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Committee for Medicinal Products for Veterinary Use

Advice on implementing measures under Article 57(3) of Regulation (EU) 2019/6 on veterinary medicinal products - Report on specific requirements for the collection of data on antimicrobial medicinal products used in animals

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Introduction

On 6 February 2019 the European Commission sent a request to the European Medicines Agency (the Agency) for a report on the specific requirements which need to be established for the collection of data on antimicrobial medicinal products used in animals, especially describing the following points:

- types of antimicrobial medicinal products used in animals, for which data are to be collected;
- quality assurance to be put in place by Member States and the Agency to ensure quality and comparability of data;
- rules on the methods of gathering these data and of their transfer to the Agency.

The Committee for Medicinal Products for Veterinary Use (CVMP) formed an expert group to prepare the scientific report. The group was composed of eight experts selected from the European network of experts, on the basis of recommendations from the national competent authorities and two Agency staff members with expertise on collection of data on antimicrobial consumption in animals.

The expert group submitted their report to the CVMP on 4 June 2019.

The CVMP adopted the scientific report on 18 July 2019.

Summary

The new legislation for the authorisation of veterinary medicines in the European Union (EU), Regulation (EU) 2019/6 on veterinary medicinal products, hereafter referred to as 'the Regulation', was published on 7 January 2019. The Regulation lays down the obligation, among others, for Member States to collect data on the volume of sales and on the use of antimicrobial medicinal products in animals. This report addresses the request from the European Commission to the Agency to provide recommendations on defining the requirements for the collection of data of antimicrobial medicinal products used in animals in the EU, as described in Article 57 of the Regulation and summarised above in the introduction.

Within the scope of the European Commission's request, the advice also provides more detailed information on animal species for which data should be collected. The data collection should be done according to the stepwise approach laid down in Article 57(5) of the Regulation. Such a stepwise approach is expected to facilitate the work necessary for progressive build-up of capacities.

The following points are therefore addressed in the report:

- types of antimicrobial medicinal products used in animals, for which data are to be collected;
- animal species for which sales and use data are to be collected;
- quality assurance to be put in place by Member States and the Agency to ensure quality and comparability of data;
- rules on the methods of gathering these data and of their transfer to the Agency.

In line with the definition of antimicrobials in the Regulation, the antimicrobials addressed in this report are antibiotics, antifungals, antivirals and antiprotozoals. In addition, antimycotics, antimycobacterials as well as antimicrobial human medicinal products that may exceptionally be used in animals are addressed.

The prioritisation of the types of antimicrobials for which data on sales and on use are to be collected by Member States was carried out taking into account the possible purposes of utilising the collected sales and use data, including the expected possibilities for analysis and reporting of the data collected

at EU level. Examples of possible purposes for the collection by Member States include efforts to determine trends in antimicrobial consumption[1], to identify possible risk factors for development of antimicrobial resistance, as a basis for setting risk management priorities and to monitor the effect of risk management measures introduced, or to support the integrated analysis of data on antimicrobial consumption and antimicrobial resistance in humans, animals and food.

The Anatomical Therapeutic Chemical (ATC) and the Anatomical Therapeutic Chemical veterinary (ATCvet) classification systems have been used to identify substances with antibiotic effect, antifungals, antimycotics, antivirals and antiprotozoals, and for recommending the relevant antimicrobial classes for the collection of sales and use data.

Quality assurance systems need to be put in place by Member States and the Agency in order to ensure the quality and comparability of data on sales of veterinary antimicrobials and use of antimicrobials in animals. Member States are responsible for the quality assurance of the data on sales and use of antimicrobials they collect and report to the Agency. It is their duty to ensure that the data fulfil the basic requirements on completeness, accuracy or correctness, validity and reliability. In order to support Member States in this task, guidance on quality requirements for sales and use data to be reported is necessary. Guidance including manuals and protocols for the reporting of sales and use data of antimicrobials should be developed and maintained.

Regarding sales data, the Agency has collected harmonised data on sales of veterinary medicinal products classified as antibiotics and antiprotozoals with antibiotic effect from Member States since 2010 through the European Surveillance of Veterinary Antimicrobial Surveillance (ESVAC) project. The number of Member States providing sales data has increased over time, with all Member States submitting data to the Agency in 2017. This implies that all Member States have systems in place for the collection of sales data on veterinary antimicrobials, including relevant quality assurance systems.

The current protocols and the web based application of the ESVAC project define the rules and key quality requirements for the collection and reporting of sales data for veterinary antibiotics including antiprotozoals with antibacterial effect. In order to accommodate the requirements of the new legislation, the protocols, data collection templates, manuals and the data model enabling electronic data transfer to the Agency of the chosen data collection system for sales data for veterinary antimicrobials, will have to capture reporting of sales data for all veterinary antimicrobials including those currently not included in the ESVAC project (e.g. antifungals, antivirals, and other antiprotozoals). The current rules on the methods for gathering and submitting sales data to the Agency should be considered when developing the new protocols, business rules, applications or templates that Member States should follow when collecting and submitting the sales data to the Agency by electronic means. Additional guidance and training for Member States will be required to ensure the collection and reporting of harmonised data to the Agency for further analysis.

The collection of harmonised and standardised use data per animal species, as required by Article 57 of the Regulation, is most reliably and easily achievable through (semi) automated continuous data collection systems. Some Member States have already developed and implemented such systems. The animal species covered and the sources of the data to be collected by these systems may vary per Member State, depending on differences in distribution of antimicrobial medicinal products, national legislation and other factors. Examples of source data in Member States with (semi)automated continuous data collection systems are prescription data, dispensed amounts of medicines, data on amounts administered by veterinarians on the farm or data from invoices. Data providers may also vary per Member State, and may be veterinarians, pharmacies, feed mills, or end-users such as farmer or breeders. While building up to a full coverage system for use data collection, data enabling the

[1] Amounts of antimicrobials consumed, includes sales and use data for antimicrobials

indirect evaluation of the use of antimicrobial medicinal products in food-producing animals at farm level may potentially also be achievable by other methods. Examples include stratification of sales data supplemented by representative sample surveys, or (semi) automated continuous data collection systems that do not yet achieve full coverage; or statistically representative sample surveys. Therefore, the collection of use data per species will require a certain level of flexibility in the rules on the methods of gathering data allowing direct or indirect evaluation of use at farm level.

For the collection of comparable data on use at EU level, a suitable data base, a data collection protocol and a data template defining essential data elements to be collected and transferred to the Agency should be developed, supplemented by a manual, and including a system enabling electronic transmission of the data (e.g. a web-based data collection system as currently used for ESVAC sales data collection) to facilitate the transfer of use data from Member States to the Agency. Further guidance on use data collection will need to be developed and training will need to be made available to Member States.

This report outlines the considerations regarding antimicrobial data collection, and its Annex provides relevant additional information and considerations, including a description of current data collection on antimicrobial resistance and consumption in the EU.

Recommendations

Types of antimicrobial medicinal products used in animals, for which data are to be collected: animal species and categories to be covered.

1. It is recommended to prioritise the collection of sales and use data of the antimicrobials at EU level as shown in Table 2 of the report and summarised below:

    - **mandatory** collection at EU level should include the collection of **sales** and **use** data of all categories of antibiotics currently included in the ESVAC sales project (antidiarrheals, intestinal anti-inflammatory/antiinfective agents, gynaecological antiinfectives and antiseptics, antiinfectives and antiseptics for intrauterine use, antibacterials for systemic use, antibacterials for intramammary use, antiprotozoals with antibacterial effect), and in addition mandatory collection of **sales** data of the following antimicrobial categories (according to the ATCvet index): antibiotics and chemotherapeutics for dermatological use, other nasal preparations (that contain antimicrobials), antimycobacterials for intramammary use, , ophthalmological antiinfectives and otological antiinfectives

    - Member States may **voluntarily** extend the collection to **sales** data for other antiprotozoals, antifungals, antimycotics, antimycobacterials and antivirals and **use** data for antibiotics and chemotherapeutics for dermatological use, antimycobacterials for intramammary use, antimycotics, antimycobacterials, nasal preparations, ophthalmological antiinfectives, otological antiinfectives, other antiprotozoals, antifungals, antimycotics, antimycobacterials and antivirals.

    It is recommended to collect sales data for veterinary medicinal products only, whereas the collection of use data also should include human medicinal products that may exceptionally be used in animals.

2. In order to comply with the obligations of Article 57, the requirement for collated data and annual reports in Article 57(2), and especially the timelines for the stepwise approach described in Article 57(5), the following gradual inclusion of animal species in the collection of **use** data is proposed, as outlined in Table 3 and summarised below:

- no later than January 2023, Member States should, taking into account species and categories included in Commission Implementing Decision 2013/652/EU, start the collection of use data for cattle (all categories, specifying use in bovines under 1 year of age), pigs (all categories including fattening pigs), chickens (all categories or stages of chickens including broilers and laying hens) and turkeys (all categories including fattening turkeys), with reporting of collated data from 2023 to the Agency from 2024 onwards;
- no later than January 2026, Member States should add to the ongoing collection of use data for the rest of food-producing animal species: other poultry (ducks, geese), sheep, goats, finfish, horses, rabbits (food-producing) and any other food-producing animals, with reporting of collated data from 2026 to the Agency from 2027 onwards;
- no later than January 2029, Member States should add to the ongoing collection of use data for the following non-food-producing animal species: dogs, cats and fur animals (minks and foxes), with reporting of collated data from 2029 to the Agency from 2030 onwards.

3. It is recommended to review the list of antimicrobials for which data on **sales** and **use** are to be collected (Table 2 of the report) periodically, especially during the later phases described in the stepwise approach (before 2027 and 2030, the years when the next steps of submission of collated data to the Agency takes effect), to allow the inclusion of new relevant substances in the data collection. Especially, other substances or classes of antimicrobials may be considered for inclusion in the collection in the light of new knowledge and/or information about their impact on antimicrobial resistance – i.e. impact on animal and/or public health.

4. It is recommended to review the list of **animal species and categories** (Table 3 of the report) during the later phases described in the stepwise approach (before 2027 and 2030, the years when the next steps of submission of collated data to the Agency takes effect), to allow, where necessary, the inclusion of additional animal species or categories for which antimicrobial data are to be collected.

Quality assurance to be put in place by Member States and the Agency to ensure quality and comparability of data

5. According to the Regulation it is the Member States' responsibility to collect and submit to the Agency relevant and comparable data on antimicrobial consumption. In order to ensure that collected data on sales and use are relevant and comparable, i.e. standardised and harmonised, it is advised that Member States follow a validation process to assess the quality of data before submission to the Agency. The general principles of the validation process are described in point 5.1 of the report. In addition, Member States shall follow the latest business rules of the applications, templates and protocols available for the chosen system for data collection and submission to the Agency.

6. It is recommended that Member States establish an active data quality management system for the collection of sales and use data to ensure appropriate quality assurance throughout the data collection process, and in particular that the minimal quality requirements (completeness, accuracy, correctness, validity and reliability) are met. The general principles of data quality management and control are described in point 5.2 of the report.

7. Guidelines for quality requirements for sales and use data to be reported by Member States should be developed and maintained.

8. Guidance including manuals, templates and protocols for the reporting of sales and use data of antimicrobial consumption should be developed and maintained.

9. Support to Member States, especially those that are setting up an antimicrobial data collection systems for the first time or those that experience difficulties in delivering quality data, will be required. This can be achieved by developing guidance on quality requirements, business rules and data quality management systems. Where necessary, training should be provided.

Rules on the methods of gathering the required data and of transferring it to the Agency, enabling surveillance

Detailed rules on the methods of gathering the required data and of transferring it to the Agency will depend on the chosen systems for collecting, transferring and storing data on antimicrobial consumption.

10. The **sales** and **use** data to be submitted to the Agency each year, by Member States, should cover the full preceding calendar year. The data should be validated by the Member State before sending it to the Agency in accordance with the technical specifications described in relevant legislation and relevant guidance including manuals, protocols, templates and/or electronic forms. It is recommended that the relevant guidance including manuals, protocols, templates and/or electronic means of transmission are provided.

11. The source of **sales** data submitted to the Agency may vary per Member State (marketing authorisation holders, wholesalers, retailers, etc.) but should cover all the sales of all relevant veterinary antimicrobial medicinal products sold or placed on their market during the calendar year covering the data collection.

12. To collect harmonised and standardised **use** data per animal species as requested in Article 57 of the Regulation, it is recommended that Member States set up a continuous (semi)automated data collection system or other appropriate systems that enable in particular direct or indirect evaluation of the use of such products in food-producing animals at farm level.

13. Data provided to the Agency should be in the form of number of packages per presentation of the veterinary or human medicinal product per animal species or category used in the Member States during the data collection period. The collected raw data on use of antimicrobials in animals should be aggregated at national level at each presentation level into the total per animal species or category. The data collection period should cover one calendar year (regardless of the length of the production cycles in individual farms).

14. The submission of the collected data on sales and on use of antimicrobials in animals from Member States to the Agency should be carried out by electronic means.

Report on specific requirements for the collection of data on antimicrobial medicinal products used in animals

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1. Terms of reference and scope

This report represents the advice of the Agency on implementing measures under Article 57(3) of Regulation (EU) 2019/6 on veterinary medicinal products (Official Journal of the European Union, 2019), hereafter referred to as "the Regulation", in particular the specific requirements for the collection of data on antimicrobial medicinal products used in animals in the EU.

The scope of this report is based on:

1. The request from European Commission to the Agency for a report describing the specific requirements which need to be established as to the following elements:
   - types of antimicrobial medicinal products used in animals, for which data are to be collected;
   - quality assurance to be put in place by Member States and the Agency to ensure quality and comparability of data;
   - rules on the methods of gathering these data and of their transfer to the Agency.
2. The legislative basis in Regulation (EU) 2019/6 and in particular:
   2.1. Article 57 on the collection of data on antimicrobial medicinal products used in animals, including the step-wise approach described in its paragraph 5;
   2.2. the definition of antimicrobials in Article 4 of the Regulation.

The report additionally discussed the following aspects:

1. Purposes of collection of data on sales and use of antimicrobials in animals;
2. Current collection of antimicrobial consumption data in animals carried out by the Agency (ESVAC project);
3. Considerations regarding data already collected by Member States, especially:
   3.1. data on antimicrobial consumption in human medicine at EU level (ESAC-Net) and at global level (WHO);
   3.2. data on antimicrobial consumption in animals at global level (OIE);
   3.3. data on antimicrobial resistance in humans at EU level (EARS-Net) and
   3.4. data on antimicrobial resistance in food and animals at EU level (Commission Implementing Decision 2013/652/EU, EFSA).

The antimicrobials included in the scope of this report are based on the definition of antimicrobials in Article 4(12) of the Regulation: "*'antimicrobial' means any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and antiprotozoals*".

The antimicrobials addressed in this report are antibiotics, antivirals, antifungals and antiprotozoals. This report addresses the collection of data on veterinary antimicrobial medicinal products and the collection of data on human antimicrobial medicinal products that may exceptionally be used in animals.

Article 2(7)(c) of the Regulation states that it does not apply to feed additives. Therefore feed additives are not included in the scope of this report. Biocides covered by Regulation (EU) No 528/2012 – in principle - are also outside the scope of this report. However, the report considers when it might become necessary to include feed additives and biocides.

Article 57(5) of the Regulation allows for a stepwise approach to antimicrobial use data collection, i.e. gradual inclusion of various animal species. Within the scope of the European Commission's request,

more detailed information on priorities for the gradual inclusion of animal species and production groups is provided. Article 57(2) requires submission of collated data to the Agency within the time lines set out in paragraph 5 of the same article. The timelines mentioned in subparagraphs (a) to (c) have been interpreted as applying to the full obligations set out in Article 57, meaning data collection and their reporting to the Agency. Experience gained with the ESVAC project, has shown the usefulness of collating data for a full calendar year. In consequence, data collection needs to start a year earlier than reporting obligations. The detailed justifications for priorities, including the stepwise approach and selection of animal species to be included in the surveillance, are comprehensively outlined in this report and supplemented with additional information in point 2 of the Annex.

Article 57

Collection of data on antimicrobial medicinal products used in animals

1. Member States shall collect relevant and comparable data on the volume of sales and on the use of antimicrobial medicinal products used in animals, to enable in particular the direct or indirect evaluation of the use of such products in food-producing animals at farm level, in accordance with this Article and within the time limits set out in paragraph 5.

2. Member States shall send collated data on the volume of sales and the use per animal species and per types of antimicrobial medicinal products used in animals to the Agency in accordance with paragraph 5 and within the time limits referred to therein. The Agency shall cooperate with Member States and with other Union agencies to analyse those data and shall publish an annual report. The Agency shall take into account those data when adopting any relevant guidelines and recommendations.

3. The Commission shall adopt delegated acts in accordance with Article 147, in order to supplement this Article, establishing the requirements as regards:

(a) the types of antimicrobial medicinal products used in animals for which data shall be collected;

(b) the quality assurance that Member States and the Agency shall put in place to ensure quality and comparability of data; and

(c) the rules on the methods of gathering data on the use of the antimicrobial medicinal products used in animals and on the method of transfer of those data to the Agency.

4. The Commission shall, by means of implementing acts, set up the format for the data to be collected in accordance with this Article. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 145(2).

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 (Official Journal of the European Union, 2013) 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.

2. Purposes of the collection of data on consumption of antimicrobials in animals

The collection of data on sales and use of antimicrobials for animals may serve several purposes, of which the most important are the following:

- to aid interpretation of patterns and trends regarding consumption and antimicrobial resistance;
- as a basis for risk profiling and risk assessment regarding antimicrobial drug resistance;
- as a basis for setting risk management priorities;
- as a basis for evaluation of the effectiveness of control measures being implemented;
- to identify (emerging) use of antimicrobial drugs, e.g. of specific drug classes such as critically important antibiotics;
- to aid comparison of usage of antimicrobial drugs between and within countries and between time periods, etc.;
- to assess the spread and effect of antimicrobial drug pollution of the environment;
- as a basis for focused and targeted research and development;
- to support integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals.

Recital (50) of the Regulation notes that there is a lack of sufficiently detailed and comparable data at EU level that would allow the determination of trends, and identification of possible risk factors that could lead to the development of measures to limit the risk from antimicrobial resistance, and the monitoring the effect of any measures introduced. The same recital also describes that, when available, the data should be analysed with data on the use of antimicrobials in humans and data on organisms resistant to antimicrobials found in humans, animals and food of animal origin. Data collection should therefore aim to provide the necessary information.

The Regulation requires the collection of antimicrobial consumption data, i.e. sales and use data, for antibiotics, antivirals, antifungals and antiprotozoals. Examples of purposes when availability of data on antimicrobial resistance is required in addition to the availability of sales or use data include the interpretation of AMR patterns (first bullet point of the above list), risk profiling as regards development of antimicrobial resistance (second bullet point) and for integrated analysis (last bullet point of the above list). Currently, at the EU level, harmonised data on antimicrobial resistance from animals are only available for some categories of the major food-producing animal species (bovines under one year, fattening pigs, the chicken categories broilers and layers, and fattening turkeys) and for some antibiotics, as summarised in Table 1 and further detailed in point 2 of the Annex. Data on consumption of antivirals, antifungals and antiprotozoals will only serve some of the purposes listed above, however not those for which simultaneous availability of resistance data for antimicrobials under consideration are required but not yet available.

Since 2015 the Agency contributes to the joint reporting with EFSA and ECDC on the integrated analysis of antimicrobial consumption in human and veterinary medicine and antimicrobial resistance in the EU (Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report). While the reporting frequency for the JIACRA report is set as every three years[2]), considering the

[2] Article 57(1)(u) of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1) as amended by Regulation (EU) 2019/5 of the European Parliament and of the Council of 11 December 2018

seriousness of the threat from antimicrobial resistance, it is desirable to increase the reporting frequency within the limits set by feasibility and data reliability[3].

Table 1. Surveillance data on antimicrobial resistance and antimicrobial consumption currently collected in the animal and human sectors in the EU

Surveillance data in the EU	Animals		Humans
	Antimicrobials		Antimicrobials
Antimicrobial resistance data	Food-producing animals	Antibiotics[(a)]	Antibiotics[(c)]
			Antivirals[(c,d,e)]
			Drugs for treatment of tuberculosis[(f)]
Antimicrobial consumption data	All animals (sales stratified into food-producing and companion animals)	Antibiotics[(b)] for systemic, intramammary and intrauterine use	Antibiotics for systemic use[(g)]
			Antimycotics and antifungals for systemic use[(g)]
			Antivirals for systemic use[(g)]
			Drugs for treatment of tuberculosis

[(a)] Tables 14-18 from the "Manual for reporting on antimicrobial resistance within the framework of Directive 2003/99/EC and Decision 2013/652/EU for information derived from the year 2018" (EFSA, 2019)
[(b)] Web Based Sales Data and Animal Population Data - Collection Protocol (version 2)(EMA/ESVAC, 2016)
[(c)] TESSy Antimicrobial resistance reporting protocol (ECDC, 2018c) and collection of antivirals commenced in 2019 for surveillance of 2018 data
[(d)] TESSy - HIV Drug Resistance Reporting Protocol and Analysis Plan 2019 - HIV drug resistance surveillance data for 2018 and historical data (ECDC, 2019a)
[(e)] TESSy - Influenza Reporting Protocol 2018 - Seasonal influenza (ECDC, 2018d)
[(f)] TESSy - Tuberculosis Reporting Protocol 2019 - Surveillance data for 2018 (ECDC, 2019b)
[(g)] TESSy - Antimicrobial consumption data collection protocol (ECDC, 2018b), it has to be taken into account that data are provided by Member States on voluntary basis

3. Antimicrobial medicinal products used in animals for which data are to be collected

The prioritisation of the types of antimicrobials used in animals, for which data on both sales and use should be collected by Member States, was carried out taking into account purposes of collecting such data at EU level as described under point 2 of this report, in particular, to serve the purpose of integrated analysis and the likelihood of large-scale use (e.g. in major food-producing animal species).

At this moment, at the EU level data on sales of veterinary antibiotics and antiprotozoals with antibiotic effect are collected from all Member States through the ESVAC project. Data on sales of the remaining antimicrobials covered by the Regulation (e.g. antivirals, antimycotics) and data on use of antimicrobials in animals are currently not collected at EU level. Regarding the collection of use data for antimicrobials in animals, Member States are at different stages.

amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Regulation (EC), No 1901/2006 on medicinal products for paediatric use and Directive 2001/83/EC on the Community code relating to medicinal products for human use, (OJ L 4, 7.1.2019, p 24)

[3] Recital 7 of Regulation (EU) 2019/5 of the European Parliament and of the Council of 11 December 2018

In the following, the text distinguishes between the collection of sales data, where the existing system needs to be expanded to include additional substances, and the collection of use data where the existing system requires more in depth adaptation to the new legislative requirements or where systems need to be newly established.

In this report, the relevant antimicrobials are identified by their ATC/ATCvet codes according to the Anatomical Therapeutic Chemical (ATC) and the Anatomical Therapeutic Chemical veterinary (ATCvet) classification systems.

3.1. Antimicrobial classes (ATCvet/ATC codes) of relevance

To commence implementation of the obligations laid down in Article 57 of the Regulation, it is recommended that mandatory data collection at the EU level should include the collection of sales and use data of all categories of antimicrobials currently included in the ESVAC project, i.e. antibiotics and antiprotozoals with antibiotic effect.

In order to extend the data collection to other substances with antibiotic effect currently not included in the ESVAC project, the collection of sales data of the following categories should also be mandatory: antimycobacterials for intramammary use, and antibiotic veterinary medicinal products for topical use, i.e. antibiotics and chemotherapeutics for dermatological use, other nasal preparations (containing antibiotics), ophthalmological antiinfectives and otological antiinfectives (Table 2).

Additional antimicrobial classes and substances of relevance to be included in the collection of sales and use data were identified by analysing which of the substances belonging to the groups of antivirals, antifungals and antiprotozoals may be authorised for use in food-producing animals. This was done by assessing whether MRLs have been assigned or whether relevant substances were identified as not needing an MRL, as having (an) MRL(s) or being designated as not needing any, is a prerequisite for use in food-producing animals.

No antivirals are listed as allowed substances in the MRL[4,5] Regulation. Therefore, no veterinary medicinal products containing antivirals are currently authorised for food-producing species and may also not be used in food-producing animals under the 'cascade'[6] unless of MRLs will be established in the future. This implies that the collection of antimicrobial consumption data for antivirals is currently not relevant for food-producing animals. Due to time constraints, it was not possible to investigate whether any antiviral veterinary medicinal products are approved for, e.g., companion animals or fur animals in any of the Member States, or if antiviral human medicinal products are used in non-food-producing animals under the cascade[7]. For antifungals, MRLs have been established for seven substances, and for antiprotozoals for eight substances.

To judge the relevance of including the above-mentioned antimicrobial categories in the mandatory data collection, the availability of data for integrated analysis of sales, use and resistance data was also considered. At the EU level, antimicrobial resistance data from the animal sector are currently collected for specific antibiotics, and only for some categories of the major food-producing animal species (isolates obtained from healthy animals, as laid down in Commission Implementing Decision 2013/652/EU) (Table 1). At present, there is no collection of antimicrobial resistance data for antifungals, antivirals or antiprotozoals in the animal sector at EU level. Therefore, at EU level, the integrated analysis of antimicrobial consumption data obtained from the animal sector for these types

[4] https://ec.europa.eu/health/veterinary-use/maximum-residue-limits/developments_en
[5] https://www.ema.europa.eu/en/find-medicine/veterinary-medicines/maximum-residue-limit-assessment-reports
[6] See Articles 113 and 114 of the Regulation on Use of medicinal products outside the terms of the marketing authorisation (commonly referred to as 'the cascade') in terrestrial and aquatic food-producing animal species;
[7] See Article 112 of the Regulation on Use of medicinal products outside the terms of the marketing authorisation (commonly referred to as 'the cascade') in non-food-producing animal species;

of antimicrobials is not possible. In human medicine, the consumption data collection protocol includes data on antifungals (antimycotics) and antivirals, but not on antiprotozoals (Table 1). However, not all Member States provide data for these types of antimicrobials to the ESAC-Net, and data are submitted irregularly in terms of years ; at EU level, available data on antimicrobial consumption in humans are reported in the ESAC-Net reports (ECDC, 2019c; ECDC, website, last accessed in 2019).

It was concluded that use and sales data collection for the categories discussed above should not be mandatory. However, Member States may voluntarily extend the collection to sales and use data for the categories above, i.e. to other antiprotozoals, antifungals, antimycotics, antimycobacterials and antivirals for systemic use (Table 2).

In the discussions on the data collection for antimicrobial products for topical administration it was noted that no defined daily doses are established for topical products for human use, because the amount given per day can vary very much according to the disease (WHO, 2018a)[8]. This implies that for such products a meaningful measure for the numerator cannot be established. As a consequence, it is considered that no meaningful indicator for exposure to topical antimicrobials can be established, which is detrimental for assessing associations between use of topical antimicrobials and the occurrence of antimicrobial resistance in animals. No sales data are collected for topical antimicrobials for human use at the EU level, and ESVAC sales data, e.g. in 2016, show that topical antibiotics represented only a minor fraction of antibiotics sold for use in animals[9].

In view of the experience gained by some countries that already started collecting sales data for topical veterinary antibiotics, and the benefits and advances in knowledge that may be expected from the monitoring of sales data for all antimicrobials, including topical products, it was concluded that sales data collection for antimycobacterials for intramammary use and antibiotic veterinary medicinal products for topical use, i.e. antibiotics and chemotherapeutics for dermatological use, nasal preparations, ophthalmological antiinfectives and otological antiinfectives, should be mandatory.

It was also noted that data collection on a voluntary basis of antimycobacterials, which in veterinary medicine are only used for *Rhodococcus equi* infections in foals, requires a close follow-up. No systematic research was done to identify the scale of use of rifampicin at the EU level, but available information indicates a low level of use of rifampicin for this indication in foals in the EU. Therefore, it was considered that antimycobacterials should be monitored on a voluntary basis; in case of any new findings, recommendations should be revisited in the future, especially, before step 2 (e.g. by 2026).

In conclusion, it is recommended to prioritise the collection of sales and use data for the categories of antimicrobial medicinal products as described in Table 2.

[8] For example, for human use no DDD[8] values have been established for any topical preparation (WHO, 2018a), although the DDD system has been in place for close to fifty years. Devising principles for establishment of DDDs for such products is generally difficult, as the dosing of the same product may vary greatly between different indications.
[9] For example, 0.2%, 0.4%, 0.52%, 0.002% and 0.7% of the total tonnes of antibiotics sold in Denmark, Czech Republic, France, Norway and United Kingdom, respectively (EMA/ESVAC, 2018)

Table 2. Categories and ATC/ATCvet codes[10] and names of antimicrobial medicinal categories for which collection and reporting of sales and use data is **mandatory** (ATC and ATCvet codes in bold) and for which it is *voluntary* (ATC and ATCvet codes in italic)

Categories of veterinary antimicrobial agents	SALES ATCvet codes		USE ATCvet and ATC codes
Antidiarrheals, intestinal anti-inflammatory / antiinfective agents	**QA07AA** **QA07AB** **QA07AX03** **QA07AX04**	Included in current ESVAC sales	**QA07AA / A07AA** **QA07AB** **QA07AX03 / A07AX03** **QA07AX04 / A07AX04**
Gynaecological antiinfectives and antiseptics	**QG01AA** **QG01AE** **QG01BA** **QG01BE**		**QG01AA/G01AA** **QG01AE/G01AE** **QG01BA/G01BA** **QG01BE/G01BE**
Antiinfectives and antiseptics for intrauterine use	**QG51AA** **QG51AG**		**QG51AA**
Antibacterials for systemic use	**QJ01**		**QJ01/J01**
Antibacterials for intramammary use	**QJ51**		**QJ51**
Antiprotozoals (with antibacterial effect)	**QP51AG**		**QP51AG**
Antibiotics and chemotherapeutics for dermatological use	**QD06**	Not included in current ESVAC sales	*QD06 /D06*
Other nasal preparations	**QR01AX06, QR01AX08**		*QR01AX06 / R01AX06,* *QR01AX08 / R01AX08*
Antimycobacterials for intramammary use	**QJ54**		*QJ54*
Ophthalmological antiinfectives	**QS01AA, QS01AB, QS01AD, QS01AE, QS01CA, QS01CC**		*QS01AA, QS01AB, QS01AD, QS01AE QS01CA, QS01CC / S01AA, S01AB, S01AD, S01AE, S01CA, S01CC*
Otological antiinfectives	**QS02AA, QS02CA, QS03AA, QS03CA**		*QS02AA, QS02CA, QS03AA, QS03CA/ S02AA, S02CA, S03AA, S03CA*
Antiprotozoals (other than QP51AG)	*QP51*	Not Included in current ESVAC sales	*QP51 /P01*
Antifungals for topical use	*QD01A*		*QD01A /D01A*
Antifungals for systemic use	*QD01B*		*QD01B/D01B*
Antimycotics for systemic use	*QJ02*		*QJ02 /J02*
Antimycobacterials	*QJ04*		*QJ04/J04*
Antivirals for systemic use	*QJ05*		*QJ05 /J05*

It is recommended to review Table 2 (list of antimicrobials for which data on sales and use are to be collected) periodically, especially during the phases described in the stepwise approach laid down in the Regulation (i.e. reporting obligations to the Agency begin in 2027 and 2030, respectively), to allow refinement or the inclusion of new relevant substances in the data collection or changing data collection from voluntary to mandatory or vice versa, as justified from experience gained. Other substances or classes of antimicrobials (point 3.2. of the report) may be considered for inclusion in the

[10] Available online: https://www.whocc.no/atcvet/atcvet_index/ and https://www.whocc.no/atc_ddd_index/

surveillance in the light of any new information on their impact on antimicrobial resistance – i.e. animal or public health.

3.2. Considerations on inclusion of other substances with effect on bacteria

Two substances with antimicrobial effect - monensin and chlorhexidine – were considered as potential candidates for inclusion in the surveillance of antimicrobial consumption in animals, but are not recommended for inclusion in the data collection at this stage for the reasons explained below.

Monensin (an ionophore) is approved as a veterinary medicinal product for the prevention of ketosis in cattle (EMA/CVMP, 2007) – i.e. monensin is not used as an antimicrobial in this product, although it has an antibacterial (and anticoccidiostatic) effect. Ionophores are not used in human medicine, have a unique mode of action, cross-resistance with antibiotics used therapeutically has not been identified, and there is no evidence for transferable resistance (Nesse et al., 2015). Current knowledge is that monensin use in animals has not shown any negative impact on public health. Should new knowledge arise to show that ionophores adversely impact public health, ionophore coccidiostats, including those used for other purposes, should be considered for inclusion in the surveillance due to their widespread use in food-producing animals, in particularly in broilers (narasin) and turkeys (monensin).

Chlorhexidine is a substance with bactericidal effect that is used in human and veterinary medicines. It has undergone an MRL assessment. In addition to its medical uses it is used as a biocide. The summary of a recent scientific expert meeting on foodborne antimicrobial resistance held by FAO and WHO (FAO/WHO, 2018) on a request of the *Ad hoc* Codex Intergovernmental Task Force on Antimicrobial Resistance (TFAMR) of Codex Alimentarius[11], noted that although there is theoretical and experimental evidence that biocides may co-select for antimicrobial resistance, there is an absence of empirical data to indicate that the use of biocides drives co-selection under the conditions present in food production. Chlorhexidine products are typically used for hand disinfection by animal health personnel, sterilisation of instruments, as well as topically on animals prior to surgery or for other medical purposes. Therefore, it may be difficult to measure the amounts of chlorhexidine used in animals. In case of new knowledge that chlorhexidine is a driver for co-selection of antimicrobial resistance, and when the methodological constraints for measuring actual use in animals have been resolved, substances such as chlorhexidine should be considered for inclusion in the surveillance.

4. Animal species for which sales and use data should be collected

Article 57(1) of the Regulation stipulates that Member States shall collect relevant and comparable data on the volume of sales and on the use of antimicrobial medicinal products used in animals. Paragraph 5 of this Article sets out a stepwise approach for inclusion of animal species in the data collection. The following sections set out the views of the expert group on relevant animal species to be addressed by this stepwise approach.

4.1. Sales data

Many of the antimicrobial veterinary medicinal products are marketed for two or more animal species. For such antimicrobials it is not possible to identify the amounts sold for each animal species. In such cases, data on overall sales of antimicrobial veterinary medicinal products is considered representing sales for the complete animal population in the reporting Member States, including farmed fish. Of

[11] Codex Alimentarius is the Joint FAO/WHO Food Standards Programme, see http://www.fao.org/fao-who-codexalimentarius/en/

note is that in the existing ESVAC sales data reporting, the data is stratified into sales for food-producing animals, including horses, and companion animals.

4.2. Use data – by animal species

To ensure comparability of the reported data, it is important that the amounts of antimicrobials used (numerator) are normalised by the animal population at risk of being treated with the antimicrobials (denominator). In order to enable this normalisation, it is vital to have access to reliable and standardised data on the animal populations in question. Therefore consideration was given to the availability of data on terrestrial animal populations and, for farmed fish, tonnes produced in Eurostat or at national level.

In order to comply with the obligations and timelines laid down in Article 57 of the Regulation and considering the availability of data on animal population or tonnes produced, the following gradual inclusion of animal species in the collection of use data is recommended (see Table 3).

Step 1:
No later than in January 2023, Member States should have in place the collection of use data for at least the animal species and categories addressed by Commission Implementing Decision 2013/652/EU, to enable submission to the Agency in 2024 (i.e. within two years from 28 January 2022).

In order to obtain representative and comparable data on use, it is recommended that use data is collected for:

- cattle: all categories, including bovines under 1 year of age;
  Member States where the production of bovine meat under one year of age is more than 10 000 tonnes slaughtered per year, should specify separately the use data for this category;
- pigs: all categories including fattening pigs;
- chickens: all categories or stages including broilers, laying hens and breeders;
- turkeys: all categories including fattening turkeys.

Step 2:
No later than in January 2026, Member States should extend the collection of use data for the rest of food-producing animal species to enable submission to the Agency in 2027 (i.e. within five years from 28 January 2022).

In order to obtain representative and comparable data on use, it is recommended that use data is collected for:

- ducks, geese;
- sheep, goats;
- finfish;
- horses[12];
- rabbits (food-producing);
- any other food-producing animals (may vary per country).

[12] Regulation (EC) No 854/2004 establishes that horses are considered as food-producing animals. Typically, statistics on living horses also cover both food-producing and non-food-producing horses. This implies that use of medicines authorised for companion horses also to be included in the surveillance.

Step 3:
No later than in January 2029, Member States should extend the collection of use data to other animals which are bred or kept in order to enable submission to the Agency in 2030 (i.e. within eight years from 28 January 2022).

In order to obtain representative and comparable data on use, it is recommended that use data is collected for the following non-food-producing animals which are considered to represent the most significant use of antimicrobials in other animals kept or bred:

- dogs;
- cats;
- fur animals (minks and foxes).

The detailed considerations regarding the food-producing and other animal species and categories recommended for inclusion in the surveillance are outlined in point 2.5. of the Annex.

It is recommended to review Table 3 during the phases described in the stepwise approach (prior to 2026 and 2029), to allow, where necessary, for the inclusion of additional species or categories for which antimicrobial use data should be collected.

Member States may submit data on animal species as they become available, earlier than outlined in Table 3, i.e. mandated by the legislation. If Member States choose to submit use data on animal species sooner than required, animal population or production data should also be provided at the same point in time.

When data on food-producing animal population are not available in e.g. Eurostat or at national level, because the production is very low, such species need not be reported separately and may be reported under “any other food-producing animal species”).

Table 3. Animal species, including fish, for which antimicrobial use data are to be provided and data sources for animal population data

By 2024	By 2027	By 2030	Data source for animal population (biomass produced farmed fish)
Cattle All production categories, and specifying use in bovines < 1 year[(a)]	**Cattle** All production categories, and specifying use in bovines < 1 year[(a)]	**Cattle** All production categories, and specifying use in bovines < 1 year[(a)]	Eurostat
Pigs	**Pigs**	**Pigs**	Eurostat
Poultry • **Chickens** • **Turkeys** All production categories or stages for each species, including breeders, layers, broilers for chickens, and fattening turkeys	**Poultry** • **Chickens** • **Turkeys** • **Ducks** • **Geese** All production categories or stages for each species	**Poultry** • **Chickens** • **Turkeys** • **Ducks** • **Geese** All production categories or stages for each species	Eurostat or national data for species or categories where production level is <10 000 tonnes slaughtered per year (e.g. geese, fattening turkeys)
	Sheep	**Sheep**	Eurostat
	Goats	**Goats**	Eurostat
	Finfish	**Finfish**	Eurostat or national data
	Horses – both food-producing and non-food-producing	**Horses** – both food-producing and non-food-producing	National data[(b)]
	Rabbits (food-producing)	**Rabbits** (food-producing)	National data
	Any **other food-producing animals**[(c)]	Any **other food-producing animals**[(d)]	National data
		Dogs	National data[(d)]
		Cats	National data[(d)]
		Fur animals • **Minks** • **Foxes**	National data[(d)]

[(a)] For Member States where production is more than 10 000 tonnes slaughtered/year in line with Commission Implementing Decision 2013/652/EU
[(b)] For some countries based on estimates obtained through sample surveys performed at regular intervals
[(c)] Specifying the species reported; may vary per Member State.

5. Quality requirements to ensure quality and comparability of data

In the framework of data quality management procedures can be divided into those for the co-ordinating centre of the registry (central, in this case responsibilities of the Agency), those for the authority who coordinates data collection at the national level, and those for the centres where the data are collected (local, responsibilities of the Member States and those remote institutions and individuals providing data to the responsible institution for data collection at the national level).

Responsibilities to ensure that the data collected and reported meet the necessary requirements are divided between Member States and the Agency. While Member States ensure completeness and accuracy of data, the Agency provides methodology and business rules for harmonised data reporting.

Poor data quality has a negative impact on business processes and may lead to false results and mistaken strategic decisions (Haug et al., 2011).

Even though data quality measures can be assessed and fulfilled, and though current methodology for denominators allows evaluating the antimicrobial use at EU level, comparison between countries and between animal sectors should be done with great care and always be considered together with information on production animals per country, availability of medicines, as well as other factors.

Due to time constraints, and taking into account that data collection protocols and templates as well as technical specifications for data to be reported to the Agency have yet to be developed to reflect the requirements of the VMP regulation, more detailed quality specifications than provided in this point of the report cannot be proposed at this stage.

5.1. Validation and confirmation of data quality

According to the International Standards Organisation (ISO), as outlined in ISO standard 8000 (ISO, 2018), data quality is a degree to which a set of inherent characteristics of data fulfil the requirements.

Validation is a confirmation, through the provision of objective evidence, that the requirements for a specific intended use of application have been fulfilled (ISO, 2018). Applied to the reporting of antimicrobial consumption data, the ESVAC database should include validated and ready-for-use data for analysis and for use in risk assessments.

The quality of data can be defined through assessment against a list of primary indicators (Amster et al., 2014; Chen et al., 2014; DAMA UK, 2013; Haug et al., 2011; Weiskopf and Weng, 2013) such as:

- accuracy – closeness of agreement between a property value and the true value;
- completeness – quality of having all that existed in the possession of the sender at the time the data message was created (for example, the current ESVAC web application checks automatically whether all requirements of characteristics (variables) of a dataset are fulfilled);
- reliability (validity);
- relevance, and
- consistency.

Secondary measures may also be used to determine the quality of a database:

- usability of the data;
- flexibility of the data – comparability with other data; useful groups/classifications/ can the purpose be easily changed;
- confidence in the data – data governance, data protection and data security; reputation of the data, verification of the data;
- value of the data – good cost/benefit case for the data; optimal use; safety and privacy or the legal responsibilities; supporting or contradicting an image of an institution.

The value of a database strongly depends on the quality of the data contained therein. To optimise data quality, special procedures have to be followed.

According to the ISO 8000-61:2016, data quality management implementation consists of data quality planning, data quality control, data quality assurance and data quality improvement, also so called Plan-Do-Check-Act cycle.

5.2. Responsibilities of Member States

Before reporting antimicrobial consumption data to the Agency, countries have to ensure that basic requirements for these data are fulfilled– i.e. completeness, accuracy or correctness, validity and reliability.

To facilitate efficient sales and use data collection, it is a responsibility of the competent authority of each Member State to ensure and to assist the progress of data quality management and data quality control coordinating activities, as outlined in Section 3.8.2 “Terms relating to data quality” of ISO 8000 (ISO, 2018) and in the publication by Chen et al. (2014). Activities involve:

1. Comprehension of legal requirements for reporting and collection of data on consumption of antimicrobial agents for animals;
2. Development of an antimicrobial consumption data quality strategy, which should cover at least following areas of responsibilities within the national institution responsible for collecting and reporting antimicrobial consumption data:

    2.1. Management and leadership

    - The responsible organisation/ institution shall establish clearly defined objectives for data quality that are agreed at management level and define framework to monitor and review data quality.
    - Data quality should be embedded in risk management arrangements, with regular assessment of the risks associated with unreliable or inaccurate data.
    - An agreement shall be developed covering data quality with data providers, e.g. in the form of a data sharing protocol, statement, allowing necessary clarification and/or confirmation for information under question.

    2.2. Policies and practices

    - Guidance or operational procedures shall determine activities, deadlines and responsible staff dealing with data on data quality, covering data collection, recording, analysis and reporting.;
    - It is suggested to have in place data protection rules that cover the principles of lawfulness, fairness and transparency in relation to the data subject.
    - Local practices and monitoring arrangements shall be defined, including organisation of regular updates to the staff on any changes.

    2.3. Data flow and procedures

    - Systems and processes for the collection, recording, validation, analysis and reporting of data shall be developed and used with a goal to eliminate the security hazard.
    - Information systems have built-in business rules to minimise the scope for human error or manipulation and prevent erroneous data entry, missing data, or unauthorised data change.
    - Arrangements for collecting, recording, compiling and reporting data should be integrated into business planning and management processes supporting the day-to-day work of staff.

- Corporate security and recovery arrangements shall be in place covering regular tests of business critical systems to ensure that processes are secure, and results are reported to top management.

2.4. Provision of adequate human and other resources

- The responsible institution of antimicrobial data collection and reporting has to ensure that staff has the knowledge, competencies and capacity for their roles in relation to data quality.
- Clearly defined and documented roles and responsibilities incorporated into job descriptions are recommended.
- Necessary trainings have to be provided on a regular basis to ensure that the staff has the capacity and skills for the effective collection, validation, recording, analysis and reporting of data.
- Inform the Agency of any changes in regards to representatives in further communication.
- Note that Information Technology (IT) builds and owns the database and the data users take ownership of the content, therefore data quality cannot only be the responsibility of IT staff.

2.5. Data use and reporting

- The responsible institution shall ensure that internal and external reporting requirements are in line with each other.
- It is advised that data for external reporting are verified and approved, and that the management is informed and involved in approval.
- Timely feedback shall be provided to data providers.
- Responsible staff shall follow a harmonised template and protocol for data reporting to the Agency.

In order to be in possession of quality data, Member States should follow a validation process to assess the quality of each submission of data. For this purpose, Member States shall follow business rules, templates, protocols and manuals that shall be provided as part of the data system to be put in place. Appropriate training will also need to be provided. It is recommended that the necessary guidance be developed.

5.3. Responsibilities of the Agency

To ensure a harmonised approach throughout the countries participating in the ESVAC project, the Agency should define variables and characteristics to be reported and provide guidance on data submission.

An adequate interface allowing the timely electronic reporting of the collated data by the national contact point or data manager to the Agency will be required and tested in cooperation between Agency and Member States data managers, to ensure that data will be transferred accurately.

Business rules, metadata, and scientific data validation principles should be made available to the Member States by the Agency timely so that countries can use these requirements and validate antimicrobial consumption data before reporting to the Agency. As an example, for ESVAC sales data

reporting, the protocol and template and define variables and formats how data should be reported are provided by the Agency. Guidance on data submission and business rules should be reviewed and where necessary revised on an annual basis.

It is recommended that the Agency shall put in place verification activities to ensure that the design and development outputs meet the input requirements (ISO, 2015).

Validation activities are conducted to ensure that the resulting products and services meet the requirements for the specified application or intended use (ISO, 2015). Data standardisation allows creating data quality assessment tools. Business rules provide data quality assessment and following current procedure, as currently for ESVAC sales submission, an instant feedback on upload of dataset is most effective.

It is recommended that support be provided to Member States, especially those setting up new AM data collection system or those experiencing difficulties in delivering quality data, by providing necessary guidance on quality requirements, business rules and data quality management systems, and where necessary, training. Such assistance could involve, for example, organisation of visits to Member States to address quality requirements and quality management, based on the request by the concerned Member States.

Additionally, organisation of at least one network meeting per year, regular trainings for national contact points and data managers, workshops, other best practice sharing activities and missions for specific assistance to Member States to achieve the implementation of the legal requirements should be provided.

Necessary guidelines, manuals, business rules, data collection protocols and templates should be provided and maintained to aid comprehension of data quality preconditions and necessary actions to be taken.

6. Surveillance of antimicrobials used in animals, including rules on methods of gathering required data and of transferring data to the Agency

Article 57(2) of the Regulation calls on Member States to send to the Agency collated data on volume of sales and on use, per animal species or category, and per type of antimicrobial product. The Article furthermore assigns the Agency to analyse these data in cooperation with Member States and other Union agencies and publish annual reports.

The approach described in this section builds on the experience gained with the ESVAC project.

6.1. Collection of sales data

The Agency has collected harmonised data on sales for antibiotic veterinary medicinal products and some antiprotozoals (with antibiotic effect) from Member States since 2010 through the ESVAC project. Since 2015 all but one of the Member States have delivered such data to the Agency; for 2017 all Member States have delivered sales data. Thus, systems for collection of sales data are already established in all Member States. The current rules on the methods for gathering and submitting sales data to the Agency should be maintained and expanded to include antimicrobials now to be included in the data collection, or similar rules be established for any future system.

6.1.1. Data sources – sales data

The distribution of veterinary medicinal products containing antimicrobial agents may vary considerably from country to country. The first step when setting up a surveillance system of sales data on antimicrobial agents is therefore to identify and describe the distribution system for veterinary medicinal products containing antimicrobial agents (EMA/ESVAC, 2016).

The source of data may vary per Member State but the Member States have to ensure that all available data are submitted by the data providers and that submitted data cover all sales within the Member State. Moreover, because trading for example between marketing authorisation holders and wholesalers is common, Member States have to ensure that sales are reported from one defined collection or stage point to avoid double reporting, keeping in mind that the appropriate stage point may depend on the pharmaceutical form.

In the current ESVAC system, Member States collect data from marketing authorisation holders, wholesalers, retailers, feed mills, pharmacies or veterinarians. These data sources are considered as acceptable for the collection of antimicrobial sales. Reporting the sales data to ESVAC should be accompanied with information on which source has been used to collect the data.

The collection of sales data should focus only on veterinary medicinal products, as data providers may not be able to distinguish between human medicinal products sold for use in animals from products sold for use in humans.

6.1.2. Sales data to be collected and transmitted to the Agency

Each year Member States should submit to the Agency the number of packages sold for each product presentations for the relevant veterinary medicinal products covering the previous calendar year, in accordance with the technical specifications described in relevant legislation and guidelines, protocols, templates and electronic forms provided by the Agency.

In order to obtain reliable and harmonised sales data in the database of antimicrobials, a standardised data collection form for the collection of data at national level and a data protocol should be provided to the Member States. The protocol should describe the possible data sources, the antimicrobial agents to be included, the variables to be collected and the applicable rules to fill in the template correctly.

The current ESVAC system is considered as an effective system to collect sales data on antibiotics. The most recent available protocol and template serve as instructions for data to be collected and reported to the Agency. An ESVAC Data Collection Protocol (EMA/ESVAC, 2016) and an ESVAC Data Collection Form have already been developed for the current ESVAC system and the update of these documents with the inclusion of the ATCvet codes for the additional antimicrobial products would allow collecting sales data for additional antimicrobials required by the Regulation. Any future system should build on the experience gained with the current system.

Before submitting the sales data to the Agency, Member States should check and validate the data, in accordance with the technical specifications described in the relevant legislation and the guidelines, protocols, templates and/or electronic forms provided by the Agency.

6.1.3. Reporting of the sales data by the Agency

The Regulation establishes that the Agency shall publish an annual report containing data collected by the Member States. It is recommended to continue publishing the annual report on sales, describing

the veterinary antimicrobial sales for the corresponding previous year and to include a comparison with the sales for prior reporting periods.

Member States should be consulted in the preparation of the annual report.

From a technical perspective, the indicator for the reported sales data currently used is the quantity in mg of active substance adjusted by PCU (expressed in kilograms, see also point 2.3 of the Annex).

6.2. Collection of use data per animal species

To collect harmonised and standardised data per species, Member States have to set up systems enabling an exhaustive data collection of use of antimicrobials in animals.

Different approaches to collect use data on antimicrobial medicinal product per animal species can be accepted provided that:

1) data collected cover all uses of antimicrobials per animal species as indicated in Table 2;

2) data are accurate and validated;

3) data include all variables necessary for further analysis;

4) the system includes automated data entry checks to reduce errors.

6.2.1. Continuous (semi) automated collection of use data

It is acknowledged that the collection of harmonised and standardised use data per animal species, as required by Article 57 of the Regulation, is most reliably and easily achievable through (semi) automated continuous data collection systems.

Several countries have already developed and implemented (semi) automated/continuous monitoring systems to collect use data (AACTING, 2018). The use data collected in these countries typically represent prescription data, dispensed amounts, data on amounts administered by the veterinarians on the farm or data from invoices. In these countries, the use data of antimicrobials are collected from the veterinarians, pharmacies, feed mills and/or end-users (farmers, breeders). All these systems give information about the species for which the treatment was intended. Some of these systems also provide information on production type, age group, the indication, the dosages and the number of treated animals, etc.

Suitable software is needed to allow such (semi) automated continuous data collection. Precise methodology on (semi) automated collection of use data and details how to set up such systems cannot be provided in this report as circumstances between Member States vary, e.g. differences in responsibilities or (legal) requirements for distribution of antimicrobials. Therefore, practice sharing activities can help Member States decide which method would be more appropriate to their own situation and gain information on how to develop the system for use data collection. Data variables to be reported should be defined in the corresponding data collection protocol provided (see point 6.2.2. of the report).

The Agency, in coordination with national contact points, should ensure that the system for allowing electronic delivery of the use data collected by Member States, e.g. the interface or online delivery tool, allows for confidential and complete transfer of the use data, and for the uploading and checking (if collected from, e.g., Eurostat or TRACES) of the animal population data (denominator).

Regular training sessions for the data managers shall be established.

6.2.2. Use data to be collected

In order to report harmonised use data to the Agency, a data protocol and a standardised data collection form for the collection of use data per animal species or category should be provided to the Member States.

The protocol and template data collection form should serve as instructions for data to be collected at national level.

Data should be reported to the Agency by electronic route, e.g. web-based delivery, in the form of number of packages per presentation of the veterinary or human medicinal product per animal species or category used in the Member States during the data collection period. The collected raw data should be aggregated at national level at each presentation level into the total per animal species or category. The data collection period should cover one calendar year (regardless of the length of the production cycles in individual farms).

The variables that need to be provided to the Agency in order to calculate the numerator for use data in a specific animal species or categories should be aligned to those established for the collection of sales data.

6.2.3. An interim approach for estimating use per animal species

Collection of data on use of antibiotics (Table 2) will become mandatory for Member States for certain species and categories of cattle, pigs and poultry (chickens and turkeys) by 2023 (Table 3), in line with the Regulation, being voluntary before then.

Achieving full coverage and high quality use data is most easily and reliably achievable through (semi) automated systems. It is acknowledged that it will take time to develop such a system through which high quality, reliable and sustainable data can be obtained. Moreover, the development of such systems also requires Member States, among other activities, to develop specific software that is fit for purpose, to put in place the training of staff at the national competent authority as well as the training of data providers (e.g. veterinarians and farmers).

Taking these challenges into consideration, it may not be feasible for some Member States to have a system in place by 2023 that can provide full coverage and high quality, reliable and comparable data. During the discussions it was noted that the experience in France and the Czech Republic to date shows that stratification in combination with additional input, e.g. extrapolation or surveys, may provide detailed data as requested in Article 57(5)(a) of the Regulation.

Therefore, as an interim step, use data by animal species which are obtained by other methodologies than (semi) automated systems, e.g. through stratification of sales data or from representative sample surveys could be considered.

Member States not able to provide use data from (semi) automated systems, should inform the network of Member States (e.g. ESVAC Network) and the Agency in advance if data via (semi) automated systems would not be available.

The Agency together with the network of Member States would subsequently evaluate the quality of the data obtained by such other methods, in line with pre-defined rules that should include verification that data are acceptable in terms of comparability with data from other Member States.

Overall, however, it is recommended that Member States develop (semi) automated continuous data collection systems rather than spend resources on building interim systems.

6.2.3.1. Stratified sales data

Stratification of sales data of antimicrobials is an estimation of the antimicrobial use per species based on an approximate allocation of the proportion of total sales to each of the species for which an antimicrobial veterinary medicinal product is used. The Agency has published a document "Stratification of sales data of antimicrobials by species – Data collection protocol 2017" (EMA, 2018b), that describes the approach. The data output from the stratification is sales by species that represents a proxy for use data by animal species. Different methodologies or approaches may be applied:

- estimates of allocation of sales by species from marketing authorisation holders;
- data obtained from sample surveys extrapolated to overall consumption per species;
- newly build (semi) automated systems that do not yet achieve full coverage of use data, but where data can serve as a basis for extrapolation to overall consumption data by species.

If extrapolation is sufficiently justified (e.g. using the rules for correct sample survey) – this approach can be considered as motivation for countries to start building full coverage (semi) automated use data collection systems, while at the same time enabling a stepwise approach to improvement.

6.2.3.2. Representative sample surveys

For representative sample surveys on use of antimicrobials by animal species, data will have to be collected mostly manually or partly via electronic tools or via (semi) automated systems. In particular manual collection systems are time and labour consuming. For Member States collecting data from a sample survey, the animal population data relevant for the surveyed sample on antimicrobial use (number of animals sent to slaughter on the sample farms and the number of live animals present on the sample farms) would have to be collected. The Agency published a reflection paper on the collection of data on consumption of antimicrobial agents per animal species (EMA/ESVAC, 2013) that explains the role of representative sample surveys in acquiring consumption data per animal species.

It is not recommended to employ representative surveys for the collection of use data due to challenges in assessing the representativeness of population and sample size, in particular for animals where population data are very limited.

6.2.3.3. Limitations of data obtained by stratification and sample surveys

Stratification of overall sales data to obtain use estimates, and representative survey are methods that provide estimations and not methods that provide accurate data. These two methods of data collection may give data that represent a proxy of the use data, but they require a certain level of either assumption or extrapolation. There will also be significant limitations when considering the comparability with data generated by (semi)automated continuous systems.

Data on use by species based on delivered by marketing authorisation holders are estimations based on market surveys, and the information about off-label use may be insufficiently reported.

As representative sampling has certain weaknesses, sample surveys cannot be considered a fully valid method. Herds should ideally be selected on a random basis in sufficiently large numbers to enhance representativeness of the surveys and to provide reasonably accurate estimates of consumption. Whenever selection criteria such as herd size, geographical location and willingness to cooperate are applied, they may impair representativeness and reduce external validity of the collected data.

Stratification and surveys enable an indirect evaluation of use, but because it is very difficult to check the consistency and ensure the validity of the data by species, the use of such data collection models is

considered as an interim or temporary solution until collection of use data covering the whole animal population can be achieved in all the countries.

6.3. Transfer of data to the Agency

6.3.1. Transfer of sales data to the Agency

The web system developed for the current ESVAC project is proven as being robust. Any system for electronic delivery of sales data to the Agency should build on the experience gained with the ESVAC delivery tool; should a new system be developed, it should have similar characteristics. The chosen system should allow Member States to provide sales data for all additional antimicrobials to the Agency. The current web system developed by the Agency collects data at package level according to a standardised protocol and enables the validation of sales data and of population data by the Member States (EMA/ESVAC, 2016). The web system was subjected to comprehensive validation following its implementation and is considered to be straightforward to use and fit for purpose.

The sales data should be reported by the Member States according to the format that will be defined in implementing acts.

A main National Contact Point, Alternates or Data Managers for sales data should be identified in each Member States with the responsibility of collecting, validating and submitting sales data and validating the Population Correction Unit (PCU) data that is currently required for the analysis by the Agency, to allow the prompt resolution of technical questions arising in relation to the sales data.

6.3.2. Transfer of use data to the Agency

It is recommended to develop a suitable system for the electronic delivery of use data by species to the Agency.

The Member States should nominate a main National Contact Point, Alternates or Data Managers responsible for collecting, validating and submitting data on antimicrobials used in animals to the Agency on a yearly basis.

The submitted data will be used by Agency for analysis and publication.

7. Denominators and indicators for the reporting of the data

Data on antimicrobial sales

In order to normalise sales data for the animal population at risk (denominator), a methodology for a Population Correction Unit (PCU) has been established as a denominator for the reporting of sales data in the on-going ESVAC project (EMA/ESVAC, 2011). Concept and methodology are comprehensively outlined in point 2 of the Annex.

It is recommended to continue to use PCU as the denominator for reporting of sales data. Of note is that some Member States, through their ESVAC national contact points, have requested a revision of the PCU methodology, including the animal categories as well as the weights used to calculate this technical unit. Discussions on this topic are ongoing, and the outcome may result in an updated denominator for normalising the animal population at risk of being treated.

For sales data, the indicator for reporting the data (point 2.3. of the Annex) is recommended to be mg/PCU, overall and by antimicrobial class, as currently used for ESVAC sales data.

Data on antimicrobial use

Currently, the ESVAC project does not collect data on use of antimicrobials by animal species, but in the Guidance on collection and provision of national data on antimicrobial use by animal species or categories published by the Agency on 6 February 2018 (EMA, 2018a) it is suggested to use an animal species PCU as the denominator, referred to as the 'species PCU'.

It is acknowledged that there may be concerns or questions regarding the use of the species PCU as a denominator to report use data, also in relation to the objectives of the analysis, e.g., trend analysis within Member States, comparison of use of antimicrobials between Member States. It is therefore recommended to conduct a scientific assessment on different denominators and indicators for analysing use data.

Until such assessment is in place, it is suggested to apply species PCU as a denominator to normalise the use data of antimicrobial in animals**.**

For use data by species, three different indicators are recommended:

- mg of active substance adjusted by species PCU (expressed in kilograms);
- Number of Defined Daily Doses for animals (DDDvet) adjusted by species PCU (expressed in kilograms);
- Number of Defined Course Dose for animals (DCDvet) adjusted by species PCU (expressed in kilograms).

DDDvet and DCDvet have been assigned only for antibiotic VMPs for cattle, pigs and broilers (EMA/ESVAC, 2015) as represented in authorised veterinary medicinal products and for injectable preparations, oral products, intramammary products and intrauterine devices. DDDvet and DCDvet have not been assigned for topical pharmaceutical forms (dermatological products such as cutaneous sprays, ophthalmological and otological preparations) for these animal species as it is very complex to establish the dose, in line with the corresponding human DDD system[13].

In the future, DDDvet or DCDvet should be assigned for sheep, goats, rabbits, fish, horses, dogs, cats and fur animals in order to align the data for differences in dosing between the various antibiotics and pharmaceutical formulations.

[13] https://www.whocc.no/atc_ddd_index/

Annex

1. Terms of Reference for the current European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project (excerpt)

In 2008 the Agency received a request from the European Commission for the development of a data base and the collection of information on the usage of antimicrobials in animals (SANCO/E2/KDS/rz D(2008) 520915). The European Commission requested the Agency specifically:

- to identify the existing data/surveillance systems established for collection of sales and use of antibacterial drugs in the Member States;
- to develop an harmonised approach for the collection and reporting of data based on national sales figures combined with estimations of usage in at least major groups of species (poultry, veal, other ruminants, pets and fish);
- to collect the data from Member States and manage the data base;
- to draft a summary annual report with the data from Member States and publish it before the end of November of the year following the year of the monitoring.

With regard to the data collection:

- comparability with the sale/use of antimicrobials should be ensured;
- a multi-annual approach should be anticipated in order to allow the evaluation of trends. The execution may be limited in time including at least one year of monitoring but integration fo the data in a follow-up request should be foreseen.

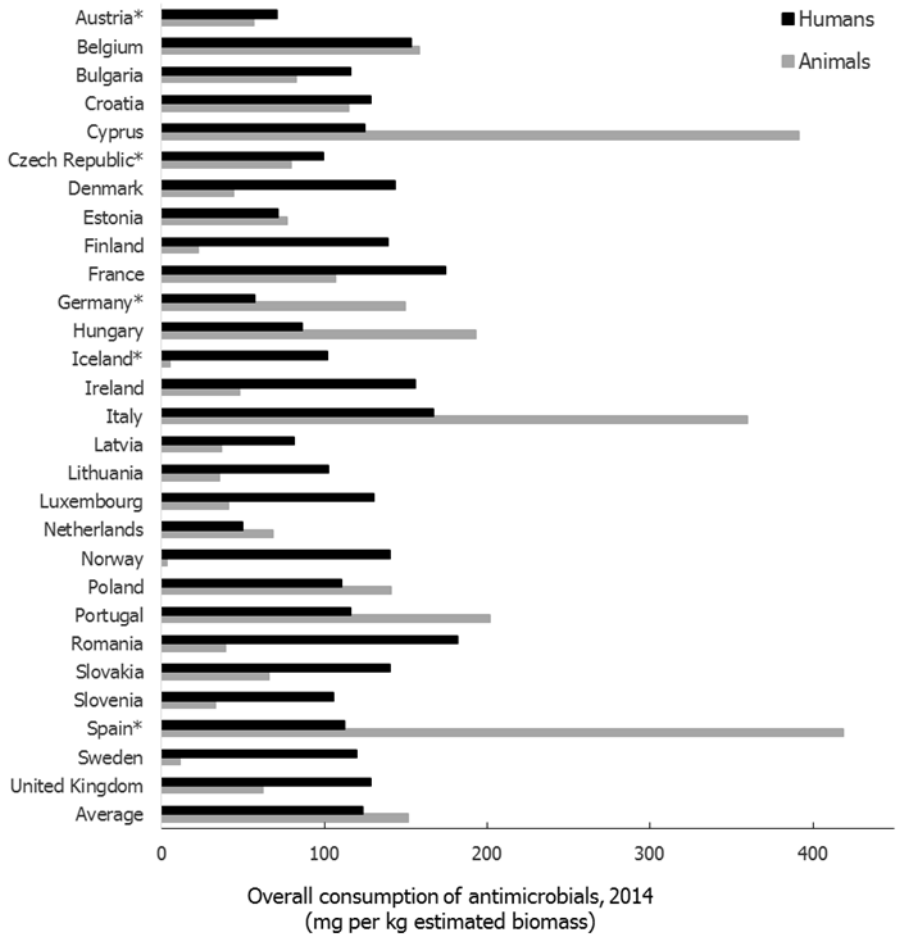
Following this request, the Agency started in April 2010 the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, which collects information on how antimicrobial medicines are used in animals across the European Union.

Comparability with human data

The Terms of Reference of the mandate establish the need of comparability with the sale/use of antimicrobials in humans.

In the ECDC/EFSA/EMA Second Joint Report on the Integrated Analysis of the Consumption of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Humans and Food-producing Animals (JIACRA II) (ECDC/EFSA/EMA, 2017) comparison between consumption of antimicrobials in humans and food-producing animals has been presented as shown in Figure A1. To have comparable data across the animal and human sectors is vital for the future JIACRA reports according to Article 57(1)(u)of the Regulation (EC) 726/2004 as amended.

Figure A1. Comparison of biomass-corrected consumption of antimicrobials (milligrams per kilogram estimated biomass) in humans and food-producing animals by country, EU/EEA MS, 2014 (Figure 6 in (ECDC/EFSA/EMA, 2017).



Asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector antimicrobial consumption of the 2014 total national antimicrobial consumption for EU/EEA Member States that provided data for both sectors is 10%.
Note: 1) The estimates presented are crude and must be interpreted with caution. For limitations that hamper the comparison of consumption of antimicrobials in humans and animals
2) The average figure represents the population-weighted mean of data from included countries.

Of note is that in the Regulation, comparability with data on sales and use of antimicrobials in human medicine is not mentioned. However, in order to perform an integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals it is important that the consumption data obtained from the animal and human sector are comparable to the extent possible.

It is suggested that the data collected on sales of antimicrobials and use of such products by animal species should, to the extent possible, be harmonised with the data collected for humans.

2. Surveillance of antimicrobial consumption in animals at EU level - current and suggested systems

2.1. Antimicrobials included in the collection of antimicrobial sales data for animals (ESVAC)

Data collected represent overall national sales and the ATCvet classes and subclasses for which antibacterial veterinary medicinal products are collected in the current ESVAC project (EMA/ESVAC, 2018) are shown in Table A1. Of note is that these include only antimicrobials belonging to antibiotics.

Table A1. Categories and ATCvet codes[14] of antimicrobial veterinary medicinal products included in the ESVAC data

Categories of veterinary antimicrobial agents	ATCvet codes
Antibiotics; sulfonamides for intestinal use	QA07AA; QA07AB
Antibiotics for gynaecological and antibacterials for intrauterine use	QG01AA; QG01AE; QG01BA; QG01BE; QG51AA; QG51AG
Antibacterials for systemic use	QJ01
Antibacterials for intramammary use	QJ51
Antibacterial agents belonging to antiparasitics[(a)]	QP51AG

[(a)] Solely sulfonamides

The sales data are reported in a stratified manner – i.e. sales for food-producing animals and sales for companion animals (tablets).

2.2. Denominator ESVAC sales data

In order to normalise the sales data for the animal population at risk of being treated with the antimicrobial in question (denominator) a population correction unit (PCU) has been established as a denominator for the reporting of ESVAC sales data. The data sources used and the methodology for the calculation of PCU are comprehensively described in Appendix 2 of the Agency's report 'Trends in the sales of veterinary antimicrobial agents in nine European countries: 2005-2009' (EMA/238630/2011), (EMA/ESVAC, 2011). It must be emphasised that the PCU is purely a surrogate for the animal population at risk.

The methodology is as follows: The PCU for each animal category is calculated by multiplying numbers of livestock animals (dairy cows, sheep, sows and horses) and slaughtered animals (cattle, goat, pigs, sheep, poultry, rabbits and turkeys) by the theoretical weight at the most likely time for treatment. However, due to the limited availability of living goat data in Eurostat, this category was not included when the PCU methodology was established for the first ESVAC report (EMA/ESVAC, 2011).

For animals exported or imported for fattening or slaughter (cattle, goat, pigs, sheep and poultry), the PCU was calculated by multiplying the number of animals by a standardised weight.

For farmed fish, Eurostat data are given only as live-weight slaughtered rather than numbers of animals slaughtered, and thus for fish biomass live-weight slaughtered is used for calculation of the total PCU. The PCU of the animals exported for fattening or slaughter in another Member States – i.e. cattle, pigs, poultry, goats and sheep - was added to the PCU of livestock and slaughter animals in the country of origin because young animals are typically treated more frequently than other age classes. The PCU for animals imported for fattening or slaughter in another Member State was subtracted from the total PCU of livestock and slaughter animals, since it is included in the data on slaughter animals

[14] Available online: www.whocc.no/atcvet/

(Eurostat data) in order to avoid double counting (counting by both the exporting and importing country).

The PCU is calculated for each species, weight class and/or production type, as follows:

PCU domestic

- Number of animals slaughtered × estimated weight at treatment
- Number of livestock × estimated weight at treatment

PCU export

- Number of animals transported to another country for fattening or slaughter × estimated weight at treatment

PCU import

- Number of animals imported from another country for fattening or slaughter × estimated weight at treatment

Total PCU is calculated as follows: PCU = total $PCU_{Domestic}$ + total PCU_{Export} – total PCU_{Import}

The total PCU by country is calculated according to the above data.

1 PCU = 1 kg of animal biomass.

Eurostat, the Statistical Office of the European Union, covers data on numbers of food-producing animals slaughtered, as well as numbers of livestock animals. Therefore, Eurostat[15] was selected as the source for these data. If data were not available in Eurostat (e.g. for rabbits and fish), national statistics were applied. In addition, national statistics on animal categories were applied for non-EU countries: Iceland, Norway and Switzerland, as data for these countries are not available from Eurostat. For horses (food-producing species according to EU legislation), national statistics provided by the ESVAC national contact points were used. Data on dogs and cats are not available in all participating countries as these species are not currently included in the PCU. As tablets are typically approved only for companion animals, this pharmaceutical form was excluded from the data sets prior to the normalisation of the sales by the PCU.

The Eurostat data on numbers of cattle, pigs, poultry, sheep and goats exported or imported for fattening or slaughter might not be complete, as exports and imports are only reported above a certain amount. Therefore, data were obtained from TRACES (TRAde Control and Expert System run by the European Commission's DG SANTE), as these are based on health certificates, which are obligatory for all animals crossing any border, and thus the data are complete.

Outside the European region, Canada (Government of Canada, 2018) and Thailand (HPSR-AMR, 2018) applies the ESVAC denominator (PCU), which allows for reporting data that are comparable with these countries.

It is recommended to continue using PCU as denominator for the sales data.

Of note is that the PCU is currently undergoing revision with regard to animal categories to be included as well as the animal weight used to calculate the PCU values.

[15] https://ec.europa.eu/eurostat/

2.3. Indicator ESVAC sales data

Based on the assumption that tablets are almost solely used for companion animals (boluses in food-producing animals), tablets are excluded from the dataset used to report sales for food-producing animals. Sales data for tablets are reported separately as sales for use in companion animals; all other pharmaceutical forms are reported as sold for use in food-producing animals, including horses. Of note is that some of the sales allocated for food-producing animals could be for non-food-producing animals such as fur animals. The main indicator applied in this report to express the consumption of veterinary antimicrobials is mg active ingredient normalised by the population correction unit (mg/PCU):

$$\frac{\text{Amount sold in tonnes} \times 10^{\wedge 9}}{\text{PCU in kg}}$$

2.4. Criteria for the selection of data sources for animal populations

The selection of data sources on animal species population or weight slaughtered for the estimation of PCU for food-producing animals in ESVAC was made based on the following criteria:

1. Collection of the data should be harmonised between countries.
2. The methodology for collection and reporting of the data should be transparent.
3. The data should be validated at regular intervals.

Eurostat covers data on numbers and biomass slaughtered of food-producing animals, and these data comply with the abovementioned criteria. Therefore, Eurostat was selected as the data source for data on this animal category. For livestock horses, national statistics were used. For farmed fish, horses and rabbits, and for some countries also sheep, national statistics were applied. Data on dogs and cats are not available in all Member States, so these species were not included in the PCU in order to achieve harmonised animal population statistics across all Member States for further analysis.

Volume of antimicrobial agents used per country is also linked to numbers of animals exported for fattening or slaughter in another Member State. Such animals are likely to have been treated with antimicrobial agents in the country of origin, whereas the number of animals is eventually included in the Eurostat data for the importing country, e.g., as number of animals slaughtered and biomass slaughtered (carcass weight). This artificially distorts data in exporting countries (higher sales values, lower animal numbers and biomass values) as well as in importing countries (lower sales values, higher animal numbers and biomass values). In ESVAC it was deemed necessary to correct for this effect for the major animal species (cattle, pigs, poultry and sheep) by deducting the number of imported animals per each PCU category. However, Eurostat reports data on numbers of animals exported or imported for fattening or slaughter to or from other countries only when they are above a certain level, not when trade is low. This implies that Eurostat data will represent an underestimate of import and export of animals for most species and countries. These intra-Union animal trade data are therefore obtained from TRACES. As the numbers of animals moved between the EU countries are based on health certificates, an obligatory requirement for all animals passing any border, they are considered to represent valid information on intra-EU animal trade since 2006. TRACES is designed to track the movements of animals, semen and embryo, food, feed and plants, so for reasons of data protection, access to this system is limited to competent authorities and other users representing involved trading parties.

For animal species for which data on the animal population is not available, national statistics are used, provided to ESVAC by the national contact point (indicating the data source).

2.5. Animal species and categories to be included in the surveillance

The animal groups/species for which the data on animal population is known as being available is shown in Table A2.

Table A2. Animal categories of food-producing animals for which reference data are available in the Eurostat database[16]

Animal species or group	Animal including fish species	PCU methodology developed
Cattle	*idem*	Yes
Pigs	*idem*	Yes
Poultry	Chickens	Yes
	Ducks	No[(b)]
	Turkeys	Yes
	Other poultry (e.g. geese)	No
Goats	*idem*	Yes
Sheep	*idem*	Yes
Fish[(a)]	Finfish[(c)]	Yes

[(a)] Up to now the publication of data is delayed so national data have been used for the ESVAC sales data in order to allow for a timely publication;
[(b)] Regarded as feasible;
[(c)] See text below

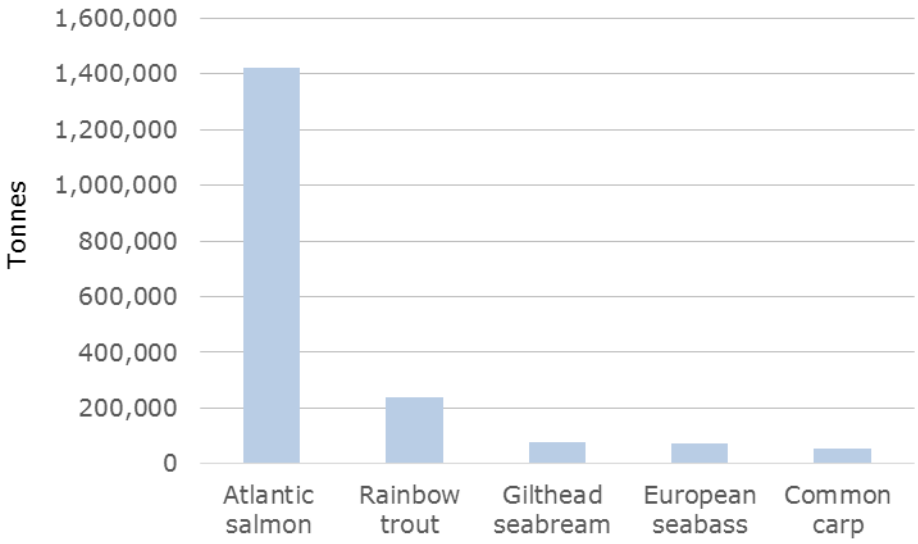
The number of farmed fish species for which the production volume is reported to Eurostat is high and it would not be feasible to collect data for all these fish species (Eurostat, website, last accessed in 2019). As such, it was not possible within the timeframe to analyse the data from Eurostat to identify the major fish species. Therefore, we used information on which, in 2016, were the ten "top" fish species in terms of production volume as published by European Market Observatory for Fisheries and Aquaculture Products (EUMOFA) (European Commission DG MARE, 2017).

In 2016, these top ten fish species accounted for 2 469 288 tonnes; of these, production of mussels, oysters and shells (in total five species) accounted for 19% of the production volume, and 81% is for finfish. However, due to the production system (semi-free ranching) and the characteristics of mussels, oysters and shells – i.e. their nutrients consist of plankton and other microscopic sea creatures which are free-floating in seawater (filtered from the water) – it is suggested that antibiotics are not used at all in these species. Thus, these are excluded as candidates for surveillance of antimicrobial consumption.

The five top finfish species represent the fish species aggregated for 28 countries reporting in ESVAC in 2016 as shown in Figure A2. Of note is that proportion accounted for by each species may vary considerably between countries. Through this approach it was not possible to identify whether one or more countries have a high production of other finfish species than those included in Figure A2. In order to avoid missing information from such countries or instances**,** it is suggested to collect data for finfish in general.

[17] https://ec.europa.eu/eurostat/data/database

Figure A2. Production volumes (tonnes) of the top five finfish species produced in aquaculture in 28 EU/EEA countries in 2016



Due to time constraint, it was not possible to collect information for which other food-producing species, in addition to those given in Table A3, data on animal population are available at national level. However, since data are not collected at EU level, it indicates that "other" food-producing animal species account for a minor contribution to the "food basket" and thus that the impact on public health from bacteria resistant to antimicrobials that could occur in e.g. meat from such minor species is insignificant.

The inclusion of horses and food-producing rabbits in the denominator (PCU) for the reporting of sales of antimicrobial veterinary medicinal products in the 1st ESVAC report was based on input from the Member States at that time.

In 2015, the Agency published a reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP, 2015). Among others, it was indicated that an important knowledge gap was the lack of data on usage in companion animals, including off-label use (e.g. use of human medicinal products). Such data would allow for a better understanding of the potential for transfer of antimicrobial resistance between companion animals and humans and thereby suggest management measures to limit such transfer.

This is largely addressed through the Regulation's requirement for reporting use data by animal species in other animals bred or kept, the most relevant companion animal species being dogs, and cats. It was not possible within the timeframe for developing this report to investigate if, e.g., other companion animals like hamsters, guinea pigs, mice, rats etc. would be relevant for the collection of use data and if data on the number of animals would be available.

Table A3. Animal species and categories, and fish categories for which the data on antimicrobial consumption is suggested to be collected

Animal group or species	Animal or fish species	PCU methodology developed	Availability national level / "quality"
Horses	*idem*	Yes	For some countries, based on sample surveys undertaken at regular intervals
Rabbits (food-producing)	*idem*	Yes	Likely to be available from countries with a relatively high production
Fish	All finfish[(a)]	Yes	Likely to be available from countries with a relatively high production
Cats	*idem*	No[(b)]	Not available in all countries; available data may represent underestimates
Dogs	*idem*	No[(b)]	Not available in all countries; available data may represent underestimates
Fur animals	Minks	No[(b)]	Likely to be available from countries with a relatively high production
Fur animals	Foxes	No[(b)]	Likely to be available from countries with a relatively high production
Any other food-producing species	To be specified	No	Likely to be available at national level for those food-producing species which are of importance in country

[(a)] Information on which fish species can be identified here: https://ec.europa.eu/eurostat/data/database
[(b)] Feasible if data on numbers are available

3. Surveillance systems and data currently available for integrated analysis at EU level

3.1. Antimicrobials included for collection of antimicrobial consumption in humans (ESAC-Net)

Data collected represent overall national sales and the ATC classes/subclasses listed in the ESAC-Net protocol (ECDC, 2019c) are shown in Table A4. Antimicrobials for intestinal use and systemic use include only substances with antibacterial effect referred to as antibiotics).

Antimicrobial consumption data for antibiotics are published annually and have full coverage for the community sector, while for the hospital sector not all Member States provides data (ECDC, 2018a).

Table A4. Categories and ATC codes of human medicinal products included in the ESAC-Net data collection protocol (ECDC, 2019c)

Categories of human antimicrobial agents	ATC codes
Antimicrobial agents for intestinal use	A07AA
Antimicrobial agents for systemic use	J01
Antimycotics for systemic use	J02; D01BA
Drugs for treatment of tuberculosis	J04A
Antivirals for systemic use	J05

Although referred to in the ESAC-Net protocol, data on antimicrobial consumption for antimycotics, antivirals and drugs for treatment of tuberculosis are not provided by all Member States on annual basis, as reporting of such data are done on voluntary basis.

Preparations for topical treatment (dermatological preparations and preparations for sensory organs) are not included in the ESAC-Net protocol (ECDC, website, last accessed in 2019).

3.2. Current surveillance of antimicrobial resistance in the animal sector at EU level (EFSA)

The monitoring of antimicrobial resistance in animals is performed at the level of the major food-producing animal production categories, such as broilers, laying hens, fattening pigs, fattening turkeys and bovines under 1 year of age (EFSA, 2019). Table A5 shows animal species and categories for which it is mandatory to collect data on antimicrobial resistance.

Table A5. Animal species and categories for which it is mandatory to collect data on antimicrobial resistance[1]

Bacteria	Animal species / Food categories
Salmonella spp.	Laying hens, broilers, fattening turkeys
	Carcases of broilers, fattening turkeys, fattening pigs and bovines under 1 year of age
Campylobacter jejuni	Broilers, fattening turkeys, fattening pigs[(a)]
Indicator *E. coli*	Broilers, fattening turkeys, fattening pigs, bovines under one year of age[(b)]
	Fresh broiler meat, pig meat and bovine meat[(b)]
Indicator *enterococci*[(c)]	Broilers, fattening turkeys, fattening pigs, bovines under 1 year of age

Note: In the years 2014, 2016, 2018 and 2020: for laying hens, broilers and fresh meat thereof, and fattening turkeys.
In the years 2015, 2017 and 2019: for pigs, bovines under 1 year of age, pig meat and bovine meat.
[(a)]: If a Member State decides to test for antimicrobial resistance in C. *coli* on a voluntary basis.
[(b)]: For the purpose of monitoring of ESBL- or AmpC- or carbapenemase-producing *E. coli*.
[(c)]: If a Member State decides to test for antimicrobial resistance in *E. faecalis* and *E. faecium* on a voluntary basis.
[1] Table 3 from the "Manual for reporting on antimicrobial resistance within the framework of Directive 2003/99/EC and Decision 2013/652/EU for information derived from the year 2018" (EFSA, 2019)

Monitoring of presumptive ESBL-, AmpC- or carbapenemase-producing Salmonella mentioned above, is derived from 'routine monitoring'.

3.3. Current surveillance of antimicrobial resistance in the human sector at EU level (EARS-Net)

Data from isolates collected in hospitals (blood stream and cerebrospinal fluid) are subject of the EARS-Net is shown in Table A6, as stated in the antimicrobial resistance reporting protocol (ECDC, 2018c)

Table A6. Microorganism and antimicrobial group combinations under regular EARS-Net surveillance[1]

Microorganism	Antimicrobial group
Escherichia coli (ESCCOL)	Aminopenicillins
	Fluoroquinolones
	Third-generation cephalosporins
	Aminoglycosides
	Carbapenems
	Polymyxins
Klebsiella pneumoniae (KLEPNE)	Fluoroquinolones
	Third-generation cephalosporins
	Aminoglycosides
	Carbapenems
	Polymyxins
Pseudomonas aeruginosa (PSEAER)	Piperacillin+/- tazobactam
	Ceftazidime
	Fluoroquinolones
	Aminoglycosides
	Carbapenems
	Amikacin
	Polymyxins
Acinetobacter spp. (ACISPP)	Fluoroquinolones
	Aminoglycosides
	Carbapenems
	Amikacin
	Polymyxins
Streptococcus pneumoniae (STRPNE)	Penicillins
	Macrolides
	Fluoroquinolones
	Third-generation cephalosporins
Staphylococcus aureus (STAAUR)	MRSA
	Rifampicin
	Fluoroquinolones
Enterococcus faecalis (ENCFAE) and *Enterococcus faecium* (ENCFAI)	High-level aminoglycoside resistance
	Vancomycin
	Aminopenicillins

[1] TESSy Antimicrobial resistance reporting protocol 2018 (ECDC, 2018c), Table 5

3.4. Summary of data currently available for integrated analysis at EU level

As shown in Table A7, antimicrobial resistance data from the animal sector is currently available only for antibacterials and for food-producing animals. As long as data on antimicrobial resistance is not collected for other antimicrobials, e.g. antimycotics and antivirals, in the animal sector, the antimicrobial consumption data obtained from the animal sector for antimycotics and antivirals may not be used for integrated analysis. It is suggested to prioritise the collection of antimicrobial consumption data for antibacterials in the animal sector as a first step.

Table A7. Surveillance data currently collected on antimicrobial resistance and antimicrobial consumption in the animal and human sector in the EU

Surveillance data in EU Member States	Animals		Humans
	Antimicrobials		Antimicrobials
Antimicrobial resistance data	Food-producing animals	Antibiotics[a]	Antibiotics[c]
			Antivirals[c,d,e]
			Drugs for treatment of tuberculosis[f]
Antimicrobial consumption data	All animals (sales stratified into food-producing and companion animals)	Antibiotics[b] for systemic, intramammary and intrauterine use	Antibiotics for systemic use[g]
			Antimycotics and antifungals for systemic use[g]
			Antivirals for systemic use[g]
			Drugs for treatment of tuberculosis

[a] Tables 14-18 from the "Manual for reporting on antimicrobial resistance within the framework of Directive 2003/99/EC and Decision 2013/652/EU for information derived from the year 2018" (EFSA, 2019)
[b] Web Based Sales Data and Animal Population Data - Collection Protocol (version 2)(EMA/ESVAC, 2016)
[c] TESSy Antimicrobial resistance reporting protocol (ECDC, 2018c) and collection of antivirals commenced in 2019 for surveillance of 2018 data
[d] TESSy - HIV Drug Resistance Reporting Protocol and Analysis Plan 2019 - HIV drug resistance surveillance data for 2018 and historical data (ECDC, 2019a)
[e] TESSy - Influenza Reporting Protocol 2018 - Seasonal influenza (ECDC, 2018d)
[f] TESSy - Tuberculosis Reporting Protocol 2019 - Surveillance data for 2018 (ECDC, 2019b)
[g] TESSy - Antimicrobial consumption data collection protocol (ECDC, 2018b), it has to be taken into account that data are provided by Member States on voluntary basis

4. Surveillance of antimicrobial consumption at global level

4.1. OIE: Antimicrobials included in the antimicrobial sales data collection

The OIE collects data on antimicrobial agents intended for use in animals from countries members of the OIE (OIE, 2018). The antimicrobials collected are those listed in the OIE list of antimicrobial agents of veterinary importance (OIE, 2007) and certain antimicrobials only used for growth promotion. The antimicrobials are listed according to names of classes and subclasses while the corresponding ATCvet codes are not given.

The Guidance for completing the OIE template for the collection of data on antimicrobial agents intended for use in animals (OIE, 2018) provides detailed information about the OIE collection system, including definitions (e.g. active ingredient, antimicrobial agent, antimicrobial classes), required information and options for reporting.

The antimicrobials included in the OIE report cover those currently included in the ESVAC project as shown in Table A8.

Table A8. Classes of antimicrobial agents for reporting to the OIE (OIE, 2018)

Antimicrobial class	Guidance
Aminoglycosides	Includes aminocyclitols (e.g., streptomycin, dihydrostreptomycin and spectinomycin) and all other aminoglycosides (e.g., gentamicin, kanamycin, neomycin, apramycin).
Amphenicols	Includes florfenicol and thiamphenicol.
Arsenicals	Includes nitarsone, roxarsone and others.
Cephalosporins	May be reported as Cephalosporins (all generations) or in relevant category groupings (1-2 generation cephalosporins and 3-4 generation cephalosporins).
Fluoroquinolones	Includes danofloxacin, difloxacin, enrofloxacin, marbofloxacin and other fluoroquinolones, but not other quinolones (e.g., flumequine, oxolinic acid, nalidixic acid), which are reported separately
Glycopeptides	Includes avoparcin and others.
Glycophospholipids	Includes bambermycin (i.e., flavomycin).
Lincosamides	Includes lincomycin, pirlimycin and others.
Macrolides	Includes substances with all macrolide structures, such as erythromycin, spiramycin, tylosin, tylvalosin, gamithromycin, tildipirosin, tulathromycin and others.
Nitrofurans	Includes furazolidone, nitrofurantoin, nitrofurazone and others.
Orthosomycins	Includes avilamycin and others.
Other quinolones	Includes flumequine, nalidixic acid, oxolinic acid and others.
Penicillins	Includes all penicillins (e.g., natural penicillins, aminopenicillins and others), but excludes other beta lactam antimicrobials like cephalosporins
Pleuromutilins	Includes tiamulin, valnemulin and others.
Polypeptides	Includes bacitracin, colistin, polymyxin B and others.
Quinoxalines	Includes carbadox, olaquindox and others
Streptogramins	Includes virginiamycin, pristinamycin, and others
Sulfonamides (including trimethoprim)	Includes all sulfonamides, as well as trimethoprim and similar compounds.
Tetracyclines	Includes chlortetracycline, doxycycline, tetracycline, and oxytetracycline
Others	All others not covered, including coumarin antimicrobials, e.g., novobiocin, fusidic acid, kirromycins, phosphonic acids like fosfomycin, rifamycins, thiostrepton.
Aggregated class data	It may not be possible to individually report sales by class name for one or more antimicrobial classes for animal use (e.g., to protect confidential (proprietary) information or as required by legislation). Such amounts may be reported in this line. Report here the individual or cumulative amounts of antimicrobial classes used in animals that cannot be reported independently for confidentiality / proprietary reasons. If more than one data aggregation exists in your country, please sum them up for the OIE template. In cases where the amounts sold for more than one class are reported as aggregated data, please enter in the table for those substances for which sales quantities have been included in the aggregated amount, and list the names of the classes of antimicrobial agents that cannot be reported individually in the free-text field called 'If 'Aggregated class data' are reported, please list here the classes combined' located underneath the table collecting the antimicrobial quantities

4.1.1. OIE: Denominator used to report antimicrobial sales data

For OIE, the animal biomass - denominator- is calculated as the total weight of the live domestic animals in a given population, used as a proxy to represent those likely exposed to the quantities of antimicrobial agents reported. Animal biomass was therefore calculated for food-producing species of countries reporting quantitative data for the year 2014, primarily using data from the OIE World Animal Health Information System (WAHIS) and the Food and Agriculture Organization Statistics (FAOSTAT) (OIE, 2017). The methodology and animal population used to calculate the OIE-denominator differs slightly from the calculation of the ESVAC denominator (PCU) and thus the denominator as such differs slightly.

4.1.2. OIE: Indicator used to report antimicrobial sales data

Quantitative data reported on antimicrobial agents intended for use in animals is adjusted for animal biomass according to the following indicator:

$$\frac{antimicrobial\ agents\ reported\ (mg)}{animal\ biomass\ (kg)}$$

This indicator corresponds to the indicator used to report sales data collected in the ESVAC project. However, the animal categories included in the calculation of the denominator (animal biomass) as well as the weights used, differ to a certain extent. Therefore, data on antimicrobial consumption collected by OIE and ESVAC are not directly comparable.

4.2. WHO: Antimicrobials included in antimicrobial consumption data collection

The collection of data on antimicrobial consumption in human medicine by WHO (WHO, 2018b) covers the same antimicrobials as ESAC-Net (Table A10); in additional antimalarials are included. Of note is that for some of the antimicrobials it is optional for the WHO member states to provide data.

Table A9. Core and optional classes of antimicrobials in the WHO global surveillance programme of antimicrobial consumption (refers to table 3.1 of WHO report (WHO, 2018b))

Class of antimicrobials	ATC	Monitoring
Antimicrobials for systemic use	J01	Core
Antibiotics for intestinal tract	A07AA	
Nitroimidazole derivates	P01AB	
Antimycotics for systemic use	J02	Optional
Antifungals for systemic use	D01BA	
Antivirals for systemic use	J05	
Antimycobacterials for treatment of tuberculosis	J04A	
Antimalarials	P01B	

Acronyms and definitions

Acronym / term	Full name (if applicable)	Definition or explanation (as appropriate)
Antimicrobial		Any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and antiprotozoals[17]
Antimicrobial consumption		Amounts of antimicrobials consumed, includes sales and use data for antimicrobial medicinal products
Antimicrobial sales		Sales data for antimicrobial veterinary medicinal products obtained from marketing authorisation holders, wholesalers, retailers, pharmacies, feed mills
Antimicrobial use		Amounts of antimicrobials prescribed, administered, delivered and/or purchased for animals
Antimicrobial resistance		The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species[18]
ATC	Anatomical Therapeutic Chemical classification	The Anatomical Therapeutic Chemical (ATC) classification system for medicines developed and maintained by the WHO Collaborating Center for Drugs Statistics Methodology, the Norwegian Institute of Public Health (https://www.whocc.no/)
ATCvet	Anatomical Therapeutic Chemical veterinary classification	The ATC classification system for veterinary medicines maintained by the WHO Collaborating Center for Drugs Statistics Methodology.
CVMP	Committee for Medicinal Products for Veterinary Use	The Agency's scientific committee responsible for providing advice in relation to the evaluation and use of

[17] Article 4 (12) of Regulation (EU) 2019/6 of the European Parliament and the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
[18] Article 4 (11) of Regulation (EU) 2019/6 of the European Parliament and the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Acronym / term	Full name (if applicable)	Definition or explanation (as appropriate)
		veterinary medicines
DDDvet, DCDvet	Defined Daily Doses for animals (DDDvet), Defined Course Dose for animals (DCDvet)	Established for the reporting of data on antimicrobial consumption by animal species in the ESVAC system. The aim is to provide standardised fixed units of measurement for reporting that takes into account differences in dosing.
ECDC	European Centre for Disease Prevention and Control	
EFSA	European Food Safety Authority	
ESAC-Net	European Surveillance of Antimicrobial Consumption Network	A Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption in human medicine, coordinated by the ECDC.
EARS-Net	European Antimicrobial Resistance Surveillance Network	EARS-Net is a European network for antimicrobial resistance surveillance. It monitors seven bacterial pathogens commonly causing infections in humans in Europe, and includes routine clinical antimicrobial susceptibility data from local and clinical laboratories reported to ECDC by appointed representatives from the Member States. Only data from invasive isolates (blood and cerebrospinal fluid) are included.
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption	Project coordinated and maintained by the European Medicines Agency, at the request from the European Commission that collects information on sales of antibacterial veterinary medicinal products across the European Union.
Numerator		In the context of this document: Amounts of antimicrobials sold or used.
Denominator		In the context of this document: Animal population at risk for being

Acronym / term	Full name (if applicable)	Definition or explanation (as appropriate)
		treated (with an antimicrobial).
Indicator		In the context of this document: Measurement to evaluate exposure to antimicrobials.
Eurostat		The statistical office of the European Union
JIACRA	Joint inter-agency antimicrobial consumption and resistance analysis	ECDC/EFSA/EMA joint reports on the integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals
Medicinal products for topical use		Antibiotics and chemotherapeutics for dermatological use; nasal preparations; ophthalmological antiinfectives; otological antiinfectives.
Marketing Authorisation Holder		In the context of this document: A company, firm or non-profit organisation that has been granted a marketing authorisation for a medicinal product (veterinary or human use) in the EU.
Maximum Residue Limit		Maximum allowed concentration of defined residues of a veterinary medicine in a food product obtained from an animal that was treated with the veterinary medicine in question.
OIE	World Organisation for Animal Health	
PCU	Population Correction Unit	Denominator developed for the reporting of data on sales of veterinary antibiotics in the ongoing ESVAC project (EMA/ESVAC, 2011). Concept and methodology are outlined in point 2 of the Annex to this report.

Acronym / term	Full name (if applicable)	Definition or explanation (as appropriate)
TRACES	Trade Control and Expert System	The European Commission's online management tool for sanitary requirements on intra-EU trade and importation of animals, semen & embryos, food, feed & plants
Veterinary Medicinal Product		A substance or combination of substances authorised to treat, prevent or diagnose disease in animals. The current requirements and procedures for granting marketing authorisations for veterinary medicinal products are laid down primarily in Directive 2001/82/EC and in Regulation (EC) No 726/2004
WHO	World Health Organisation	

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