Update on the EU policy in the area of control of residues of veterinary medicines

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Overview

- Legislative act on performance criteria of analytical methods: Commission Implementing Regulation (EU) 2021/808
- Legislative acts in replacement of Council Directive 96/23/EC
  - Delegated act (DA) 2022/1644 and Implementing act (IA) 2022/1646 on veterinary medicinal product residue (VMPR) control plans
  - Delegated act (DA) 2022/2292 on import requirements of food-producing animals, products of animal origin and composite products intended for human consumption as regards pharmacologically active substances, pesticides and contaminants

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

Commission Implementing Regulation (EU) 2024/2052 of 30 July 2024 amending Implementing Regulation (EU) 2021/808 as regards its scope and certain performance criteria of analytical methods for residues of pharmacologically active substances used in food-producing animals

Amendment to the scope – limitation of the scope as regards feed

As regards feed, it is specified that the rules of the Implementing Regulation21021/808 concerns the methods of analysis used for sampling and for laboratory analysis in relation to control of residues of pharmacologically active substances in feed samples taken only in the frame of national control plans as defined in Commission Implementing Regulation (EU) 2022/1646.

It does not (necessarily) concern the methods used e.g. to verify compliance with rules on cross-contamination of antimicrobial active substances in non-target feed, referred to in Commission Delegated Regulation (EU) 2024/1229

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC - Commission Implementing Regulation (EU) 2024/2052

Other changes by Regulation (EU) 2024/2052

- Update of references to international standards
- Requirement added to the general requirements of the analytical methods that in case of any deviations from the established technical criteria (trueness, coefficient of variation), the impact of these deviations on the outcome of the validation should be analysed and documented in a traceable manner, to ensure that performance criteria are adequately checked.

Requirements of confirmatory methods:

- Based on the experience gained, the coefficient of variation (CV) under repeatability conditions in certain cases cannot fulfil the requirements laid down as regards their precision and therefore this requirement should be amended to take into account reproducibility conditions. → For analyses carried out under repeatability conditions, the coefficient of variation under repeatability conditions ~~shall be~~ **is usually** below two thirds of the reproducibility CVs listed in Table 2 **and shall be lower than or equal to the CV under reproducibility conditions**.

Performance characteristics to be determined for analytical methods:

- Explanation of a semi-quantitative screening method (quantitative results but precision requirements not fulfilled).

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC - Commission Implementing Regulation (EU) 2024/2052

Other changes by Regulation (EU) 2024/2052

Validation – trueness, repeatability and within laboratory reproducibility

- Providing for the possibility of validation at the lowest calibrated level (which can be lower than 0,5 times the RPA)
- Clarification of the total number of replicates (i.e. 18 replicates per level) required for the determination of repeatability and within-laboratory reproducibility,
- Addition of the international standard ISO/TS 23471:2022 as another possibility for calculation of the method characteristics.

Validation – stability

- Addition of an isochronous approach to determine potential analyte instabilities as well as an estimation of appropriate storage periods.
- Clarification of the procedure for the determination of the stability of analyte in matrix, in particular in the steps of fortification of the analyte and in the use of proper terms of aliquots and portions.

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC - Commission Implementing Regulation (EU) 2024/2052

Other changes by Regulation (EU) 2024/2052

Validation – detection capability for screening (CCβ)

- In addition to the cases where the chosen screening target concentration (STC) ≤ 5% false compliant results, providing that in case > 5 % false compliant results are obtained, the STC shall be increased, and the investigation repeated to verify compliance with the ≤ 5 % false compliant results requirement when using method 2 (investigation of fortified blank material – 20 fortified blanks - at concentration levels at and above the STC).
- For the screening methods, only the CCβ for the individual substance is reported. Therefore, the additional provision for the sum of CCβ, included in the provisions for calculation of CCβ, is redundant and has been deleted.

Validation – Absolute recovery

- The need to determine the absolute recovery of the method depends on the unavailability of the internal standard or on whether a matrix-fortified calibration is used or not. The previous wording that the absolute recovery of the method is to be determined when no internal standard or no matrix-fortified calibration is used can be confusing, as it could be understood that both cases occur together, when only one of two conditions is sufficient to determine the absolute recovery. This has now been clarified

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC - Commission Implementing Regulation (EU) 2024/2052

Other changes by Regulation (EU) 2024/2052

Validation – Relative matrix effects

- Regarding relative matrix effects, previously the value of the coefficient of variation refers to a maximum numerical percentage without differentiation of the mass fractions. Since Table 2 of Annex I to Implementing Regulation (EU) 2021/808 presents various acceptable coefficients of variations depending on the different mass fractions, the acceptable coefficient of variation refers now the mass fractions in that table.

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

Transitional provisions:

- until 10 June 2026, the requirements laid down in points 2 (performance criteria and other requirements for analytical methods) and 3 (validation) of Annex I to Decision 2002/657/EC shall continue to apply to methods, which have been validated before the date of entry into force of Reg. 2021/808

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

Transitional provisions:

- for the calculation of decision limit for confirmation (CCα) for unauthorised or prohibited pharmacologically active substances (see point 2.6 of the Annex) :
  - in case of methods validated before the date of entry into force of this Regulation Method 2 (i.e. analysing at least 20 blank materials to be able to calculate the signal to noise ration at the time window in which the analyte is expected – 3 times the signal to noise ratio can be used as decision limit) can only be used until 1 January 2026
  - Methods validated after the entry into force of this Regulation - only Method 1 (i.e. calibration curve procedure according to ISO 11843-1:1997) or Method 3 (lowest calibrated level + expanded measurement uncertainty) shall be used

Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

Envisaged changes

- Extension of transitional period for revalidation of all methods for all matrices until 31 December 2027 to fulfill the requirements of Regulation (EU) 2021/808
- Sampling of ostrich eggs
- Sampling of feed: The sampling of feed shall be carried out in accordance with the methods of sampling set out in Annex I to Commission Regulation (EC) No 152/2009

Commission Regulation (EU) 2019/1871 of 7 November 2019 on reference points for action (RPA) for non-allowed pharmacologically active substances present in food of animal origin and repealing Decision 2005/34/EC

Changes in Reference Points for Action since 27/11/2022

Substance	***MRPL (2002/657/EC)*** ***No longer applicable***	**RPA (Reg (EU) 2019/1871 Applicable since 27/11/2022**
Chloramphenicol	*0.3 µg/kg*	0.15 µg/kg
Medroxyprogesterone acetate	*1 µg/kg*	---
Nitrofurans and their metabolites	*1 µg/kg for all: furazolidone, furaltadone nitrofurantoin, nitrofurazone*	0.5 µg/kg for each of the metabolites of furazolidone (AOZ), furaltadone (AMOZ), nitrofurantoin (AHD), nitrofurazone (**SEM**) (*), and nifursol (DNSH)
Sum of malachite green and leucomalachite green	*2µg/kg*	0.5 µg/kg

Commission Regulation (EU) 2023/411 of 23 February 2023 amending Regulation (EU) 2019/1871 as regards the application of reference points for action (RPA) for nitrofurans and their metabolites

(*) 1) Due to the natural occurrence of SEM in crayfish at levels above the RPA, only levels of AOZ, AMOZ, AHD and DNSH above the RPA are a clear indication of the illegal use of nitrofurans and their metabolites. The RPA of 0,5 µg/kg for SEM in crayfish shall only be applied when the illegal use of nitrofurazone or SEM on crayfish has been established, i.e. at least one of the other nitrofuran metabolites has been detected.

2) Due to the occurrence of SEM at levels above the RPA as the consequence of processing in gelatine, **collagen (**Commission Regulation (EU) 2024/2858 of 12 November) collagen hydrolysate, hydrolysed cartilage products, spray dried blood products, whey and milk protein concentrates, caseinates and milk powder (excluding infant formulae and follow-on formulae) only levels of AOZ, AMOZ, AHD and DNSH above the RPA are a clear indication of the illegal use of nitrofurans and their metabolites. The RPA of 0,5 µg/kg for SEM in gelatine, collagen hydrolysate, hydrolysed cartilage products, spray dried blood products, whey and milk protein concentrates, caseinates and milk powder (excluding infant formulae and follow-on formulae) shall only be applied, when the illegal use of nitrofurazone or SEM has been established, i.e. at least one of the other nitrofuran metabolites has been detected.

Commission Regulation (EU) 2023/411 of 23 February 2023 amending Regulation (EU) 2019/1871 as regards the application of reference points for action (RPA) for nitrofurans and their metabolites

Food business operators and other interested parties shall communicate by 1 March 2024 to the Commission the results of investigations on the parameters and factors in the processing steps resulting in the formation of SEM in gelatine, collagen hydrolysate, hydrolysed cartilage products, spray dried blood products, whey and milk protein concentrates, caseinates and milk powder (excluding infant formulae and follow-on formulae) during processing. They shall also communicate the measures taken to ensure that the levels of SEM in these products are kept as low as reasonably achievable. In the absence of satisfactory data and information, measures shall be taken to end this exemption.

→Was deleted by Commission Regulation (EU) 2024/2858 of 12 November

→Mandate to EFSA for risk assessment on semicarbazide (22/07/2014)

Request for a scientific opinion on the risks for human health related to the presence of semicarbazide in food

Deadline for opinion: 1 July 2026

Commission Regulation (EU) 2019/1871 of 7 November 2019 on reference points for action (RPA) for non-allowed pharmacologically active substances present in food of animal origin and repealing Decision 2005/34/EC

Envisaged change

- Other nitrofurans and nitrofuran metabolites (envisaged changes in red)

Substance	RPA (µg/kg)	Other provisions
Nitrofurans and their metabolites	0,5 (1) (2)	0,5 µg/kg for each of the nitrofurans or metabolites of **furazolidone** (AOZ or 3-amino-2-oxazolidinone), **furaltadone** (AMOZ or 3-amino-5-methylmorpholino-2-oxazolidinone), **nitrofurantoin** (AHD or 1-aminohydantoin), **nitrofurazone** (SEM or semicarbazide) and **nifursol** (DNSH or 3,5-dinitrosalicylic acid hydrazide) In case other nitrofurans or nitrofuran metabolites are analysed, the RPA is also applicable to those other nitrofurans or nitrofuran metabolites.

Commission Delegated Regulation (EU) 2022/1644 of 7 July 2022 supplementing Regulation (EU) 2017/625 of the European Parliament and of the Council with specific requirements for the performance of official controls on the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof

- Defined combinations of substances and commodities to be controlled for each of the 3 plans (national risk-based control plan for national production, national randomised surveillance plan for national production, national risk-based control plan for third country imports (for more details on the 3 plans see slide under IA)
- For the risk based control plans: Relevant criteria for the selection substances for testing, farms/producers for sampling, selection of slaughterhouses and establishments, selection of animals, selection of matrix. For third country imports some additional criteria identified.
- Sampling strategy for all plans: timing, stage, targeted

Commission Delegated Regulation (EU) 2022/1644 of 7 July 2022 supplementing Regulation (EU) 2017/625 of the European Parliament and of the Council with specific requirements for the performance of official controls on the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof

Commission Delegated Regulation (EU) 2024/2562 of 3 June 2024 amending Delegated Regulation (EU) 2022/1644 as regards certain criteria for the selection of samples

- Based on practical experience with the application of Delegated Regulation (EU) 2022/1644, there are no relevant substances from substance group A(3), point (b) (plant protection products/biocides) for raw bovine, ovine and caprine milk and for honey in the national risk-based control plans for production in the Member States to be checked.

- There are no relevant substances from substance group A(3), point (f) (Anti-inflammatory substances, sedatives and any other pharmacologically active substances) for certain commodities (aquaculture and hen eggs and other eggs) to be checked.

→ Therefore, the mandatory requirement of sampling has been removed from the table in point A.1 of Annex II to Delegated Regulation (EU) 2022/1644 for these combinations of substance groups and commodity groups concerned.

Commission Delegated Regulation (EU) 2022/1644 of 7 July 2022 supplementing Regulation (EU) 2017/625 of the European Parliament and of the Council with specific requirements for the performance of official controls on the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof

Commission Delegated Regulation (EU) 2024/2562 of 3 June 2024 amending Delegated Regulation (EU) 2022/1644 as regards certain criteria for the selection of samples

- Based on practical experience with the application of Delegated Regulation (EU) 2022/1644, there are no relevant substances from substance group B(1), point (e) (other pharmacologically active substances) for all commodity groups and no relevant substances from substance group B(2) (coccidiostats and histomonostats) for raw bovine, ovine and caprine milk in the national randomised surveillance plans for production in the Member States to be checked.

→ Therefore, the mandatory requirement of sampling has been removed from the table in Annex IV to Delegated Regulation (EU) 2022/1644 for the combinations of substance groups and commodity groups concerned

Commission Delegated Regulation (EU) 2022/1644 of 7 July 2022 supplementing Regulation (EU) 2017/625 of the European Parliament and of the Council with specific requirements for the performance of official controls on the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof

Envisaged changes

No requirement for sampling anymore for A3f substances (Anti-inflammatory substances, sedatives and any other pharmacologically active substances) in honey

National risk control plan: the table for Group B substances in Annex IV (randomized surveillance plan) will be added/copied to Annex II (national risk control plan)

Commission Implementing Regulation (EU) 2022/1646 of 23 September 2022 on uniform practical arrangements of official controls as regards the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof on specific content of multi-annual national control plans and specific arrangements for their preparation

3 control plans:

- Plan 1: National risk-based control plan for production in the Member States
  - controls on a wide range of substances within the sub-groups of Group A and Group B

- Plan 2: National surveillance plan for production in the Member States
  - use of unauthorised pharmacologically active substances (A), which are not included in the national risk-based plan, but they may be misused for the treatment of food-producing animals
  - controls on authorised pharmacologically active substances (B), ensuring that at a minimum, each sample is analysed for all of the substance groups listed in group B.

- Plan 3: National risk-based control plan for third country imports
  - controls on a wide range of substances within the sub-groups of Group A and Group B

Commission Implementing Regulation (EU) 2022/1646 of 23 September 2022 on uniform practical arrangements of official controls as regards the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof on specific content of multi-annual national control plans and specific arrangements for their preparation

Minimum sampling frequency:

- Plan 1: National risk-based control plan for production in the Member States
  - based on the Member States' production data

- Plan 2: National surveillance plan for production in the Member States
  - fixed numbers for each Member State (mainly based on population size) (in total about 7700 samples)

- Plan 3: National risk-based control plan for third country imports
  - Based on the number of imported consignments (specific minimum percentage of imported consignments per animal species/animal product)

Commission Implementing Regulation (EU) 2022/1646 of 23 September 2022 on uniform practical arrangements of official controls as regards the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof on specific content of multi-annual national control plans and specific arrangements for their preparation

Commission Implementing Regulation (EU) 2024/2563 of 24 September 2024 amending Implementing Regulation (EU) 2022/1646 as regards additional content of the national risk-based control plans and the national randomized surveillance plan, the submission of those plans and data by Member States and minimum sampling frequencies

- Provisions on additional content of the national control plans and the national randomized surveillance plan and arrangements as regards submission of these plans and data by Member States
- Removal of the obligation of minimum 5 % of the samples taken for substance group A3 (b) (plant protection products and biocides) for all commodity groups.

Commission Implementing Regulation (EU) 2022/1646 of 23 September 2022 on uniform practical arrangements of official controls as regards the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof on specific content of multi-annual national control plans and specific arrangements for their preparation

Envisaged changes

A2 substances (Plan 1: Annex I, Additional provisions)

• To improve the performance of controls on A2 substances (all subgroups i.e. chloramphenicol, nitrofurans, nitro-imidazoles, … shall be covered), additional provision will be added:
(n) For the Group A(2), the samples shall be taken from all subcategories (A(2)a, A(2)b, A(2)c, A(2)d) based on the decision taken in accordance with criteria listed in Annex II to Delegated Regulation (EU) 2022/1644.

A3f and B1d categories (Plan 1: Annex I, Additional provisions)

• A3f (Anti-inflammatory substances, sedatives and any other pharmacologically active substances) and B1d (non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and glucocorticoids) substance groups are heterogeneous as regards the range and the action of the substances and the covered groups are not always all checked

Commission Implementing Regulation (EU) 2022/1646 of 23 September 2022 on uniform practical arrangements of official controls as regards the use of pharmacologically active substances authorised as veterinary medicinal products or as feed additives and of prohibited or unauthorised pharmacologically active substances and residues thereof on specific content of multi-annual national control plans and specific arrangements for their preparation

Envisaged changes (**continued**)

Therefore, these provisions are foreseen:
(o) For the Group A(3)f, the samples shall be taken from all substance groups covered by this category (anti-inflammatory substances, sedatives and any other pharmacologically active substances) based on the decision taken in accordance with criteria listed in Annex II to Delegated Regulation (EU) 2022/1644.
(p) For the Group B(1)d, the samples shall be taken from all substance groups covered by this category (non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and glucocorticoids) based on the decision taken in accordance with criteria listed in Annex II to Delegated Regulation (EU) 2022/1644.

Sampling of one sample for both A and B subgroup (Plan 3: Annex III, Additional provisions)
The possibility of taking samples for both substance groups A and B from single animal is provided for Plan 1 in Annex I (Additional provisions). Such provision is foreseen to be included also for Plan 3;

Commission Delegated Regulation (EU) 2019/2090 of 19 June 2019 supplementing Regulation (EU) 2017/625 of the European Parliament and Council regarding cases of suspected or established non-compliance with Union rules applicable to the use or residues of pharmacologically active substances authorised in veterinary medicinal products or as feed additives or with Union rules applicable to the use or residues of prohibited or unauthorised pharmacologically active substances

- An amendment of Delegated Regulation (EU) 2019/2090 is in preparation providing for an explicit reference in Articles 3, 5 and 6 to Articles 137 and 138 of the Official Control Regulation (EU) 2017/625 for possible enforcement actions following delayed information on non-compliance at certain stages of processing (Allowing more flexibility for the follow-up actions to be taken for products of animal origin already mixed with other non-affected batches and/or further processed (and no isolation of the affected batch is anymore possible).

Other issues under discussion

- Sampling of large consignments of casings
- Update of the EURL Guidance on minimum method performance requirements (MMPRs)
- Background information on the “No MRL required” provision to assist enforcement
- Nifursol in honey
- Salicylic acid in food of animal origin
- ….

Article 118 of Regulation (EU) 2019/6 on veterinary medicinal products (“The veterinary Medicines Regulation”)

- Regulation (EU) 2019/6 on veterinary medicinal products prohibits the use antimicrobials for growth promotion and yield increase, as well as the use of antimicrobials reserved for treatment of infections in humans.
- Article 118(1) of the Regulation bans the use of such antimicrobials in respect of animals and products of animal origin that are imported into the Union.
- Article 118(2) requires the Commission to adopt delegated acts on the detailed rules on the application of this prohibition.
- For the application of the ban in Article 118(1), a delegated Regulation and an implementing Regulation designating the list of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans has been adopted.

  Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by establishing the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans

  Commission Implementing Regulation (EU) 2022/1255 of 19 July 2022 designating antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council

Article 118 of Regulation (EU) 2019/6 on veterinary medicinal products (“the Veterinary Medicines Regulation)

- The delegated act under Article 118(2) defines the requirements that must be met for the entry into the Union of consignments of animals and products of animal origin pursuant to Article 118(1) of Regulation (EU) 2019/6.

  Commission Delegated Regulation (EU) 2023/905 of 27 February 2023 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council as regards the application of the prohibition of use of certain antimicrobial medicinal products in animals or products of animal origin exported from third countries into the Union

- Regulation (EU) 2017/625 (OCR) has been amended by Regulation (EU) 2021/1756 to include verification of compliance with the prohibitions in Article 118(1) of the Veterinary Medicines Regulation within the scope of the Official Controls Regulation.

- Applicable to consignments entering the Union as **from 3 September 2026**

- More information on https://food.ec.europa.eu/animals/animal-health/vet-meds-med-feed/implementation_en

Thank you for your attention

European Commission