RESOLUTION – RDC NO. 328 OF 19 DECEMBER 2019

Provides for the assessment of risk to human health of veterinary medicinal products and the methods of analysis for the purposes of conformity assessment.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and item V, paragraphs 1 and 3 of Article 53 of the Internal Regulation approved by the Collegiate Board Resolution – RDC no. 255 of 10 December 2018, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 17 December 2019, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Article 1. This Resolution provides for the assessment of risk to human health of veterinary medicinal products and the methods of analysis for the purposes of conformity assessment.

Article 2. The maximum residue limits (MRL) and the acceptable daily intake (ADI) adopted by Anvisa shall be published in the Normative Instruction no. 51 of 19 December 2019, which established the list of maximum residue limits (MRL), acceptable daily intake (ADI), and acute reference dose (ARfD) for active pharmaceutical inputs (API) of veterinary medicinal products in foods of animal origin.

CHAPTER II

DEFINITIONS

Article 3. For the purposes of this Resolution, the following definitions shall apply:

I – exposure assessment: step of the risk assessment process that estimates the acute or chronic intake of residues from veterinary medicinal products originated from the consumption of foods of animal origin by the population or population group;

II – risk assessment: process based on scientific evidence, which assess the probability of adverse effects to human health and the severity of such effects as a consequence of the use of veterinary medicinal products in food-producing animals, involving the steps of hazard identification and characterization, exposure assessment, and risk characterization;

III – acute reference dose (ARfD): estimated amount of residues from veterinary medicinal products, expressed in milligrams or micrograms of the substance per kilogram of body weight, which may be ingested in a period of 24 (twenty four) hours without significant risk to human health;

IV – acceptable daily intake (ADI): estimated amount of residues from veterinary medicinal products, expressed in milligrams or micrograms of the substance per kilogram of body weight, which may be ingested throughout life without significant risk to human health;

V – estimated daily intake (EDI): estimated intake of residues from veterinary medicinal products, calculated from the average concentration in the studies of depletion, corrected by marker residues or total residues for the foods to be considered in the exposure assessment, expressed in milligrams or micrograms of residue per person per day;

VI – theoretical maximum daily intake (TMDI): estimated intake of residues from veterinary medicinal products, from the MRL, for the foods to be considered in the exposure assessment, expressed in milligrams or micrograms of residue per person per day;

VII – active pharmaceutical ingredient (API): pharmacologically active component of the veterinary medicinal product;

VIII – dual-use pharmaceutical ingredient (dual-use API): pharmacologically active component used in both veterinary medicinal products and pesticides;

IX – maximum residue limit (MRL): maximum concentration of residue from a veterinary medicinal product, expressed in milligrams or micrograms per liter or kilogram, legally permitted in foods of animal origin;

X – veterinary medicinal product: product applied or administered to any animal intended for food production, for therapeutical, prophylactic, or diagnosis purposes, or to alter physiological functions or behavior;

XI – validated analysis method: analysis method that proves, through the production of objective evidence, that the requirements for the specific intended application or use were complied with;

XII – grace period: period of time between the last administration of veterinary medicinal product and the collection of edible tissues or products from the treated animal, which ensures thar the amount of residues from veterinary medicinal products is equal to or lower than its MRL;

XIII – residues from veterinary medicinal products: API and its metabolites that are present in any edible portion of the product of animal origin;

XIV – bound residues: residues from veterinary medicinal products bound in a covalent way to soluble or insoluble cell macromolecules, which are not extractable by exhaustive processes of extraction, denaturation, or solubilization;

XV – marker residues: residues from veterinary medicinal products, the concentration of which diminishes in a known proportion to the concentration of total residues in any edible portion of the food of animal origin; and

XVI – total residues: sum of all APIs and their metabolites that remain in the product of animal origin after the veterinary medicinal product administration, determined from studies using radiomarked APIs.

CHAPTER III

REQUIREMENTS FOR THE RISK ASSESSMENT OF VETERINARY MEDICINAL PRODUCTS

Article 4. The risk assessment of veterinary medicinal products must be requested by the interested party, through the submission of a specific petition, for the following cases:

I – veterinary medicinal products containing in their formula an API without MRL published by Anvisa;

II – inclusion of new animal species or matrices for API with MRL already published by Anvisa; or

III – alteration of the MRL already published by Anvisa for a determined animal species.

Article 5. The specific petition for the risk assessment of veterinary medicinal products must have a technical-scientific report with the following information:

I – identification of the veterinary medicinal product and its API;

II – pharmacokinetic studies;

III – toxicological studies;

IV – microbiological studies, in the case of API and its metabolites with antimicrobial action;

V – marker residue depletion studies; and

VI – identification if the API is of dual use.

Paragraph 1. The technical-scientific report must include the studies for the API metabolites that are relevant to human health.

Paragraph 2. The studies must be conducted and reported in accordance with updated protocols described in the series published by the Organization for Economic Cooperation and Development (OECD), or the directives published in the Veterinary International Conference on Harmonization (VICH) Guides, and follow the Good Laboratory Practices (GLP) principles.

Paragraph 3. Situations that require adaptation or a new study protocol must be justified and include a description of the procedures used.

Paragraph 4. Old studies where GLP principles were not adopted may be accepted, as long as their scientific quality and the design adequacy for the assessment of APIs and their metabolites are confirmed.

Paragraph 5. The study submission provided for in items III and IV may be waived for the APIs and their metabolites that have a risk assessment published and an ADI established by the Codex Alimentarius.

Paragraph 6. The study submission provided for item V may be waived for the APIs and their metabolites that have a MRL established by the Codex Alimentarius.

Paragraph 7. The risk assessment published by foreign authorities that have regulatory requirements similar to the Brazilian ones may provide information to support the risk assessment requested.

Article 6. In order to identify the veterinary medicinal product and its APIs, the following information must be presented:

I – International Non-proprietary Name – INN;

II – IUPAC (International Union of Pure and Applied Chemistry) nomenclature;

III – synonyms;

IV – CAS (Chemical Abstract Service) number;

V – structural formula;

VI – molecular formula;

VII – molar mass;

VIII – physical-chemical properties;

a) appearance;

b) purity;

c) qualitative and quantitative composition of impurities;

d) fusion point;

e) solubility in water and organic solvents, expressed in grams per liter, with indication of temperature, logKow, or logP;

f) pH;

g) optical rotation;

h) maximum absorption wavelength in the ultraviolet region; and

i) stability.

IX – therapeutic classification, formulation, and indication of use, including dosage, administration route, and recommended grace period of the medicinal product; and

X – marketing authorization data of the veterinary medicinal product in Brazil and other countries, including conditions of use, dosage, and grace period.

Article 7. Pharmacokinetic studies must cover the pharmacokinetic behavior of APIs in laboratory animals and in the food-producing target species, including data on absorption, distribution, and elimination, half-life in plasma and tissues, and metabolic pathways.

Sole paragraph. For target species, the studies must use the APIs radiomarked in the veterinary medicinal product.

Article 8. Metabolism studies with food-producing animals must allow the definition of marker residues, the ratio of marker residues to total residues, and the edible tissue selected to monitor the marker residues in the target species.

Sole paragraph. The marker residues must have a validated analysis method to quantify their concentration in the product of animal origin.

Article 9. Toxicological studies must include the following trials:

I – genotoxicity;

II – acute toxicity;

III – toxicity of repeated doses;

IV – reproduction toxicity (multigeneration);

V – development toxicity; and

VI – chronic toxicity or carcinogenicity.

Paragraph 1. Additional neurotoxicity, immunotoxicity, allergenicity, or endocrine disfunction studies may be required to identify specific effects related to structure, class, and mode of action of the APIs or their metabolites.

Paragraph 2. The absence of any of the studies listed in the caption of this article must be technically justified.

Article 10. Microbiological studies must assess:

I – potential effects on the human intestinal colonization barrier; and

II – the increase in resistance of the bacteria living in the human colon.

Article 11. Residue depletion studies must be conducted in the following tissues:

I – muscle;

II – fat;

III – liver;

IV – kidney; and

V – milk, eggs, and honey, as applicable.

Paragraph 1. In the case of fish, the provisions in item I include skin in natural proportions.

Paragraph 2. In the case of poultry and swine, the provisions in item II include skin in natural proportions.

Paragraph 3. Residue depletion studies must be conducted in the target species and include information on total residues, free residues, and bound residues from the different tissues.

Paragraph 4. Residue depletion studies must be conducted with the available formulations, in the administration routes, and in target species, using the maximum recommended dosage and treatment duration.

Paragraph 5. For intramuscular or subcutaneous injectable formulations containing API with ARfD concern, data on residue depletion in the injection site must be included.

Paragraph 6. Aquiculture residue depletion studies must include water temperature data on every day of the trial.

Paragraph 7. Residue depletion studies cannot be conducted for a period lower than the grace period proposed by the interested party to justify the suggested MRL.

Paragraph 8. Residue depletion studies must contain raw data.

Paragraph 9. A detailed description of the analysis method and the method validation parameters to determine residues in tissues, eggs, milk, or honey must be presented.

Paragraph 10. In addition to performance parameters, the efficiency of extraction or recovery must be informed.

CHAPTER IV

ESTABLISHING THE ACCEPTABLE DAILY INTAKE (ADI) AND THE ACUTE REFERENCE DOSE (ARfD)

Article 12. The ADI and the ARfD shall be defined by Anvisa based on the results from toxicological studies.

Sole paragraph. For an API and its metabolites with antimicrobial action, the ADI and the ARfD shall be defined based on the results from toxicological and microbiological studies, and the lowest value found in such studies shall be adopted.

Article 13. An ADI shall not be defined for an API and its metabolites when the risk assessment indicates mutagenicity, carcinogenicity, teratogenicity, or adverse effects in reproduction or development.

CHAPTER V

ESTABLISHING THE MAXIMUM RESIDUE LIMIT (MRL)

Article 14. The MRL shall be defined by Anvisa based on the results from depletion studies.

Article 15. Anvisa shall adopt a non-recommended MRL when, based on the scientific information available, there is a conclusion that there is not a safe level of residues that represents an acceptable risk to human health.

Article 16. An MRL shall not be defined for situations with a large safety margin, when the API and its metabolites:

I – do not have toxicological significance;

II – are recognized as safe;

III – are weakly absorbed or bioavailable;

IV – are quickly metabolized or eliminated;

V – are components present in human food;

VI – represent a small fraction of the body's endogenous production; and

VII – have unlikely presence in the foods of animal origin or present residues, the exposure to which represents unlikely risk to the population.

Sole paragraph. The APIs and their metabolites referred to in the caption of this article will be listed in Annex II of Normative Instruction no. 51 of 2019.

CHAPTER VI

EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

Article 17. The assessment of chronic exposure to residues from veterinary medicinal products shall be made through the TMDI.

Paragraph 1. When the TMDI estimate exceeds the ADI, the exposure assessment must be refined using EDI calculation or through a similar approach accepted internationally.

Paragraph 2. In case of dual-use API, the chronic exposure assessment must jointly consider the use of veterinary medicinal product and pesticide.

Article 18. For the chronic exposure calculation, the average daily consumption *per capita* shall be adopted and, for the acute exposure calculation, the maximum possible consumption of the food in a 24-hour period shall be considered.

Article 19. When the data on concentration of residues found in depletion studies are below the analysis method quantification limit, the method quantification limit divided by two must be considered.

Article 20. For residues from veterinary medicinal products that have a specified acute reference dose (ARfD), the acute food exposure in a 24-hour period must be estimated.

Article 21. When the MRL or the high concentration of residues obtained from depletion studies vary in the different animal species, for the largest serving consumed, the highest MRL defined or the highest concentration of residues obtained must be considered.

Article 22. For risk characterization, the ADI and the ARfD must be compared to exposure estimates.

Paragraph 1. When the exposure estimate is lower than or equal to the ADI and the ARfD, the MRL shall be adopted by Anvisa.

Paragraph 2. When the exposure estimate is greater than the ADI or the ARfD, the following procedures shall be followed:

I – refinement of the exposure assessment;

II – restriction of use for some animal species; or

III – revision of the grace period and/ or the good veterinary practices.

Article 23. Emergencies involving risk to animal health shall be considered a priority for the risk assessment of veterinary medicinal products and the establishment of the ADI, the ARfD, when applicable, and the MRL.

Article 24. The risk to human health due to the use of veterinary medicinal products in animals may be reassessed at any time and, whenever justified, the ADI, the ARfD, when applicable, and the MRL may be altered or excluded.

CHAPTER VII

ANALYSIS METHODS FOR THE PURPOSES OF CONFORMITY ASSESSMENT

Article 25. The laboratories that conduct the determination of residues from veterinary products in foods must use a validated analytical methodology.

Paragraph 1. The methods from technical regulations, official compendia, internationally accepted compendia, and methods validated through collaborative studies must be verified under laboratory conditions.

Paragraph 2. The methods developed or altered by the laboratory itself must be validated to show it is adequate for its purpose, in accordance with the performance criteria defined in the Codex Alimentarius Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme Associated with the Use of Veterinary Drugs in Food Producing Animals (CAC/GL 71-2009), its updates, or another reference internationally accepted.

CHAPTER VIII

FINAL AND TRANSITIONAL PROVISIONS

Article 26. For veterinary medicinal products authorized in Brazil until the date this Resolution is published, and that include in their formulation an API without MRL published in Normative Instruction no. 51 of 2019, the interested party must present, in the period of 5 (five) years, documentation corroborating the establishment of ADI and MRL.

Paragraph 1. The period referred to in the caption of this article may be extended once, by a maximum period of 2 (two) years, if it is proven that such extension is necessary for the conclusion of ongoing scientific studies.

Paragraph 2. For the situation provided for in the caption of this article, the matrix analyzed may contain a maximum of 10 micrograms per kilo.

Article 27. For APIs present in veterinary medicinal products authorized in Brazil until the date this Resolution is published, with a long history of use and without evidence of adverse effects in humans, for which there are no MRLs defined in the Codex Alimentarius, Anvisa shall adopt an MRL of 10 micrograms per kilo, through a case-by-case analysis.

Article 28. The failure to comply with the provisions in this Resolution constitutes a health infraction, in the terms of Law no. 6,437 of 20 August 1977 and its updates, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 29. The following provisions are hereby revoked:

I – Collegiate Board Resolution – RDC no. 4 of 2 January 2001, which approves the technical regulation on glossary of terms and definitions for residues from veterinary medicinal products;

II – Collegiate Board Resolution – RDC no. 5 of 2 January 2001, which approves the technical regulation on sampling methods for programs to control residues from veterinary medicinal products in foods of animal origin; and

III – Collegiate Board Resolution – RDC no. 53 of 2 October 2012, which provides for the Mercosur technical regulation – analytical methodologies, acceptable daily intake, and maximum residue limits for veterinary medicinal products in foods of animal origin.

Article 30. This Resolution enters into force on the date of its publication.

WILLIAM DIB

Director-President