



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on the reporting of antimicrobial sales and use in animals at the EU level – denominators and indicators' (EMA/CVMP/882931/2022)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Danish Agriculture & Food Council
2	Ministry of Agriculture, The Netherlands
3	Veterinary Medicines Directorate, The United Kingdom
4	Department of Agriculture, Food and the Marine, Ireland
5	Copa Cogeca
6	Centre on Antimicrobial Consumption and Resistance in Animals (FAMHP/AMCRA), Belgium
7	Dogs Trust, UK and Ireland
8	The Netherlands Veterinary Medicines Institute (SDa)



1. General comments – overview

Stakeholder no.	General comment	Outcome
1	We are concerned to see that EMA had decided not to follow the recommendation made by the ESVAC ad hoc expert group on the recommended changes of the denominator adjusted with the <u>animal's life span</u>. The proposed methodology will continue to add up data with different measures, violating basic epidemiological principles. Using the weight at slaughter will deteriorate the PCU, overestimating the population-at-risk even more than previously, e.g. by more than 2200% for broilers.	We are grateful for your comments. Please note that the draft Guideline (GL), as published for consultation, constitutes the recommendations of the ESVAC Denominators and Indicators ad hoc review group (ESVAC <i>ad hoc</i> review group). The ESVAC <i>ad hoc</i> group endorsed the GL on 25 April 2023 and, subsequently, the GL was discussed at CVMP and adopted for consultation. As described in lines 298-319, the ESVAC <i>ad hoc</i> group acknowledges other methodologies for the calculation of the denominator are described in the literature but favoured the methodology proposed in this draft Guideline. Nevertheless, as explained above, the proposed methodology is the recommendation of the ESVAC ad hoc review group. Several considerations were taken into account when assessing methodologies to calculate the denominator in the context of Article 57 of Regulation (EU) 2019/6 and related delegated and implementing acts. Firstly, the requirements set in the regulations also set the limits for the advice given in this GL. Article 5(1) of Commission Implementing Regulation 2022/209 reads <i>'The Agency shall adjust the data for the relevant animal populations referred to in Article 4 according to so-called denominators, which are calculated on the basis of a combination of the number of animals slaughtered and of the number of live animals present in a Member State during the data collection period, multiplied by</i>

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		standardised animal weights'. Lines 301-316 have been amended to accurately reflect the text in the implementing regulation and include additional considerations. Secondly, the necessity for reliable, robust, comparable, and harmonised data was acknowledged and prioritised to the extent possible so that year-over-year comparisons of sales and use data within the Member States and the Union can be made while facilitating the comparison of data with data available from non-Union countries and at global level, as written in recital 7 of Commission Implementing Regulation 2022/209. Thirdly, it was also recognised the importance of implementing methodology that is feasible whilst also minimising the resources required by Member States. The ESVAC <i>ad hoc</i> group acknowledges the success European countries have achieved in reducing the antimicrobial consumption in food-producing animals, which has declined by almost 50% since 2011 as reported in the 12th ESVAC project (29 EU/EEA Member States, Switzerland and the UK participate in the project). At the country level, most ESVAC participating countries with high use show a progressive and sustained decline in antimicrobial VMP sales. For a few countries, sales were already low when they joined the project and although the reduction potential was smaller, sales remained low and/or continued to decline. Compared to 2010, in 2021 five countries showed a decrease superior to 50% (-67% Netherlands, -61% France, -59% Italy, -58% Lithuania and the UK). The remaining 15 countries that reported data between 2010-2021 show decreases between -14% and -47% (Portugal, Ireland, Finland,

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		Sweden Denmark, Slovenia, Estonia, Austria, Latvia, Norway, Spain, Hungary, Iceland, Czechia, Belgium). The Network on quantification of veterinary Antimicrobial usage at herd level and Analysis, CommunicaTION and benchmarkING to improve responsible usage (AACTING) has published an "Overview of farm-level AMU monitoring systems" (https://aacting.org/monitoring-systems/; revised June 18th 2021) where national monitoring system are presented for 14 EU/EEA countries plus Canada and United Kingdom. These country systems differ in many ways, including the data collected, the analyses performed and the respective indicators used, as highlighted by P. Sanders <i>et al.</i> (Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes - PMC (nih.gov)). Despite the differences in methodologies used in each system, it is noticeable that many countries still report their data using PCU or a similar denominator. The authors recognise this type of denominator is useful if the system aims for trend monitoring, which is aligned with the requirements of the legislation (Article 16(4) of Commission Delegated Regulation (EU) 2021/578 reads: <i>The Agency shall analyse the data on the volume of sales of veterinary antimicrobial medicinal products and on the use of antimicrobial medicinal products and identify trends and pattern changes over time, both at national and Union levels.(...)</i>). It is acknowledged that the denominator that will be used to adjust sales and use data has certain limitations, as do other denominators. It is inevitable that there might be differences

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		between the various surveillance and monitoring initiatives in the EU/EEA, not just in how and which data are collected but also in how results are presented. Identification of relevant trends is one of the main purposes of the collection system as it reads in Recital (1) of Commission Delegated Regulation 2021/578 <i>"In order to develop targeted measures to fight antimicrobial resistance, it is paramount to determine possible risk factors to public and animal health. The identification of relevant trends in the volume of sales and use of antimicrobials in animals at national and Union level should in turn allow to identify such risk factors following the use of antimicrobials in animals. This should set the basis for establishing appropriate risk management priorities, defining targeted measures to fight antimicrobial resistance and monitoring their effect. (...)</i>. The ESVAC <i>ad hoc</i> group concluded that the animal biomass denominator proposed in this GL is robust and sufficiently detailed to enable (indirect) comparison of sales and use data at the EU level with global levels in line with Recital (7) of Commission Implementing Regulation 2022/209. Results will be reported by the Agency as outlined in the guidance, ensuring the data presented are harmonised and standardised. However, this does not preclude Member States of adapting their national reports to local circumstances, e.g., using different denominators and indicators and implementing benchmarking.
	We are particular concerned about data across different species and production types will continue to be added up. It should be noted that the proposed methodology makes it impossible to	Regarding your comment 'We are particular concerned about data across different species and production types will continue to be added up', our interpretation is that it is

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	use the data for carrying out quantitative risk assessments. If the dominating species in one country has a very low use of antibiotics it would hide high-risk antibiotic use in any other species, like it is the case in Norway with a very large fish population. Similar, a high usage in one species, like the large population of imported dairy calves in the Netherland, can cover up an otherwise an otherwise low usage in other species. We would like to highlight the importance of being very careful when interpreting the outcome as long as different measures of animal production are used. As long as numbers with different units are added up, the denominator cannot be used for quantitative assessments. Quantitative assessments will not be possible to carry out before the usage are reported as used per animal species and categories. Until then only qualitative risk assessments can be made.	the sales data that are addressed in this comment and Article 57 of Regulation (EU) 2019/6 requires Member States to collect relevant and comparable data on the volume of sales of antimicrobial veterinary medicinal products (VMPs). As VMPs are typically marketed for more than one species, it is not possible to split the sales data by animal species thus both the numerator and denominator have to be aggregated. Regarding the use data – e.g. for cattle, the data has to be reported distinguishing beef cattle from dairy cattle and specifying use in bovines under one year of age separately when the production of meat from slaughtered bovines under one year of age exceeds 10 000 tonnes per year. According to the draft guideline, use data for beef cattle < 1 year will be reported separately using animal population data for beef cattle below < 1 year to calculate the denominator. Hence, when use data become available, these should be more suitable for risk assessment purposes.
2	NL would like to aim for an indicator of antibiotic use (AMU) that accurately reflects the exposure of animals to antibiotics. Exposure is the measure that determines the risk of resistance development and the essence of why we want to measure antibiotic use and reduce it as much as possible. Indicators that take into account time at risk of exposure to antimicrobials, such as daily doses per animal, are to be preferred as they reflect the risk of developing antimicrobial resistance most accurately.	Thank you for your comments. As the 'time at risk of exposure' is linked to the animal lifespan topic, please refer to the response to Stakeholder 1 general comments.

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	The method used in the Netherlands - daily defined dose - reflects the exposure of animals to antibiotics over time, is independent of production mass, production system, animal sector and potency of the antibiotic, and is a measure that can be directly linked to resistance development (in commensal bacteria from the slaughter animals). The antibiotic policy is very successful in the Netherlands. Nowadays the reduction of antibiotic use is 77,4% since 2009. Data and insights are the key for this result and underlying the change in behavior. This can only be achieved when the people who work with this have an indicator that brings them knowledge about their own treatment on their farm and for veterinarians shows them their subscription behavior. This reduction would never happened when there was not such a good indicator which reflects the behavior of farmers and veterinarians. Only an indicator which helps them easy to see how this behavior can change, lower their antibiotic use. And lower the use of the animal livestock sector, and lower the use of the country and finally lower the use of antibiotic use in the EU. Not the other way around. The display in DDDvet/animal live time (I.e. real time lived) stimulates and motivates animal keepers and veterinarians because they see the effect in the national resistance data when taking measures and reducing antibiotic treatments.	
3	We agree with the introduction of living animals for cattle, especially for beef – which we think more fairly represents the biomass of beef cattle at risk.	Thank you for your support. At present, EU-harmonised estimates of live average weight at the time of treatment or on the average adult weight are not

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	We think the methodology is a bit confusing in that slaughtered animal weights now represent the “average weight at slaughter” whereas some (but not all) of the living animal weights (e.g. breeding sows/ living sheep/ living horses) still represent the “average weight at time of treatment”. This will make explaining the metric more difficult. We think it would be better if the methodology was consistent across slaughter and living animals – so if the weight at slaughter is used for slaughter animals, then the average adult living weight should also be used for living animals. We agree with using DDDvet/ DCDvet indicators to take into account doses and course lengths. However, having 7 different indicators could cause confusion. Maybe a prioritisation decision needs to be made as to what the core (leading) metrics could be e.g. perhaps focusing primarily on the mg/kg (all products), DDDvet figures for injectable/oral and lactating cow, alongside DCDvet for dry cow. I don’t think you need two metrics dedicated to intrauterine use (given the relatively low level of use for these products overall); including intrauterine products in the all product forms mg/kg is probably sufficient.	available for all the animal species, categories and stages for which data on the use of antimicrobial medicinal products must be collected and reported. Hence, there is a need to make use of available data, whenever possible, to establish a harmonised and standardised approach to calculate animal weights for each of the relevant species while being representative of Member States. The European Statistical Office, Eurostat, publishes validated statistics on slaughtered animals (number of heads and slaughtered biomass), with which live animal weights at slaughter can be calculated (using appropriate carcass to live weight conversion factors). In contrast, for livestock only the number of living animals is published. Therefore, it was considered that using live weights at slaughter for both slaughter and living food-producing animals would be an appropriate approach. However, for the few cases where relevant data were not available in Eurostat for certain food-producing animal populations (i.e. breeding sows, goose, living horses, live sheep, live goats, and rabbits), preference was given to published and acknowledged sources (e.g. ESVAC, Montforts), following the hierarchy provided in lines 372-374. The Agency and the ESVAC <i>ad hoc</i> group agree with the suggestion to prioritise leading indicators. However, it is considered important to take into account that the duration of treatment for premixes is typically considerably longer than that for other oral forms (see https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-

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		dddvet-defined-course-dose-animals-dcdvet_en.pdf). Thus DCDvet has been kept for oral and injectable products while the indicators for intrauterine products have been deleted and just referred to in the text as an option. Section 6.2 has been revised accordingly. Table 20 and Annex 4 have been updated to describe 5 key indicators: • mg/kg: all products • DDDvet/kg: Oral and injectable forms (systemic use) • DCDvet/kg: Oral and injectable forms (systemic use) • DDDvet/dairy cows: intramammary products for lactating cows • DCDvet/dairy cows: intramammary products for lactating cows and cows in the drying-off period
4	DAFM welcomes the draft 'Guideline on the reporting of antimicrobial sales and use in animals at the EU level-denominators and indicators'. The document provides a framework for the reporting of antimicrobial sales and use in animals at the EU level. Sales and use data reporting and monitoring is integral work and a key action required by MS and the Union to address the global health threat of antimicrobial resistance.	Thank you for your comment.
5	We are concerned to see that EMA had decided not to follow the recommendation made by the ESVAC ad hoc expert group on the recommended changes of the denominator adjusted	Thank you for your comment. See response to Stakeholder 1 general comment.

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	with the animal's lifespan. The proposed methodology will only continue to add up data with different measures, violating basic epidemiological principles. Using the weight at slaughter will deteriorate the PCU, overestimating the population-at-risk even more than previously, e.g. by more than 2200% for broilers. We are particularly worried about the fact that data across different species and production types will continue to be added up. It should be noted that the proposed methodology makes it impossible to use the data for carrying out quantitative risk assessments. If the dominating species in one country has a very low use of antibiotics it would hide high-risk antibiotic use in other species. Similarly, a high usage in one species can cover up an otherwise low usage in other species. We would like to highlight the importance of being very careful when interpreting the outcome as long as different measures of animal production are used. As long as numbers with different units are added up, the denominator cannot be used for quantitative assessments. Quantitative assessments cannot be carried out before the usage is reported per animal species and categories. Until having that data, only qualitative risk assessments can be made.	
6	Regarding section 5.1: Four criteria are listed in the beginning of the section, however it seems that afterwards no reference is made to these criteria to assess the proposed data sources. This should be considered in order to guarantee transparency and objectivity of the decisions proposed.	Thank you for your comment. Contrary to the comment, section 5.1 outlines that these criteria (lines 231-233) were used as the basis for the selection of the Eurostat as the main data source for the food-producing animal population statistics.

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		Article 16(5) of Commission Delegated Regulation (EU) 2019/578 sets out that <i>'the Agency shall identify the necessary data on relevant animal populations per Member State via publicly accessible existing Union databases and ask Member States to verify and validate them. In the event that the necessary data on relevant animal populations is not available in such Union databases, or that those data would not comply with the data quality requirements laid down in Article 6, the Agency shall require Member States to provide or amend such data via the web interface.'</i> Therefore, if the relevant animal population data are publicly available in Union databases, these databases should be used as primary data sources. The European Statistical Office, Eurostat, publishes validated statistics on the numbers of livestock and slaughtered food-producing animals, and these data comply with the first three criteria. Therefore, Eurostat was selected as the main data source for food-producing animal population statistics (lines 241-242 of the GL). For certain animal species, such as rabbits, geese, horses and farmed fish, dogs, cats, minks and foxes, data are not available in Eurostat, and national statistics, when available, should be used. To fulfil the requirements laid down in Article 4(2) of Implementing Regulation (EU) 2022/209, the Trade control and Expert System (TRACES) was selected as data source to correct animal population data with number of animals brought in from other Member States and sent to other Member States for fattening or slaughter, as appropriate (lines 260-262), as the numbers of animals moved between the

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		EU countries are based on health certificates, an obligatory requirement for all animals passing any border. Tables 1-19 indicate the animal population data for each animal species and category and the corresponding data source. Only when animal population data are unavailable in Union databases (Eurostat and TRACES), or those data would not comply with the data quality requirements in Article 6, Member States will have to provide or amend such data via the web interface. When Member States report the data on the relevant animal populations in their territories, they must submit to the Agency a detailed description of the methodologies they used to generate the relevant animal population data, as per Article 4(3) of Implementing Regulation (EU)2022/209.
8	Comment: The mg/PCU indicator is fundamentally different from indicators used to quantify animal AMU in most national systems, research projects and also in the human field to describe AMU. This has several major implications: - Comparisons between animal species and comparisons between countries will be complicated and biased The mg/PCU neglects the time at risk of antimicrobial treatment by not adjusting for production cycle length and thus introduces bias. The different production cycle lengths have a pronounced effect on the calculated PCU for different animal species. Also, the proportion of different animal species differs between countries, impacting a countries PCU. Therefore, using mg/PCU as	Thank you for your comments. Please see the response to Stakeholder 1 general comment concerning consideration of the lifespan (cycle length) of animals in respect the metric.

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	the primary indicator for AMU does not allow for comparisons of AMU between animal species and/or countries. The bias introduced by using the PCU becomes apparent for short lived animals, such as broilers. These animals are only at risk for the course of their lifespan (for broilers ~ 45 days) and not for the entire year, as suggested by the mg/PCU. Use in mg/PCU will be heavily diluted for such short-lived animals. In fact, AMU measured in mg/PCU could technically be reduced by slaughtering animals earlier as this leads to a higher PCU value per year. This is illustrated by the examples in appendix 1 and 2 (below our comments). - Integrated analysis on antimicrobial use and antimicrobial resistance in the human- and animal sectors are not possible Integrated analysis is only possible if comparable denominators are used in the indicators for antimicrobial use in animals and humans. In the JIACRA reports the denominator used to standardize animal AMU is the PCU while for humans it is the sum of the average weight of all individuals in the population. Using indicators with fundamentally different denominators to compare human and animal AMU therefore leads to biased results as animal AMU is underestimated. This leads to wrong conclusions, as included in the most recent JIACRA report: e.g.; "animal AMU is lower than human AMU".	Thank you for your comment. This point is out of the scope of this GL but will be passed to the JIACRA working group for their consideration.

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	We recognize that it is preferable to stick to the use of the PCU for the overall national sales data because long-term trends have been described using these data. However, in case of presentation of usage data on the level of animal species the bias will be large and will lead to spurious comparisons and wrong interpretations of the data. These comments are generally recognized in the scientific literature, and again emphasised in a recently submitted paper which focusses on the human-animal comparison in the JIACRA report (see appendix 3). Proposed change: Use a different proxy for population animal weight in the AMU calculation, such as the adjusted PCU. The denominator for AMU indicators (for both animal and human AMU) should represent the population at risk of antimicrobial treatment in a certain period of time. Ideally daily doses per animal year would be used as an indicator. An adjusted PCU could be calculated by dividing the PCU by the number of production cycles that exist for a certain livestock sector. The information needed for this is the already available number of slaughtered animals (basis for calculated PCU's) and the average number of animals present within a livestock sector. The average number of animals present within a country is available for most livestock sectors in most member states. This makes it possible to calculate the number of production cycles per livestock sector per country. However, we	

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	do realize that this information is currently not available for all countries. Therefore, we propose to use an average, non-country specific, number production cycles per livestock sector that can be calculated with the information on animal counts and PCUs currently available.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
94-95	1	Comment: It is generally acknowledged among experts in the field, including the WHO, that due to important data gaps, it is still not possible to determine the importance of different resistance reservoirs for occurrence of resistance in the human sector. Therefore, it is not possible to perform desired risk assessments for the risk to humans at present. Genomic data are needed for determining the quantitative transfer between reservoirs. Increasing evidence indicates that the vast majority of resistance in human pathogens originates from human-to-human transfer, and that the production animal reservoir probably has very little importance (except for zoonotic pathogens). Studies indicate that the most important animal reservoir (largest risk for transfer), at least for some of the high-risk human pathogens, are the pet animals (e.g. www.nature.com/articles/s41564-022-01263-0). Regarding the risk assessment for the development of resistance in the animal reservoirs, it is pertinent that the epidemiologically meaningful measures are used, so that the outcome represents the antimicrobial selection pressure. Therefore, the new measures should represent the live animal biomass at risk. As recommended by the advisory group, new measures	Thank you for your comment. The text in lines 87-96 of the GL is intended to paraphrase the objective stated in recital (50), which is to fill a data gap by collecting [sales and use] data that can be used to determine trends, identify risk factors and to develop RMM and monitor their effectiveness. It is recognised that recital 50 does not go so far as to propose that these data can be used directly for a (quantitative) AMR risk assessment or propose how they should be modified for such use. Therefore, lines 92-94 has been changed as follows: Set the basis for risk assessment and risk management, leading to Assist the development of measures to limit the risk from antimicrobial resistance and to monitoring the effectiveness of measures already introduced.

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		should take into account life-span, that is, the time at risk. The new measures proposed by EMA do the opposite and are in no way applicable for quantitative risk assessment. Proposed change: New measures (denominator) should be developed by expert groups comprising experts with competences in both veterinary science and epidemiology. Otherwise, this objective regarding risk assessment should be deleted entirely. Under all circumstances, it should be underlined that this kind of data can only be used for qualitative risk assessment.	
	5	Comment: It is generally acknowledged among experts in the field, including the WHO, that due to important data gaps it is still not possible to determine the importance of different resistance reservoirs for occurrence of resistance in the human sector. Therefore, it is not possible to perform the desired risk assessments for the risk currently posed to humans. Genomic data are needed for determining the quantitative transfer between reservoirs. Increasing evidence indicates that the vast majority of resistance in human pathogens originates from human-to-human transfer, and that the production animal reservoir probably has very little importance (except for zoonotic pathogens). Regarding the risk assessment for the development of resistance in the animal reservoirs, it is pertinent that	Thank you for your comment. Please see previous response.

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		the epidemiologically meaningful measures are used, so that the outcome represents the antimicrobial selection pressure. Therefore, the new measures should represent the live animal biomass at risk. As recommended by the advisory group, new measures should take into account lifespan, that is, the time during which the animal is at risk. The new measures proposed by EMA do the opposite and are in no-way applicable for a quantitative risk assessment. Proposed change: New measures (denominators) should be developed by the EMA expert groups comprising experts with competences in both veterinary science and epidemiology. Otherwise, this objective regarding risk assessment should be deleted entirely. Under all circumstances, it should be underlined that the data proposed can only be used for qualitative risk assessment.	
96-97	8	Please see the general comment and specifically the discussion about the integrated analysis of animal and human antimicrobial use.	Thank you for the comment – response provided under General comments, above.
121	1	Comment: Does “strength” mean the actual concentration of the active compound?. Or the “strength” given in the approval (SPC) of the product? Proposed change: It should be specified that it should be the actual strength = concentration of active substance (not the compound).	Thank you for your comment. The paragraph mentioned lists variables and data format described in Annex I and II of Commission Implementing Regulation (EU) 2022/209, where 'strength' is the name of the variable described as '<i>numerical value of the strength or the quantity of the antimicrobial active substance(s), as declared in</i>

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			<i>the product information, in order to enable the calculation of the quantity of antimicrobial active substance(s) in each product presentation'.</i> More information on the variables defined in the legislation can be found in the Agency's protocols for sales and use data: • Antimicrobial Sales and Use (ASU) data reporting protocol Part 1 Reporting volume of sales (europa.eu) • Antimicrobial Sales and Use (ASU) data reporting protocol Part 2 Reporting use data (europa.eu)
	5	Comment: Does "strength" mean "actual concentration of the active compound"? Or is it the "strength" given in the summary of product characteristics (SPC) of the product? Proposed change: It should be specified that "strength" should be the actual concentration of the active substance and not the compound.	Thank you for your comment. Please see previous response.
153	1	Comment: "number of animals" is unprecise. Does this mean number of live animals at risk? Or number of animals born? Or number of animals slaughtered? NB: number of animals born and number slaughtered are not at animals at risk of treatment, because "at risk" implies also a time-period. This is basic epidemiological knowledge.	Thank you for your comments. Lines 152-154 have been adjusted to correctly described the format of the data as per Article 4(1) of Commission Implementing Regulation (EU) 2022/209, where 'number of animals' are given as <i>'living animals or slaughtered animals, depending on the animal species or categories concerned'</i>.

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		An incidence (of treatment) can only be measured for a defined period, e.g. treatment per year-at-risk. An alternative method to measure antimicrobial usage is to measure how many doses has been used from birth to slaughter (eg. 5 doses per animal produced) This is a very different measure. For example for a chicken: 5 doses/lifespan 60 doses per year-at risk). This two types of data CAN NOT be added up. If the data for different species is to be added up, only the denominator "year at risk" or "days at risk" is meaningful, because the animal lifespan varies tremendously between species and also between production types. If slaughter data are to be used, the life-span and average weight need to be estimated, in order to calculate the usage per animal at risk. Multiple scientific papers demonstrate that this is indeed feasible. The methods proposed by EMA are violating basic laws in epidemiology by adding numbers with different units. Throughout all the text it needs to be specified whether the unit used is usage per lifespan (Weight at slaughter as for chickens) or usage per year at risk (census data, as for Dairy cows).	Please see the response to Stakeholder 1 general comment concerning consideration of the lifespan of animals in respect of the metric.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "number of live animals at risk" instead of "number of animals" (and the methodology should be changed accordingly)	
	5	Comment: "number of animals" is unprecise. Does this mean "number of live animals at risk", "number of animals born", or "number of animals slaughtered"? <u>NB</u>: number of animals born and number slaughtered are not animals at risk of treatment, because "at risk" implies also a time-period. This is basic epidemiological knowledge. An incidence (of treatment) can only be measured for a defined period, e.g. treatment per year-at-risk. An alternative method to measuring antimicrobial usage is to quantify how many doses have been used from birth to slaughter of the animal (eg. 5 doses per animal produced) This is a very different measure from the one proposed. For example for a chicken: 5 doses/lifespan or 60 doses per year at risk. These two types of data cannot be added up. Besides, if the data for different species is to be added up, only the denominator "year at risk" or "days at risk" would be meaningful as the animal's lifespan can vary tremendously between species and also between production types. If slaughter data are to be used, the lifespan and average weight need to be estimated as well in order to calculate the usage per animal at risk.	Thank you for your comment. Please see previous response.

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		The methods proposed by EMA go against basic epidemiological rules by adding numbers with different units. Throughout all the text it needs to be specified whether the unit used is usage per lifespan (e.g., weight at slaughter as for chickens) or usage per year at risk (census data, as for dairy cows). Proposed change: "number of live animals at risk" instead of "number of animals" (plus, the methodology should be changed accordingly)	
155	1	Comment: "Commission Implementing Regulation (EU) 2022/209 requires that animal population data must be corrected with the number of animals brought in from or sent to other Member States". It is pertinent that this is done correctly, taking into account that the need for antibiotics varies during the life span, typically higher in the young growing animals of all species, e.g., the majority of antimicrobial use in pigs is used before 25-30 kg (before export). Furthermore, when dairy calves are exported at an early age, the antimicrobial usage in the dairy sector is underestimated in the exporting country, because the antimicrobial use in the receiving country is a consequence of the export. This problem can be solved when antimicrobial usage data become available on species level.	Thank you for your comment. We agree that the data will be more precise when use data on species and category level are available.

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155	1	Comment: "Data on the volume of veterinary antimicrobials sold and of antimicrobials used per animal species, categories and stages must be reported". The usefulness of the data would improve tremendously if the usage was reported on animal species level. But at present and within a foreseeable future this will not happen. This is why the agency is calculating the usage in mg and not in DDDvet, even though it is acknowledged by the Agency, that the DDDvet is more appropriated/less misleading. Proposed change: Comment on the fact that usage per species is not yet available, and what (if any) actions will be taken in this regard.	Thank you for your comment. Article 57 of Regulation (EU) 2019/6 requires Member States to collect and send to the Agency relevant and comparable data on the volume of sales of antimicrobial veterinary medicinal products (VMPs) and on the use of antimicrobial medicinal products used in animals. Member States are allowed a progressive stepwise approach regarding these obligations, as laid out in Article 15 of the Commission Delegated Regulation (EU) 2021/578. The methodologies proposed in this GL have been developed considering that use data by animal species and categories will be reported to the Agency, in a stepwise approach, starting in 2024, with data concerning 2023. The first Agency report (to be published by March 2025), must report sales and use data, the latter for relevant animal species, categories or stages. The indicators for use data proposed in section 6.2 of this GL, will have weight-, dose- and course dose-based numerators (see Table 20).
184-185	1	Comment: The following wording is imprecise: "the denominator is a proxy for the animal population likely to be treated with antimicrobials within a reporting year, expressed as animal biomass (kg)" The wording "likely to be treated within a year" suggest that the actual unit is "per animal biomass at	Thank you for the comment. Line 185 and Table 20 have been revised to indicate the temporal period ('<i>per year</i>' was added).

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		risk”, which implies a temporal period (the epidemiological term “at risk” implies a period). This kind of report describing a methodology needs to be precise, not misleading. Proposed change: “the denominator is a proxy for the animal population likely to be treated with antimicrobials within a reporting year, expressed as animal biomass (kg) at risk per year”	
	5	Comment: The following wording is imprecise: “<i>the denominator is a proxy for the animal population likely to be treated with antimicrobials within a reporting year, expressed as animal biomass (kg)</i>”. The wording “likely to be treated within a year” suggest that the actual unit is “per animal biomass at risk”, which implies a temporal period (the epidemiological term “at risk” implies a period). A report that describes a methodology needs to be more precise than the proposed one. Proposed change: “the denominator is a proxy for the animal population likely to be treated with antimicrobials within a reporting year, expressed as animal biomass (kg) at risk per year”	Thank you for your comments. Please see previous response.
190-191	1	Comment: “ESVAC participating countries have indicated the need to revise this denominator, as recommended in EMA’s concept paper on the reporting of antimicrobial sales and use in animals at the EU	Thank you for the comment. Lines 190-197 were adjusted to: ‘<i>However, it is important to note that some animal categories are not accounted for in the</i>

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		level” We agree on this, but apparently for different reasons. Proposed change: It should be clarified what the criticism is about, i.e. why revision is needed.	<i>PCU. For instance, due to the non-availability of the data held by Eurostat on the number of live goats when the PCU methodology was first established, this category was not included in the PCU calculation. As a result, countries with a large goat population have an underestimate of their total PCU. ESVAC participating countries have indicated the need to revise this denominator, i.e. animal categories to be included and weights of animals used for calculation of the sales PCU, as recommended in EMA’s concept paper on the reporting of antimicrobial sales and use in animals at the EU level.'</i>
	5	Comment: “ESVAC participating countries have indicated the need to revise this denominator, as recommended in EMA’s concept paper on the reporting of antimicrobial sales and use in animals at the EU level” We agree on this, but for different reasons. Proposed change: It should be clarified what the criticism is about (e.g., why a revision is needed).	Thank you for your comments. Please see previous response.
213-214	1	Comment: “In principle, all food-producing animals and other animals kept or bred are at risk of being treated antimicrobial VMPs.” This is correct, PLEASE NOTE that the animals are being at risk when they are “kept”. They are NOT at risk the day they are slaughtered. Also, they are not at risk before they are born or after they are slaughtered. The proposed methodology assumes that the animals are at risk before being born and after being slaughtered (if they live less than one year).	Thank you for your comment. It is agreed that animals are not likely to be treated at slaughter. Nevertheless, the proposed methodology for calculating the denominators for sales and use data offers a standardised approach to estimating animal biomass that is harmonised across the Member States.

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		Proposed change: The proposed methodology should take into account that the animals are not at risk before being born or after being slaughtered.	
	5	Comment: <i>"In principle, all food-producing animals and other animals kept or bred are at risk of being treated antimicrobial VMPs."</i> This is correct, but please note that the animals are being at risk when they are kept alive. They are not at risk the day they are slaughtered. Also, they are not at risk after they are slaughtered, and the risk of being affected for instance by VMP residues in-utero may depend on a case-by-case basis (species, active substance considered...). The proposed methodology assumes that the animals are at risk before being born and after being slaughtered if they live less than one year, no matter what are the circumstances. Proposed change: The proposed methodology should take into account that the animals do not have the same exposure to VMP treatment before being born than during their lifespan. There is no exposure to treatment as such after the slaughter.	Thank you for your comments. Please see previous response.
225	6	Comment: 'The collected data should be harmonised', it is not clear if this means 'harmonised data collection'? If so, Eurostat gathers information from the national statistical authorities in compliance with common EU statistical regulations and standards, monitored by Eurostat. Does this guarantee that	Thank you for your comment. As part of its role to develop, produce and publish comparable statistics and data at the European level, Eurostat works to ensure common concepts, methods, structures and technical standards are used across the EU. This provides data that are harmonised as far as possible. Data collection is done by

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		animal number data is collected in the same harmonised way at the level of the MS?	national statistical authorities in compliance with common EU statistical regulations and standards, monitored by Eurostat. National authorities verify and analyse national data and send them to Eurostat. Eurostat then carries out data validation and quality control checks. Lines 238-240 have been adjusted for clarification: '(...) <i>national statistical authorities transmit data to Eurostat in compliance with common EU statistical regulations and standards and Eurostat carries out data validation and quality control checks.</i>'
227	6	Comment: Please clarify who should validate the data and how this should be done.	Thank you for your comment. Please refer to previous response.
273-274	1	Comment: "The overall aim is to obtain a harmonised denominator that represents – to the extent possible – the biomass of animals likely to be treated with antimicrobials in each Member State." Again - the animals are only likely to be treated when they are alive. For a large proportion of the species, the proposed methodology overestimates the "animal biomass at risk" (= animal biomass-year) by a factor 4-25 depending on the species. Proposed change: The denominator should be "animal biomass at risk" for all species and production type, not only for some of the species. It is definitely feasible to estimate the live biomass at risk from slaughter data. We propose to involve epidemiologists with expertise in the field to develop the methodology.	Thank you for your comment. As indicated in lines 184-185, the denominator is a proxy (synonyms are among others surrogate and substitute). The slaughtered biomass will be converted to live weight at slaughter, as explained in lines 345-351: <i>Considering the availability of data on slaughtered animals (number of heads and slaughtered biomass) at EU level, it was decided to follow an approach similar to that of WOAHA using estimates of live average weight for all species and categories without focusing on time at treatment. Using Eurostat slaughter data (EU/EEA countries), the total slaughtered (carcass) biomass (in kg) was divided by the total number of animals (heads) slaughtered and transformed to live weight at slaughter using standard conversion factors of carcass weight equivalent as defined by Eurostat.</i>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	5	Comment: “<i>The overall aim is to obtain a harmonised denominator that represents – to the extent possible – the biomass of animals likely to be treated with antimicrobials in each Member State.</i>” Again, there needs to be a clarification that the animals are only likely to be treated when they are alive. For a large proportion of the species, the proposed methodology overestimates the “animal biomass at risk” (= animal biomass-year) by a factor between 4-25 depending on the species. Proposed change: The denominator should be “animal biomass at risk” for all species and production type, not only for some of the species. It is definitely feasible to estimate the live biomass at risk from slaughter data. We propose to involve epidemiologists with expertise in the field to develop the methodology.	Thank you for your comment. Please see previous response.
	6	Comment: The description ‘biomass likely to be treated’ seems incorrect as this seems to imply that all animals are bound to be treated. The description also lacks a time indication. Proposed change: ‘the total biomass of animals that could have been treated with antibiotics in a year’	Thank you for your comment. Lines 280-282 have been revised to: ‘<i>The overall aim is to obtain a harmonised denominator that represents – to the extent possible – the total biomass of animals that could have been likely to be treated with antimicrobials in a year in each Member State.</i>’
283-284	1	Comments: “The animal biomass (in kg) will be obtained by multiplying the number of animals (from livestock and slaughtered statistics) by the standard	Thank you for your comment.

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		weight of the animal species, category or stage in question" This methodology is all right, if the recommendation from the ESVAC Ad hoc advisory group is followed, i.e., that the defined standard weight is taking into account the life span of the animal. The standard weight should be the average standard weight per animal over a year (i.e., the period before and after birth should be included in the calculation with bodymass=0kg) Proposed change: "The animal biomass (in kg) will be obtained by multiplying the number of animals (from livestock and slaughtered statistics) by the standard weight of the animal species, category or stage, and life span in question"	The draft GL as published for consultation constitutes the recommendations of the ESVAC Denominators and Indicators <i>ad hoc</i> review group (ESVAC <i>ad hoc</i> review group). The ESVAC <i>ad hoc</i> group endorsed the GL on 25 April 2023 and subsequently the GL was discussed at CVMP and adopted for consultation. Please refer to the response to Stakeholder 1 general comment regarding lifespan.
	5	Comment: "<i>The animal biomass (in kg) will be obtained by multiplying the number of animals (from livestock and slaughtered statistics) by the standard weight of the animal species, category or stage in question</i>". This methodology is right, if the recommendation from the ESVAC Ad hoc advisory group is followed (e.g., that the defined standard weight is taking into account the life span of the animal). The standard weight should be the average standard weight per animal over a year (i.e., the period before and after birth should be included in the calculation with body mass = 0 kg)	Thank you for your comment. Please see previous response.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The animal biomass (in kg) will be obtained by multiplying the number of animals (from livestock and slaughtered statistics) by the standard weight of the animal species, category or stage, and lifespan in question"	
290-296	8	Please see the general comment and specifically the discussion about comparison of antimicrobial use in different countries and/or livestock sectors.	Thank you for your comment. Please see response to Stakeholder 8 general comments.
290-302	1	Comment: "The ESVAC Ad hoc review group also considered adjusting the biomass of animals likely to be treated with antimicrobials with the animal's lifespan, as suggested by Radke, B. R. [14] and Sanders et al. 291 [15]." The advice from the ESVAC ad hoc advisory group should not be ignored. This is a pertinent issue. In the report it is argued that "Article 5(1) of Commission Implementing Regulation 2022/209 considers a combination of the number of animals slaughtered and of the number of live animals present in a Member State during the data collection period, multiplied by standardised animal weights, for the adjustments of the animal population." However, this is not a valid argument for not following the Expert group's recommendation, because the life-span of an animal can be considered in the "standard animal weight", in accordance with the suggestion from the Ad hoc advisory group.	Thank you for your comments. The draft GL as published for consultation constitutes the recommendations of the ESVAC Denominators and Indicators ad hoc review group (ESVAC <i>ad hoc</i> review group). The ESVAC <i>ad hoc</i> group endorsed the GL on 25 April 2023 and subsequently the GL was discussed at CVMP and adopted for consultation. Please refer to the response to Stakeholder 1 general comment regarding lifespan.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: A new working group including epidemiological expertise should propose new methodologies, which consider the suggestions from the Ad hoc Expert group.	
	5	Comment: <i>"The ESVAC ad hoc review group also considered adjusting the biomass of animals likely to be treated with antimicrobials with the animal's lifespan, as suggested by Radke, B. 291 [15]."</i> The advice from the ESVAC ad hoc advisory group should not be ignored. This is a pertinent issue. In the report it is argued that <i>"Article 5(1) of Commission Implementing Regulation 2022/209 considers a combination of the number of animals slaughtered and of the number of live animals present in a Member State during the data collection period, multiplied by standardised animal weights, for the adjustments of the animal population."</i> However, this is not a valid justification for not following the Expert group's recommendation, because the lifespan of an animal can be considered in the "standard animal weight", in accordance with the suggestion from the Ad hoc advisory group. Proposed change: A new working group including epidemiological experts should propose new methodologies which shall consider the suggestions from the Ad hoc Expert group.	Thank you for your comment. Please see previous response.
293-296	6	Comment: It is regretful that the lifespan of the animal is not taken into account. With the proposed use of standard weights at slaughter, this means an	Thank you for your comments. Please refer to the response to Stakeholder 1 general comment regarding lifespan.

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		overestimation of the animal biomass at risk of being treated, as these are predominantly young animals.	
299	6	Comment: '... for the adjustments of the animal population.' Adjustments to what and why?	Thank you for your comment. Article 5 of the Commission Implementing Regulation (EU) 2022/209 requires the Agency to adjust the animal population data according to 'so-called denominators' for analysis purposes. The denominators should be calculated '<i>on the basis of a combination of the number of animals slaughtered and of the number of live animals present in a Member State during the data collection period, multiplied by standardised animal weights</i>'.
308-313	1	Comment: The lifespan and average weight before export should be considered, converting this into something comparable to census data. Also, the typical weight at treatment should be taken into account. Please see comment above (Re: line 155).	Thank you for your comment. Please refer to the response to Stakeholder 1 general comment regarding lifespan.
	5	Comment: The lifespan and average weight before export should be considered, converting this into something comparable to census data. Also, the typical weight at treatment should be taken into account. Please see comment above (line 155).	Thank you for your comment. Please refer to the response to Stakeholder 1 general comment regarding lifespan.
321-359	8	Comment: The proposed equation for calculating the standardized weight is the slaughter weight of the animals. The most accurate weight would be the weight at treatment. We understand that the treatment weight is often not available and that a standardized weight must be used. However, by using	Thank you for your comment. Please refer to the response to Stakeholder 1 general comment regarding lifespan.

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		the slaughter weight you overestimate the animal population at risk of antimicrobial treatment. This is especially the case for fast growing species, like broilers or pigs. Proposed change: Using an estimated treatment weight by introducing an additional factor to the equation. This species-specific factor (between 0 and 1) would allow to estimate the treatment weight per livestock. For species where the majority of treatments take place in the early life this factor will be lower. For long lived species (like dairy cattle) this factor can be (close to) 1.	
346	6	Comment: Please provide a more detailed rationale for converting carcass weight to live weight at the time of slaughter. It only seems to be relevant to make inter-species comparisons since the factor is the same within one animal species.	Thank you for your comment. The detailed justification can be found in lines 345-350: considering the availability of data on slaughtered animals (number of heads and slaughter biomass) at the EU level, it was decided to follow an approach similar to that of WOAH using estimates of live average weight for all species and categories without focusing on time at treatment. This is in line with the intent stated in Recital (7) of Commission Implementing Regulation 2022/209, enabling (indirect) comparison of sales and use data at EU level with global level. To clarify the purpose of using conversion factors, the following was added in line 350: <i>'(...) using standard conversion factors of carcass weight equivalent as defined by Eurostat'</i>. A footnote was added with a link to Eurostat's definition of carcass weight.

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354	6	Comment: For food producing animals it seems illogical to switch to estimated weight at treatment when for the categories listed above considerable efforts are made to convert carcass weight to live weight. Should it not be better to use <u>estimated weights at slaughter</u> in order to be able to make a correct comparison with the animal categories above?	Thank you for your comment. Estimates of live average weight at the time of treatment are not available for all the animal species, categories and stages for which data on the use of antimicrobial medicinal products must be collected and reported. Therefore, an effort was made to establish standardised weights for all animal species and categories for which use data will have to be collected by Member States and sent to the Agency. Given the availability of slaughter data (number of animals and slaughter biomass), it was decided to follow an approach similar to that of WOH and calculate live weights at slaughter whenever possible.
468	1	Comment: This is a typical example on the extreme overestimation introduced by the proposed methodology: A chicken lives only approximately 30-35 days and contributes to the census biomass (the biomass at risk) with approximately (2.4 kg/2) *1.1/12= app. 110 grams. As an example: 1000 chickens slaughtered have contributed with approximately 110 kg biomass-at-risk in a year. But ESVAC proposes to estimate the biomass as 2400 kg "at risk". This is a 2200 % overestimation of the "biomass at risk". Proposed change: Epidemiology experts with competence in the field should be included in the working group setting up a new proposal for changes in methodology.	Thank you for your comment. Please see the response to Stakeholder 1 general comment concerning consideration of the lifespan (cycle length) of animals in respect of the metric.

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	5	Comment: This is a typical example on the extreme overestimation introduced by the proposed methodology: A chicken lives only approximately 30-35 days and contributes to the census biomass (the biomass at risk) with approximately $(2.4 \text{ kg}/2) * 1.1/12 = \text{app. } 110 \text{ grams}$. As an example: 1000 chickens slaughtered have contributed with approximately 110 kg biomass-at-risk in a year. But ESVAC proposes to estimate the biomass as 2400 kg "at risk". This is a 2200 % overestimation of the "biomass at risk". Proposed change: Epidemiology experts with competence in the field of antimicrobial use should be included in the working group setting up a new proposal for changes in methodology.	Thank you for your comment. Please see previous response.
761	6	Comment: '...it is therefore not possible to report the sales data in terms of doses administered.' This is in contradiction with the volume of sales reporting guidelines for MAHs (EMA/772580/2022): "MAHs shall submit the estimated split of the use per species for each submitted package with sales (including non-EEA sales), and a dose factor, indicating how many animals of a specific species can be treated with one pack on average. In combination, this will allow the subsequent calculation of the estimated number of treated animals."	Thank you for your comment. The ESVAC reports show that most countries obtain sales data from sources other than MAHs - e.g. wholesalers purchasing VMPs from MAHs or other wholesalers. Wholesalers are expected to have a different level of detail regarding the use of antimicrobial VMPs than MAHs are likely to have. MAHs are expected to have a general understanding of how their products are used in the relevant target species. The primary intent of sales data reporting by MAHs in line with Regulation (EU) 2019/6 is to enable estimation of the incidence of adverse reactions. A stronger level of robustness and detail would be

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			required for reporting sales data for veterinary antimicrobials in terms of doses administered, which is yet to be available at this point.
778-793	7	Comment: It should be acknowledged in the reporting of antibiotic use per animal species that this statistic is often an estimate. For example, where oral antibiotics are licenced for use in both dogs and cats, it is difficult to definitively report the exact split between these species and any reported split based on the relative proportions of cat and dog biomass would be an estimation. Similarly, where injectable antibiotics are administered to animals in a mixed-species practice, even the split between small and large animal usage would be difficult to report definitively. Proposed change: Therefore, mandatory use data will be reported as total use, <u>estimated</u> use per animal species and categories, use by antimicrobial class/subclasses and use by administration route/product form, for the EU overall and by country as appropriate, using the indicators listed in Table 20.	Thank you for your comment. In response please consider the requirements in Article 57 (5) of Regulation (EU) 2019/6: 5. Member States shall be allowed to apply a progressive stepwise approach regarding the obligations set out in this Article so that: (a) within two years from 28 January 2022, data shall be collected at least for the species and categories included in Commission Implementing Decision 2013/652/EU (24) in its version of 11 December 2018; (b) within five years from 28 January 2022, data shall be collected for all food-producing animal species; (c) within eight years from 28 January 2022, data shall be collected for other animals which are bred or kept. The animal species and categories for which the data shall be reported are specified in Article 15 of the Commission Delegated Regulation (EU) 2021/578. For dogs and cats the data shall be collected and reported separately. Regarding the proposed change to add 'estimated' in line 812, this was not implemented to avoid contradicting Article 6 of the Commission Delegated Regulation (EU) 2021/578 where it reads '<i>Data collected and reported by Member States to the Agency</i>

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			<i>shall be accurate, complete and consistent</i> '. The Stakeholder's point is acknowledged and will be taken into consideration for the Agency's future reports.
819	6	Comment: '...target to reduce of overall EU sales' Proposed change: '...target to reduce overall EU sales'	Thank you for your comment. The text has been revised.
1076	8	Comment: "50 DDDvet/kg cattle biomass in year X for MS A". This suggest that each kg of cattle was treated for with 50 defined daily doses per year. So this means a cow weighing 595 kg (standard weight) is treated with $50 * 595 = 29750$ daily doses per year? Proposed change: The outcome of the equation, calculated with the unit DDDvet/kg is corrected for the total weight of the sector (calculated with the standardized weight per animal), and therefor represents the number of DDDvet per animal (with the standardized weight) and NOT per kg.	Thank you for your comment. The examples provided were only intended to demonstrate the mathematical operations of calculating the denominator. The example provided in #2 is indeed unreasonable in terms of the magnitude of the denominator. Examples in Annex 4 have been revised to include closer to real data based on available data (e.g. ESVAC, Eurostat, national reports).