Provisional translation

The Food Safety Commission

Decision in April 2018

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Guidelines for the Risk Assessment of veterinary medicinal products

Contents

Chapter 1: General Provisions

Article 1: Purpose

The purpose of this Guideline is to clarify data required for risk assessment and to ensure the consistency of evaluation approaches among respective hazards and respective categories of risk assessment methods as well as the harmonization of risk assessment approach with the international standard as much as possible, which is expected to contribute for keeping and facilitating the transparency of assessment process.

Article 2: Definition

1. Veterinary Medicinal Product

Veterinary medicinal product is a medicinal product specifically used in animals which is designated by Article 2, paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Act No. 145, 1960).

2. Active Substance

The substance on which opinions on the risk assessment are requested from the Minister of Health, Labour and Welfare according to item (ii) of paragraph (1) of Article 11 of the Food Safety Basic Act (Act No.48, 2013. Hereinafter referred to as “the Act”), on establishing the MRLs for veterinary medicinal products in food according to the provision of Food Sanitation Act (Act No. 233, 1947)

3. Pharmaceutical Product

Pharmaceutical product is a product on which the Minister of Agriculture, Forestry and Fisheries requests for opinions about the risk assessments based on item 8 of paragraph 1 of Article 24 of the Act, on approval, re-examination or re-evaluation of a veterinary medicinal product according to the provision of the Pharmaceutical Affairs Act.

4. Excipients

Excipient is a substance that is mixed or contained in the pharmaceutical product designated in 3, except for the active substance.

5. Provisional Standards

Provisional standards is defined as MRLs for substances of which the risk assessments by Food Safety Commission of Japan (hereinafter referred to as the “Commission”) were not conducted yet, but were provisionally set based on the notification to partially revise the Specifications and Standards for Food, Food Additives, Etc. (Ministry of Health, Labour and Welfare Notification No. 499, 2005) along with the introduction of Positive List, referring to the standards established by international organizations and foreign nations.

6. Re-Examination

Re-examination of veterinary medicinal products according to the provision by Article 14, paragraph 4, item 1 of Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (including the re-examination by applying mutatis mutandis the provision to Article 19, paragraph 4 of the same Act).

7. Re-Evaluation

Re-evaluation of veterinary medicinal products according to the provision by Article 14, paragraph 6, item 1 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (including the re-examination by applying mutatis mutandis the provision to Article 19, paragraph 4 of the same Act).

Article 3. Principle of the Risk Assessment of Veterinary Medicinal Products

1. Codex Alimentarius Commission has described that “Risk assessment should incorporate the four steps of risk assessment, i.e. hazard identification, hazard characterization, exposure assessment and risk judgment” in “Working Principles for Risk Analysis for Food Safety for Application by Governments” (CAC/GL 62-2007).
The commission shall conduct the risk assessment (hereinafter referred to as the “Assessment”), for the time being, with a focus on the hazard characterization.

2. The Assessment shall be conducted scientifically and comprehensively based on the information including the target substance, the metabolites and degradates in food, and the results from the toxicity studies.

3. Veterinary medicinal products naturally will exert biological effects on animals, since the medicinal products are used in expectation of certain medicinal effects.
Therefore, hazard characterization shall be based on NOAEL but not NOEL.

4. Veterinary medicinal products will be metabolized or degraded in the animal bodies. Processes of the metabolism or degradation may produce substances that are equally toxic to or more toxic than the parent substance, and thus produced substances as such may be ingested into human body through livestock and fishery products.
Therefore, the assessment shall be conducted, in addition to the assessment of the parent substance, on the substances derived from the parent substance as needed that may have adverse effects on human health.

5. Biological Preparations for Veterinary Use prescribed by Article 1, paragraph 4 of the Control Regulations of Veterinary Medicinal Products (MAFF Ministerial Ordinance No.107, Series of 2004) are out of the scope of this Guideline, since the assessment approach for the relevant preparations are different from that of veterinary medicinal products which contain a chemical substance(s) as an active substance(s).

Article 4. Approach for the Documents Required

1. Documents Used for the Assessment

The Assessment shall be conducted based on the documents regarded as appropriate to characterize the target substance.

In principle, the appropriate documents provided by risk management agencies should be used for the Assessment. If the provided information is insufficient for the Assessment, the risk management organization shall be requested to provide the additional documents as necessary.

In order to ensure reliability of the Assessment, these documents shall include the data from studies that were conducted principally complying with the GLP and following various Guidelines effective in Japan, the Organization for Economic Co-operation and Development (OECD) and by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), as well as the reports prepared by the internationally recognized assessment organizations both inside and outside Japan.

Furthermore, the published references and literatures used for the Assessment must be the documents that have been judged as reliable for use in the Assessment by the Expert Committee on Veterinary Medicinal Products or the Expert Committee on Fertilizers and Feeds of FSCJ.

2. A case where Limiting the Documents used for the Assessment

In the assessments of a substance with very low potential to exert adverse effects on human health through livestock and fishery products, and in the assessment of viable bacterial preparations, the

reference documents that are to be used for the Assessment may be limited based on the existing scientific knowledge, such as characteristics of toxicity or persistence, evaluation by international organizations, or the fact that the substance of target is a biological component.

When the documents are limited, the reason and validity must be described in the assessment report.

Article 5: Evaluation of Studies including Toxicokinetics and Residues

1. Comprehension of toxicological characteristics of a target substance.

Toxicological characteristics of a target substance shall be revealed in the Assessment through comprehensive and careful analysis of the observation in toxicokinetics studies, residue studies and various toxicity studies.

Adverse effect(s) relevant to human health, such as genotoxicity, carcinogenicity, reproductive toxicity, etc., observed at LOAEL, which derives NOAEL, are used as endpoint.

With respect to the judgment of endpoints, the responses observed in each toxicity study should be analyzed, through reasonable and scientific interpretation, whether or not the difference is statistically significant and whether or not there is a dose-response relationship, considering difference in animal species among studies, dose of the substance, duration of exposure, and toxicokinetics. Throughout this procedure, mechanism of the toxicity should be discussed as much as possible.

2. Identification of NOAEL

When a NOAEL of the target substance is identified in a toxicity study, it should be considered whether the appropriate doses were assigned or not. For example, the maximum dose in a toxicity study is a dose at which some effects are observed, and the minimum dose is a dose at which no adverse effect is observed. Moreover, each dose examined in a study should be selected so as to provide a dose-response relationship.

3. Interpretation of findings of cecum in the experimental animals under the exposure to antibacterial substances.

Relevant interpretation follows “Interpretation of findings of cecum in the experimental animals under the exposure to antibacterial substances” (decision of the Expert Committee on Fertilizers and Feeds, on November 20, 2009).

4. Identification of NOAEL in carcinogenicity studies

Principles for the identification of NOAEL in a carcinogenicity study of veterinary medicinal products (decision of the Expert Committee on Veterinary Medicinal Products on January 15, 2015) should be followed.

5. Interpretation of the liver hypertrophy

Relevant interpretation follows “Interpretation of the liver hypertrophy in the toxicological evaluation of pesticides (agricultural chemicals) (Decision of FSCJ on September 7, 2016)” and “Interpretation of the liver hypertrophy in the toxicological evaluation of veterinary medicinal products and fertilizers/feeds. (Decision of FSCJ on October 25, 2017).

Article 6: Risk Assessment

1. Establishment of ADI

Acceptable Daily Intake (ADI) should be established as follows.

(1) Establishment of toxicological ADI

When an ADI is established based on the multiple NOAELs after comprehensive evaluation of toxicity studies for assessing the adverse effects of veterinary medicinal products on human health through livestock and fishery products, NOAEL should be identified in each study then the lowest value of those NOAELs shall be selected for the assessment of the target substance. However, if one particular study is regarded apparently more appropriate in the experimental design (such as experimental period and the dosage) or in the results in terms relevancy than other studies, the more appropriate study shall be considered with a special emphasis on determining the NOAEL for the conclusive evaluation. In addition, if extrapolatability of results to human is more appropriate than others, the NOAEL from the appropriate study should be used for the conclusive evaluation.

(2) Establishment of microbiological ADI

When the veterinary medicinal product of target being assessed is an antibacterial substance, the microbiological ADI shall be established based on the minimum inhibitory concentration (MIC) in order to consider the effects on human intestinal microflora through consumption of livestock and fishery products.

(3) Establishment of ADI of veterinary medicinal products

When the veterinary medicinal product of target being assessed is an antibacterial substance, the smaller should be selected as the ADI comparing the toxicological ADI and the microbiological ADI.

(4) Safety Factor

Considering inter-species differences between the experimental animals and humans and variability in responses among humans, the default safety factor of 100 is applied. This value, however, is not unchangeable, but is appropriately specified based on the data from toxicity studies, etc., as follows.

1) When the data from human studies are used, consideration for inter-species difference is not necessary. An appropriate safety factor shall be specified based on the population of study to consider variability among humans.
2) When ADI is established based on LOAEL instead of NOAEL, an additional safety factor of 1~10 is applied. Alternatively, a benchmark dose may be used.
3) An additional safety factor of 1~10 shall be applied for each factor in the light of factors such as the relevancy/quality of the data (e.g. availability of a long-term toxicity study, sufficiency of data from each toxicity study) and severity of the toxic response.

2. Cases where ADI “not specified” is established

The establishment of ADI for substances that are considered to have no or minimal toxicity or low persistence because of the rapid metabolism and excretion may be considered to be unnecessary, even if the ADI can be established based on characteristics of toxicity or persistency of the relevant substances. In such case, the reason why ADI “not specified” is established should be clearly described.

Article 7. Re-Evaluation

The evaluation of the adverse effects in the previous assessment shall be reviewed appropriately, whenever it is found necessary as the results of a newly conducted toxicity study. In such case of re-evaluation, up-to-date international evaluation standards and others shall be taken into consideration.

Article 8. Revision of the Guideline

When the Expert Committee on Veterinary Medicinal Products and the Expert Committee on Fertilizers/Feeds individually summarize the interpretation of toxicity studies in response to the up-to-date international risk assessment or advances in sciences, this Guideline shall be revised accordingly and appropriately.

Chapter 2: Detailed Exposition

Article 1: Evaluation of the active substance

1. Information on the target substance

Following information on the target substance are used for the assessment on request for establishing the MRLs for veterinary medicinal products, such as; generic name, chemical name, molecular form, molecular weight, chemical structure, purpose and approved uses of the target substance. (Refer to Appendix 1)

2. Information concerning safety of the target substance

The following data from the toxicity studies shall be required as the information concerning safety of the target substance that are used for the assessment for establishing the MRLs for veterinary medicinal products, such as; data on toxicokinetics, residue, genotoxicity, acute toxicity, subacute toxicity, chronic toxicity, carcinogenicity, reproductive developmental toxicity, microbiological ADI (in the case of antibacterial substances) and others. (Refer to Appendix 1)

3. Studies for establishment of microbiological ADI

As for antibacterial substances, according to the MAFF Guidelines 9-1, item 8, microbiological ADI shall be established based on the toxicokinetics data, microbiological activity in stool, the minimum inhibitory concentration (MIC) against standard strains and clinical isolates.

4. Evaluation of veterinary medicinal products for which the assessment is requested on revising provisional MRLs

The assessment follows the Implementation Procedures for the Risk Assessment of Pesticides for which Provisional MRLs are proposed (Decision of the Committee on June 29, 2006).

Article 2. Evaluation of the Pharmaceutical Product

1. Information on the target pharmaceutical product

Following information shall be used for the assessment concerning the marketing/manufacturing approval , re-examination or re-evaluation of veterinary medicinal products, that is; information on the active substance contained in the target pharmaceutical product that is described in the dossier and the attached documents for the approval submitted on the basis of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, such as the active substance, indications, dosage, route of administration, history of development and others. (Refer to Appendix 2.)

2. Information concerning safety of the pharmaceutical product for human

Documents required for the assessment concerning the marketing/manufacturing approval, re-examination or re-evaluation of veterinary medicinal products are the information including the active substance, excipients and residue studies. (Refer to Appendix 2.)
The assessment of excipients shall follow the Guidance for the Risk Assessment of excipients in Vaccine for food-producing Animals (Decision of the Committee on October 14, 2014).

3. Information concerning safety for the target animal

(1) Target animal safety

Documents to be used shall be on the study with which the safety was confirmed using the dose above the maximal of normal dosage to the target animal.

(2) Clinical study

Documents on clinical studies shall be used as necessary.

4. Documents concerning safety confirmation

The system of re-examination and re-evaluation have been established based on the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, for post-marketing confirmation of safety of the veterinary medicinal products that are approved based on the results from studies programmed and conducted in limited conditions. Documents required for relevant confirmation shall be as follows.

(1) Documents used in re-examination

Documents that are used in re-examination are documents described in the application for the re-examination and the attached documents submitted on the basis of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, such as; summary of use results survey of the product, information on the use results, and information of surveys on the indication, performance, or safety.

(2) Documents used in re-evaluation

Documents that are used in re-evaluation shall be documents such as the summary of product characteristics and the summary of evaluation described in the application for the re-evaluation as well as the attached documents submitted on the basis of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.

5. Assessment concerning antimicrobial-resistant bacteria selected by antimicrobial use

The Assessment shall follow the Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food producing animals (Decision of the Committee on September 30, 2004).

References: Glossary of terms

1. Safety Factor (SF)
Safety factor is a reductive factor used to secure further safety in deriving HBGV including ADI from NOAEL, LOAEL, or etc. for a certain substance, taking inter-species variability, inter-individual variability and uncertainties into consideration.

2. Hazard Identification
The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods..

3. Hazard Characterization
The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if such data are obtainable.

4. Minimum Inhibitory Concentration (MIC)
The lowest concentration of an antimicrobial compound that inhibits growth of the test microorganism as determined by standardized test procedures.

5. Guidelines by the Ministry of Agriculture, Forestry and Fishery
This indicates the Appendix 2 of “On the Handling of Legal Service concerning Assurance System of Quality, Performance, and Safety of Veterinary Medical Devices Based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (Notification by NVAL Director, MAFF, on 31 March 2000)”.

6. Exposure Assessment
The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

7. Microbiological ADI
An ADI established based on microbiological data according to VICH Guideline (GL 36(R)).

8. Endpoint
Qualitative or quantitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.

9. Benchmark Dose (BMD)
The BMD is a dose level that is estimated from the fitted dose-response curve obtained from an animal study, and associated with a specified change in response (Benchmark Response: BMR, generally 5% in developmental toxicity and 10% in general toxicity).

10. Positive List System
On May 29, 2006 the MHLW introduced the positive list system for the agricultural chemicals such as pesticides, feed additives and veterinary medicinal products to prohibit the distribution of the food that contain these chemicals above a certain level if maximum residue limits (MRLs) have not been established. The uniform limit has been set at 0.01 ppm for agricultural chemicals without MRLs.

11. Risk Characterization

The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

12. Acceptable Daily Intake (ADI)
An estimate of the amount of a substance, used intentionally in food producing procedure such as pesticides or food additives, which is ingestible on a daily basis over a lifetime without adverse health effects.

13. Good Laboratory Practice (GLP)
The GLP refers to standards for quality of practice and equipment of a testing institution, as well as its organization, staff and operational procedures. The aim is to ensure the reliability of results of safety tests of various chemical substances.

14. Lowest-Observed-Adverse-Effect Level (LOAEL)
The LOAEL is the lowest dose of a substance that causes a detectable adverse effect, found by toxicity study under defined conditions of exposure.

15. No-Observed-Adverse-Effect Level (NOAEL)
The NOAEL is the highest dose of a substance that causes no detectable adverse effect, found by toxicity study under defined conditions of exposure.

16. No-Observed-Effect Level (NOEL)
The NOEL is the highest dose or exposure level of a substance or material that produces no observable toxic effect on tested animals in toxicity studies such as a repeated toxicity study or a reproductive and developmental toxicity study using different doses.

17. OECD Guidelines for the Testing of Chemicals
The OECD Guidelines were established by Organization for Economic Co-operation and Development (OECD) and accepted internationally as standard methods for safety testing for assessment of the potential effects of chemicals on human health and the environment. This group of tests covers physical-chemical properties, effects on environmental systems, biodegradability and bioaccumulation of chemicals.

18. VICH Guidelines
Guidelines that is developed by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). The guidelines provide a basis for international harmonised guidelines of registration requirements, and also covers data requirements for post-marketing pharmacovigilance surveillance systems.

Appendix 1. Items to be described in assessment report of active substance

		New	Revision[1]
Outline of the target substance			
	1. Usage	○	
	2. General name of active substance	○	
	3. Chemical name	○	
	4. Molecular form	○	
	5. Molecular weight	○	
	6.Chemical structure	○	
	7. Purpose and status of use (or history of development)	○	△
Information concerning safety			
	1. Toxicokinetics study	○	△
	2. Residue analyses	○	△
	3. Genotoxicity study	○	△
	4. Acute toxicity study	○	△
	5. Subacute toxicity study	○	△
	6. Chronic toxicity study	○	△
	7. Carcinogenicity study	○	△
	8. Reproductive and developmental toxicity study	○	△
	9. Other studies	○	△
	10. Pertinent studies for specification of microbiological ADI (for antibacterial substances)	○	△

○: Document to be attached.

△: Document to be attached if necessary, such as when there is a new finding.

[1] A case where the evaluation result is existing.

Appendix 2. Items to be described in assessment report of pharmaceutical products

	Outline of the target pharmaceutical products	Approval	Re-examination[2]
	1. Information on the main agent	○	△*
	2. Indications	○	△*
	3. Dosage and administration	○	△*
	4. Additives	○	△*
	5. History of development (or Purpose and status of use)	○	△*
	Information concerning safety		
	1. Information on the main agent (Conclusion derived from safety studies on the active substance)	○	△*
	2. Information on the additives	○	△*
	3. Residue analyses	○	△*
	4.Safety study	○	
	(1) Safety for the target livestock	○	
	(2) Side effect report	○	○
	(3) Report of safety study that came out after the approval	○	○
	(4) Report of the study of persistence		○
	5. Clinical study	○	
	6. Assessment concerning antimicrobial-resistant bacteria selected by antimicrobial use	○	△*
	7. Documents on antimicrobial-resistant bacteria	○	○

○: Document to be attached.

△: Document to be attached if necessary, such as when there is a new finding.

*: If the assessment of target pharmaceutical product shall be a new assessment despite relevant request is for “re-examination”, the same documents as that for “approval” should be attached.

[2] A case where the evaluation result is existing.