal disorders in a variety of species	Inhibition of thromboxane B2 production by platelets
Gestagenic	Oestrus synchronisation in gilts and mares	Effects on menstrual cycle length and serum hormonal levels in monkeys
Beta adrenoceptor blocker	Anti-stress, facilitation of parturition /expulsion of placenta, increasing fertility	Inhibition of isoprenaline-induced tachycardia in rabbits
Inhibition of GNRH release	Synchronisation of oestrus in cattle, sheep and goats	Endometrial proliferation in juvenile rabbits
β_2-adrenoceptor agonist	Bronchodilation in horses and tocolytic in cattle & horses	Bronchospasmolysis in humans
Inhibits reabsorption of chloride (and to a lesser extent, other ions in the ascending loop of Henle; also causes vaso dilation via prostaglandin synthesis	Diuresis (to treat oedema, fluid in body cavities, intoxications, and renal failure with oliguria); also used in diagnostic procedures	Diuresis
β-adrenoceptor agonist with antagonist activity at α-adrenoceptors	Peripheral vasodilation (to treat navicular disease) and relaxation of uterine muscle	Cardiovascular effects (heart rate)