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SANTE 11188-2018 Rev3.

Yellow highlight: changes in Rev. 3 compared to Rev.2.

COMMISSION IMPLEMENTING REGULATION (EU) .../...

of XXX

on the performance of analytical methods for pharmacologically active substances, the interpretation of results and the methods to be used for sampling.

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2017/625¹ of the European Parliament and the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection product, amending Regulations (EC) No 999/2001, (EC) No 396/2005, (EC) No 1069/2009, (EC) 1107/2009, (EU) 1151/2012, (EU) No 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) No 1/2005 and (EC) No 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) No 854/2004 and (EC) No 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 60/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation), and in particular Article 34(6) thereof,

- (1) Regulation (EU) 2017/625 lays down rules for the performance of official controls and other official activities by the competent authorities of the Member States to verify compliance with Union legislation inter alia in the area of food safety at all stages of production, processing and distribution. It provides for specific rules on official controls in relation to substances whose use may result in residues in food and feed.
- (2) Articles 34(1) to 34(5) of Regulation (EU) 2017/625 set general requirements for the methods to be used for sampling, laboratory analysis and tests during official controls

¹ OJ L95, 7.4.2017, p1.

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and other official activities and Article 34(6) lays down that the Commission by means of implementing acts may lay down additional rules on the methods to be used for sampling, for laboratory analysis and tests and performance criteria, on analysis and test parameters, on measurement uncertainty and on procedures for the validation of those methods, the interpretation of analytical and testing results. In order to ensure the reliability and consistency of official controls and other official activities on residues of pharmacologically active substances, such additional rules should be set.

- (3) Commission Decision 2002/657/EC² sets requirements for the performance of analytical methods and the interpretation of results and Commission Decision 98/179/EC³ lays down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products. In view of new scientific developments, these rules should be updated and they should be integrated into the framework for official controls defined by Regulation (EU) 2017/625.
- (4) Commission Decisions 98/179/EC³ and 2002/657/EC² should be repealed as their provisions are replaced by the provisions included in this Regulation.
- (5) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Subject matter and scope

This Regulation provides rules for methods of analysis and sampling for residues of pharmacologically active substances in live food-producing animals, their body parts and fluids, excrements, tissues, products of animal origin, animal by-products, animal feed and water and it provides rules for the interpretation of analytical results of these laboratory analyses. These rules are without prejudice to the rules laid down in Reg. (EC) No 152/2009 on the methods of sampling and analysis for the official control of feed.

² 2002/657/EC: Commission Decision of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results (Text with EEA relevance) (notified under document number C(2002) 3044) (OJ L 221, 17.8.2002, p. 8)

³ 98/179/EC: Commission Decision of 23 February 1998 laying down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products (OJ L 65, 5.3.1998, p. 31).

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Article 2

Definitions

For the purpose of this Regulation, the definitions of Regulation **SANTE-11987-2017**⁴, Regulation **SANTE-10413-2015**⁵, Regulation (EC) No 470/2009⁶, Regulation (EU) 2017/625⁷ and Council Regulation (EEC) No 315/93⁸ shall apply. The following definitions shall also apply:

- 1) Accuracy means the closeness of agreement between a test result and the accepted true reference value. It is determined by estimating trueness and precision.⁹
- 2) Alpha (α) error means the probability that the tested sample is compliant, even though a non-compliant measurement has been obtained (the probability of a false non-compliant decision).
- 3) Analyte means the substance that has to be detected, identified and/or quantified and derivatives emerging during its analysis.
- 4) Beta (β) error means the probability that the tested sample is truly non-compliant, even though a compliant measurement has been obtained (the probability of a false compliant decision).
- 5) Bias means the difference between the estimated value of the test result and an accepted reference value⁹.
- 6) Calibration standard means a traceable reference for measurements that represents the quantity of substance of interest in a way that ties its value to a reference base.
- 7) Certified reference material (CRM) means a material that has a specified analyte content with associated uncertainty assigned to it.

⁴ Please add reference

⁵ Please add reference

⁶ 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 (OJ L 152, 16.6.2009, p. 11–22).

⁷ Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products, amending Regulations (EC) No 999/2001, (EC) No 396/2005, (EC) No 1069/2009, (EC) No 1107/2009, (EU) No 1151/2012, (EU) No 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) No 1/2005 and (EC) No 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) No 854/2004 and (EC) No 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 90/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation) (OJ L 95, 7.4.2017, p. 1–142).

⁸ Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food (OJ L 037, 13.2.1993, p. 1–3).

⁹ ISO 3534-1: 2006 Statistical Methods for quality control — Vol. 1 vocabulary and symbols.

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- 8) Co-chromatography means a procedure in which the sample extract prior to the chromatographic step(s) is divided into two parts. Part one is chromatographed as such. Part two is mixed with the standard analyte that is to be measured. Then this mixture is also chromatographed. The amount of added standard analyte has to be similar to the estimated amount of the analyte in the extract. Co-chromatography is used to improve the identification of an analyte when chromatographic methods are used, especially when no suitable internal standard can be used.
- 9) Collaborative study means analysing the same sample(s) using by the same method to determine performance characteristics of the method in different laboratories. The study allows to calculate the random measurement error and laboratory bias for the method used.
- 10) Confirmatory method means a method that provides full or complementary information enabling the substance to be unequivocally identified and if necessary quantified:
 - at the MRL or ML for authorised substances; or
 - at the RPA for prohibited or unauthorised substances, for which an RPA is established; or
 - at a concentration as low as analytically achievable for prohibited or unauthorised substances, for which no RPA is established.
- 11) Coverage factor (k) means a number which expresses desired level of confidence and which is associated with the expanded measurement uncertainty.
- 12) Decision limit ($CC\alpha$ for confirmation, hereunder referred to as $CC\alpha$) means the limit at and above which it can be concluded with an error probability of α that a sample is non-compliant.
- 13) Detection capability of screening ($CC\beta$ for screening, hereunder referred to as $CC\beta$) means the smallest content of the analyte that may be detected and or quantified in a sample with an error probability of β .
 - a. In the case of prohibited or unauthorised pharmacologically active substances, the $CC\beta$ is the lowest concentration at which a method is able to detect and/or quantify with a statistical certainty of $1 - \beta$, samples containing residues of prohibited or unauthorised substances.
 - b. In the case of authorised pharmacologically active substances, the $CC\beta$ is the concentration at which the method is able to detect the permitted limit concentrations with a statistical certainty of $1 - \beta$.
- 14) Expanded measurement uncertainty (U) provides an interval within which the value of the measurand is estimated to lie with a higher level of confidence. U is obtained by multiplying the combined standard measurement uncertainty by a coverage factor (k).

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- 15) Fortified (spiked) sample material means a sample enriched with a known amount of the analyte to be detected and/or quantified.
- 16) Interlaboratory study (comparison) means the organisation, performance and evaluation of tests on the same sample(s) by two or more laboratories in accordance with predetermined conditions to determine testing performance. According to its purpose, the study can be classified as collaborative study or proficiency test.
- 17) Internal Standard (IS) means a substance not contained in the sample and having physico-chemical properties as similar as possible to those of the analyte to be identified and/or quantified. The internal standard is added to each sample as well as to each calibration standard.
- 18) Level of interest means the concentration of a substance or analyte in a sample that is significant to determine its compliance with the legislation.
- 19) Lowest calibrated level (LCL) means the lowest concentration on which the measuring system has been calibrated.
- 20) Matrix effect means the difference in analytical response between a standard dissolved in the solvent and a matrix-matched standard (fortified post extraction and clean-up) either without a correction using an (internal) standard (absolute matrix effect) or with correction using an internal standard (relative matrix effect).
- 21) Matrix-matched standard: a blank (analyte-free) matrix to which following solvent extraction and sample clean-up, the analyte is added at a range of concentrations after sampling processing.
- 22) Matrix-fortified (spiked) standard: a blank (analyte-free) matrix, which prior to solvent extraction and sample processing, is spiked with the analyte at a range of concentrations.
- 23) Measurement uncertainty means a non-negative parameter associated with the result of measurement, which characterises the dispersion of values that could reasonably be attributed to the measurand (analyte), based on the information used¹⁰.
- 24) Performance criteria means requirements for a performance characteristic according to which it can be judged that the analytical method is fit for the purpose and generates reliable results.
- 25) Precision means the closeness of agreement between independent test results obtained under stipulated (predetermined) conditions. It is usually expressed in terms of imprecision, this can be expressed, e.g. as the standard deviation or coefficient of variation (relative standard deviation) of the test result. Less precision is determined by a larger standard deviation⁹.

¹⁰ JCGM 200:2008, Third Edition 2008: <https://www.iso.org/sites/JCGM/VIM-JCGM200.htm>

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- 26) Qualitative method means an analytical method, which detects or identifies a substance or a group of substances on the basis of its chemical, biological or physical properties.
- 27) Quantitative method means an analytical method, which determines the amount or mass fraction of a substance so that it may be expressed as a numerical value of appropriate units.
- 28) Absolute recovery means the proportion of the analyte remaining at the point of the final determination, following its addition (usually to a blank sample) immediately prior to extraction, expressed as a percentage.
- 29) Reference material means a material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process or in examination of nominal properties¹¹.
- 30) Repeatability means precision under repeatability conditions⁹.
- 31) Repeatability conditions means conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment at the same day⁹.
- 32) Reproducibility means precision under reproducibility conditions⁹.
- 33) Reproducibility conditions means conditions, where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment^{9,12}.
- 34) Ruggedness means the susceptibility of an analytical method to changes in experimental conditions such as the sample materials, analytes, storage conditions, environmental and/or sample preparation conditions under which the method can be applied as presented or with specified minor modifications. For all experimental conditions, which could in practice be subject to fluctuation (e.g. stability of reagents, composition of the sample, pH, temperature) any variations which could affect the analytical result shall be indicated.
- 35) Screening method means methods that are used for screening of a substance or class of substances at the concentration of interest. These methods have the capability for a high sample throughput and are used to sift large numbers of samples for potential non-compliant results. They are specifically designed to avoid false compliant results.
- 36) The Screening Target Concentration (STC) is the concentration at which a screening test categorises the sample as "Screen Positive" (potentially non-compliant) and triggers a confirmatory testing. It is a concentration, which is lower than the CC beta.

¹¹ CAC/GL 72-2009

¹² ISO 5725-1:1994: Accuracy (trueness and precision) of measurement methods and results -- Part 1: General principles and definitions

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- 37) Selectivity means the ability of a method to distinguish between the analyte being measured and other substances. This characteristic is predominantly a function of the measuring technique described, but can vary according to class of compound or matrix.
- 38) Single laboratory study (in-house validation) means an analytical study involving a single laboratory using one method to analyse the same or different test materials under different conditions over justified long time intervals.
- 39) Standard addition means a procedure in which the official sample is divided in two (or more) test portions. One portion is analysed as such and known amounts of the standard analyte are added to the other test portions before analysis. The amount of the standard analyte added, can for example be between two and five times the estimated amount of the analyte in the sample. This procedure is designed to determine the content of an analyte in a sample, taking account of the recovery of the analytical procedure.
- 40) Standard analyte means an analyte of known and certified content and purity to be used as a reference in the analysis.
- 41) Substance means matter of constant composition best characterized by the entities (molecules, formula units, atoms) it is composed of. Physical properties such as density, refractive index, electric conductivity, melting point etc. characterize the chemical substance.
- 42) Test portion means the quantity of material drawn from the official sample on which the test or observation is carried out.
- 43) Trueness means the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value. Trueness is usually expressed as bias⁹.
- 44) Units means those units described in ISO 31 and Council Directive 80/181/EEC¹³.
- 45) Validation means the demonstration by examination and the provision of effective evidence that the particular requirements of a specific intended use are fulfilled¹⁴. It may be single laboratory study or collaborative study.
- 46) Within-laboratory reproducibility/intermediate precision means precision obtained in the same laboratory under stipulated (predetermined) conditions (concerning e.g. method, test materials, operators, and environment) over justified long time-intervals (for example over several weeks to simulate possible changes in realistic analytical conditions).

¹³ Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement and on the repeal of Directive 71/354/EEC, OJ L 39, 15.2.1980, p. 40–50).

¹⁴ ISO/IEC 17025: General requirements for the competence of testing and calibration laboratories

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Article 3

Methods of Analysis

The Member States shall ensure that official samples taken pursuant to Regulation (EU) 2017/625 are analysed using methods that:

- (a) are documented in test instructions, preferably according to ISO 78-2 ¹⁵.
- (b) comply with performance criteria and other requirements for analytical methods laid down in Chapter 1 of Annex I to this Regulation.
- (c) have been validated in accordance with the requirements laid down in Chapters 2 and 4 of Annex I to this Regulation.
- (d) allow enforcements of the reference points for action, laid down in Regulation (EU) 2019/XXXX¹⁶.

Article 4

Quality Control

The Member States shall ensure the quality of the results of the analyses carried out within the scope of the Regulation, in particular by monitoring tests and/or calibration results in accordance with ISO/IEC 17025 ¹² and with the requirements for quality control during routine analysis as laid down in Chapter 3 of Annex I of this Regulation.

Article 5

Interpretation of results

1. The result of an analysis shall be considered non-compliant if it is equal to or above the decision limit ($CC\alpha$) of the confirmatory method.

¹⁵ ISO 78-2: 1999 Chemistry — Layouts for standards — Part 2: Methods of chemical analysis.

¹⁶ Reference to be added.

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2. For authorised substances for which an MRL or ML has been established, the decision limit is the concentration at and above which it can be decided with a statistical certainty of $1 - \alpha$ that the MRL or ML has been truly exceeded.
3. For unauthorised or prohibited substances for which a RPA has been established, the decision limit is the concentration at and above which it can be decided with a statistical certainty of $1 - \alpha$ that the sample contains a concentration at or above the RPA.
4. For unauthorised or prohibited substances (for which no RPA has been established) or for authorised substances for which no MRL or ML has been established, the decision limit is the lowest concentration level at which it can be proven by experiment that a method is able to discriminate with a statistical certainty of $1 - \alpha$ that the particular analyte is present.
5. For unauthorised or prohibited pharmacologically active substances the α error shall be 1 % or lower. For all other substances, the α error shall be 5 % or lower.

Article 6

Methods for sampling

The detailed rules for official sampling, as laid down in Annex II to this Regulation, shall be complied with.

Article 7

Repeal

Decisions 2002/657/EC² and 98/179/EC³ are repealed.

Article 8

Date of application

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.