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Guidance on collection and provision of national data on antimicrobial use by animal species/categories

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guidance on collection and provision of national data on antimicrobial use by animal species/categories

Table of contents

Executive summary

This guidance document defines the data which could be provided in the future to the European Medicines Agency (EMA) by countries collecting antimicrobial use data by animal species/category. It can be read in conjunction with the Question and Answer document (EMA/716249/2016) which contains the rationale behind various decisions taken during the drafting of the guidance. As per the current legal provisions, monitoring of veterinary antimicrobial use is not mandatory at EU/EEA level (nevertheless, nearly all EU/EEA countries provide data on overall sales of veterinary antimicrobial agents to EMA for the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project). This guidance document may be subject to revision pursuant to changes in the applicable legal provisions and on the basis of experience gained with the application of this guidance, as the case may be.

Chapter 1 details the objectives of the guidance, which should enable EMA to collate, analyse and report harmonised and standardised data – to the extent possible – on antimicrobial use by animal species/category in MSs and across time periods. It further details the scope, in terms of species/categories and data coverage, and for whom the guidance document is intended.

Chapter 2 of the guidance document covers the antimicrobial use and animal population data that would have to be provided to EMA by MSs wishing to do so, for the purpose of reporting antimicrobial use by animal species/category. Data could be provided to EMA to establish antimicrobial use in pigs, broilers, turkeys, bovine animals slaughtered below one year of age, dairy cattle and beef cattle. Data collection by species should involve at least the same antimicrobial categories (ATCvet groups) as covered by the ESVAC sales data collection (antimicrobials for use in animals, except dermatological preparations and preparations for sensory organs (ophthalmological and otological preparations)). The data collection period should cover one calendar year, and data could be provided annually or on alternating years per species, following the antimicrobial resistance monitoring in accordance with the Commission Implementing Decision 2013/652/EU. Data could be collected using a census model (where data collection covers (practically) a whole animal production sector in a country) or a sample survey model by collecting data from a well-designed random selection of farms. For data management purposes and to ensure completeness of the data, antimicrobial use data would have to be provided to EMA by use of a template developed and provided by EMA. Data could be provided in the form of total volume or weight used per veterinary medicinal product (VMP) or the number of packages used in the MS per VMP presentation per animal species/category. For MSs collecting data using a census model, the size of the animal population at risk of being treated with antimicrobial agents would be established by considering the number of animals slaughtered in the MS and, where appropriate, the number of live animals in the MS (dairy cows and breeding sows). These data would be collected by EMA from Eurostat and TRACES animal population statistics. For MSs collecting data from a sample survey, the animal population data (number of animals sent to slaughter on the sample farms and the number of live dairy cows and live breeding sows present on the sample farms) would have to be collected from other sources by the authorities of participating MSs.

Chapter 3 describes the indicators that would be used to report the data (mg, number of animal Defined Daily Doses (DDDvet) and number of animal Defined Course Doses (DCDvet) per species Population Correction Unit (species PCU, kg)) per animal species/category. The chapter further explains why descriptions of the national data collection systems will be reported as well, and how data protection and confidentiality will be ensured.

The Annexes provide information on use and benefits of use data by species (Annex 1), further details on collection of data at national level, including information on how to set up a system (Annex 2),

variables on the description of the national systems (Annex 3), approach to establish a representative sampling design (Annex 4), overview of variables and data to be provided to EMA (Annex 5), links to reports and guidelines for existing data collection systems (Annex 6) and details on the ESVAC species Expert Advisory Group (Annex 7).

1. Introduction

1.1. Background of ESVAC data collection by species

Since 2011, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) activity from the European Medicines Agency (EMA) annually reports national sales figures of veterinary antimicrobial agents in food-producing animals (overall sales data[1]). The mandate from the European Commission on the collection of national sales figures further included the estimation of use for the major groups of food-producing animals in the European Union/European Economic Area (EU/EEA). The 'Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals (EMA/286416/2012-Rev.1)' suggested that use data by species preferably should be collected at farm level. The objective for collecting these data would not only be to analyse these data in combination with data on the occurrence of antimicrobial resistance (AMR) in those animal species, but also to enable monitoring of patterns of antimicrobial use over time and the effect of implemented measures regarding, for example, prudent use of antimicrobials. Detailed information on the use and benefits of collecting use data by species at EU/EEA and at national level is provided in Annex 1.

A well-established data collection system providing representative and validated data will enable an accurate estimate of the use of antimicrobial agents. In recent years, such data collection systems have been implemented or are under development in several EU/EEA Member States (MSs). These data collection systems currently differ in a variety of key elements: animal species/category monitored, coverage of animal production, data sources, variables collected and indicators used to report the data. The ESVAC work stream on the collection of antimicrobial use data by animal species aims to foster the collection of harmonised and standardised data across the EU/EEA. This document provides guidance on the collection of such data.

The guidance document has been drafted for those MSs that would be willing to provide data on a voluntary basis. Accordingly, statements like "data to be provided to EMA" should not be understood as a requirement, but as the data to be provided once a MS has decided to provide such data. The guidance document should ensure standardisation of the key elements of the data collection process (data collection period, antimicrobial agents, names of active substances, etc.). It does so by setting standards for the collection of data on the use of antimicrobial agents by defined animal species/categories and the animal population at risk of being treated with those antimicrobials, for those MSs that are currently, or might wish to start, collecting such data and would provide those data to EMA in the future. Data collected according to the guidance document will be harmonised and standardised – to the extent possible – and therefore enable the monitoring of trends in use by species/categories in participating MSs. Ultimately, such data would allow for an integrated analysis with data on antimicrobial resistance in certain species and/or categories of animals (e.g. in future Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) reports).

For the development of the guidance document the abovementioned reflection paper, the lessons learnt during the 'ESVAC trial for collecting data on consumption of antimicrobial agents in pigs (EMA/836856/2015)', comments received on the 'Draft ESVAC Vision and Strategy 2016 – 2020 (EMA/326299/2015)' and the 'Concept paper on guidance for the collection of data on antimicrobial

[1] All ESVAC documents and reports on sales data are available from the Agency's website via: Home > Veterinary regulatory > Overview > Antimicrobial resistance > European Surveillance of Veterinary Antimicrobial Consumption.

consumption by species from national data collection systems (EMA/321085/2016)' were taken into account. The guidance document was developed in conjunction with the ESVAC species Expert Advisory Group (see Annex 7 for details).

1.2. Objectives and scope of guidance document

The objectives of the guidance document are:

- to define the data that could be provided to EMA by countries collecting antimicrobial use data by species/category[2]:
  - for those EU/EEA MSs wishing to provide such data to EMA;
  - in order for EMA to collate, analyse and report harmonised and standardised data on antimicrobial use by species/category in EU/EEA MSs.
- to encourage the collection of harmonised and standardised data on antimicrobial use by species/category by EU/EEA MSs.

The guidance document:

- is not mandatory, but details how EMA proposes the collection of antimicrobial use data by species/category at EU/EEA level;
- is intended to promote the collection of data that are harmonised and standardised across EU/EEA MSs and time periods;
- is intended to be used by national competent authorities of EU/EEA MSs that are currently, or might wish to start, collecting antimicrobial use data by animal species/category and would like to provide those data to EMA in the future;
- covers the collection of data as close as possible to the end user (i.e. at farm level, for which data can be obtained from farms, veterinarians, pharmacies, etc.) but data provided to EMA would be aggregated at national level for analysis and reporting by animal species/category by EMA;
- is developed for three priority groups of food-producing animals – pigs, poultry and cattle – but might be adapted to other animal species (e.g. sheep/goats, companion animals) or categories (e.g. breeding chickens/turkeys) at a later stage;
- is intended to be pragmatic to ensure that the required data can be provided by all EU/EEA MSs wanting to do so and, at the same time, ensure that those data are sufficiently accurate to meet the objectives for which they are provided to EMA.

This guidance document may be subject to revision pursuant to changes in the applicable legal provisions and on the basis of the experience gained with the application of this guidance, as the case may be.

For correspondence: ESVAC@ema.europa.eu.

[2] When reference is made on the guidance to providing data to EMA (e.g. *variables needed to be provided to EMA)* it should be understood as if such data collection would be agreed by the relevant authorities and not as an imperative request.

2. Data that could be provided to EMA for reporting antimicrobial use by species

This chapter covers the data that could be provided to EMA for the purpose of reporting antimicrobial use data by animal species/category. Data could be collected through a census model (covering the whole animal production) or a sample survey model (covering a representative sample of the animal production). See Annex 2 for an explanation of these models, detailed information on the required data and suggestions for how to collect those data, and see Annex 4 for detailed information on establishing a representative sample. Variables and data to be provided for antimicrobial use by animal species/category and for the animal population at risk of being treated in the case of a sample survey are listed in Annex 5. Further background information on the rationale behind this guidance document can be found in a separate Question and Answer document (EMA/716249/2016).

2.1. Animal species/categories covered

The animal species and categories which this guidance document covers include the priority livestock species as identified in the reflection paper (EMA/286416/2012-Rev.1) and included in the AMR monitoring as provided under the Commission Implementing Decision (CID) 2013/652/EU:

- pigs;
- broilers;
- turkeys (where annual production of turkey meat in a MS is more than 10,000 tonnes);
- bovine animals slaughtered under one year of age (where annual production of meat of those bovine animals in a MS is more than 10,000 tonnes).

In addition, the guidance document covers data collection in:

- dairy cattle;
- beef cattle (includes cows, heifers, bullocks and bulls).

Due to the lack of specific requirements with regard to the animal species or categories for which data should be collected, it is up to each individual MS to decide for which species or category data would be provided.

2.2. Antimicrobial agents to be covered

ATCvet groups (Anatomical Therapeutic Chemical classification system for VMPs) of antimicrobial agents that at least should be covered in the collection of data to be provided to EMA are listed in Table 1.

Table 1. ATCvet groups and codes of veterinary antimicrobial agents to be included in data collection

ATCvet group	ATCvet code
Antimicrobial agents for intestinal use	QA07AA; QA07AB
Antimicrobial agents for intrauterine use	QG01AA; QG01AE; QG01BA; QG01BE; QG51AA; QG51AG
Antimicrobial agents for systemic use	QJ01
Antimicrobial agents for intramammary use	QJ51
Antimicrobial agents used as antiparasitic agents[a]	QP51AG

[a] Only sulfonamides are to be collected and reported.

2.3. Data collection period to be covered

The data collection period should cover one calendar year (regardless of the length of the production cycles on individual farms).

2.4. Frequency of providing data to EMA

Data could be provided to EMA on an annual basis or for each animal species/category on alternating years, following the schedule of the AMR sampling in accordance with the CID on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU).

Due to the lack of specific requirements with regard to the schedule with which data should be provided to EMA, it is up to each individual MS to decide how often data would be provided to EMA.

2.5. Data to be provided to EMA

Data could be provided to EMA by web-based delivery in the form of a) number of packages used per VMP presentation, or b) total weight or volume used per VMP in the MS per animal species/categories during the data collection period. Therefore, the collected (raw) data should be aggregated at national level into the total per animal species or category (in the case of cattle) listed in paragraph 2.1. This should also include products on special license, certified products, etc.

2.5.1. Variables on antimicrobial use

The variables needed to be provided to EMA in order to calculate the amount of active substance used for each VMP presentation or medicated feed used in the specific animal species/category are listed in Table 2a and b, as well as the justification for inclusion of those variables. A complete list of variables on antimicrobial use can be found in Annex 5 Table 9.

Table 2a. Variables for each VMP presentation that would need to be provided to EMA to calculate the amount of active substance if data were provided in the form of number of packages; with justification

Variable	Justification
Country	To identify the country which collected the data
Year	To identify the time period (calendar year) for the collected data
Species	To identify the animal species (or category where applicable) for which data are collected
Name of the VMP	To identify the antimicrobial veterinary medicinal product used

Variable	Justification
Form	To identify the pharmaceutical form (needed for further analysis of data)
Pack size	To enable calculation of the amount of active substance in each VMP presentation
Pack size unit	To enable calculation of the amount of active substance in each VMP presentation
Strength of active substance in VMP	To enable calculation of the amount of active substance in each VMP presentation
ATCvet	Only the latest version of ATCvet codes should be used
Number of packs	To calculate the weight of active substance used for each VMP presentation

Table 2b. Variables for each VMP (or medicated feed) that would need to be provided to EMA if data were provided in the form of total weight or volume per VMP (or medicated feed); with justification

Variable	Justification
Country	To identify the country which collected the data
Year	To identify the time period (calendar year) for the collected data
Species	To identify the animal species (or category where applicable) for which data are collected
Name of the VMP	To identify the antimicrobial veterinary medicinal product used
Form	To identify the pharmaceutical form (needed for further analysis of data)
Strength of active substance in VMP/ medicated feed	To enable calculation of the amount of active substance used
Weight or volume used of VMP/ medicated feed	To enable calculation of the quantity of active substance used for each VMP or medicated feed
Unit	To enable calculation of the quantity of active substance used for each VMP or medicated feed (e.g. kg, L)
ATCvet	Only the latest version of ATCvet codes should be used

2.5.2. Variables on animal population

For EMA purposes, the denominator with which use data can be adjusted (i.e. taking into account the animal population at risk of being treated with antimicrobial agents) will be calculated from a combination of the number of animals slaughtered and live animals present during the data collection period in a MS or on a sample of farms, multiplied by standardised weights. This approach is similar to the calculation of the ESVAC sales population correction unit (PCU) and the resulting denominator will be referred to as the 'species PCU'[3].

Table 3 lists the data that would be used to calculate the species PCU for each animal species/category covered in the guidance. For the census model the number of animals imported and exported for fattening or slaughter by a MS would, where appropriate, also be included in the denominator. Of note is that in the case of a census model, data to calculate the denominator for the animal

[3] It is considered that the (species/sales) PCU is based on standardised average weight at treatment, whereas other denominators, e.g. 'animal biomass', are based on live weight or weight at slaughter.

species/category under surveillance are already collected for the reporting of sales data at EU/EEA level and thus the MSs would not have to provide these. Definitions and standardised average weight at treatment of the various animal categories as applied by ESVAC are given in Table 5 in Annex 2.

For MSs where data are collected from a sample survey, depending on the animal species/category, the total number of live animals present and the total number of animals sent to slaughter on all farms included in the sample during the year of data collection would have to be provided to EMA. The required variables depend on the animal species/category and are listed in Table 3.

Table 3. Data to establish the species PCU that would need to be collected by EMA for MSs collecting census data or provided to EMA by MSs providing sample survey data

Animal species/ category	Variables for census model	Variables for sample survey model
Pigs		
	Number of live breeding sows	Number of live breeding sows
	Number of slaughtered pigs	Number of pigs sent to slaughter
	Number of pigs imported/exported for slaughter	
	Number of pigs imported/exported for fattening	
Broilers		
	Number of slaughtered chickens	Number of broilers sent to slaughter
	Number of chickens imported/exported for slaughter	
Turkeys		
	Number of slaughtered turkeys	Number of turkeys sent to slaughter
	Number of turkeys imported/exported for slaughter	
Bovine animals		
Bovine animals slaughtered below 1 year of age		
	Number of slaughtered calves (less than 8 months)	Number of calves (less than 8 months) sent to slaughter
	Number of slaughtered young cattle (between 8 and 12 months)	Number of young cattle (between 8 and 12 months) sent to slaughter
Dairy cattle		
	Number of live dairy cows	Number of live dairy cows
Beef cattle		
	Number of slaughtered bulls and bullocks	Number of bulls and bullocks sent to slaughter
	Number of slaughtered heifers	Number of heifers sent to slaughter
	Number of slaughtered cows	Number of cows sent to slaughter
	Number of imported/exported cattle for slaughter	
	Number of imported/exported cattle for fattening	

3. Reporting of antimicrobial use by species by EMA

3.1. Indicators of use of antimicrobials

Three indicators would be used to report annual antimicrobial use by animal species/category:

- 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).

When results on antimicrobial use are reported, it should be clearly stated which methods have been applied to establish the denominator (e.g. formulas and standardised weights) as well as the numerator (e.g. which version of DDDvet/DCDvet values).

The data would be presented as overall antimicrobial use by animal species/category in the MS and separately for the various antimicrobial classes and pharmaceutical forms by animal species/category in the MS. DDDvet and DCDvet are technical units of measurement that take into account differences in dosing between active substances, formulations and animal species. Detailed information on DDDvet and DCDvet can be found in the 'Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet) (EMA/710019/2014)' and lists with the DDDvet and DCDvet values are available from the EMA website.

3.2. Description of national data collection system

The data provided by the reporting MSs can be collected through different data collection systems (i.e. 'census' or 'sample survey' model) using different data sources (e.g. prescriptions, treatment log books, delivery notes), which may lead to systematic differences in results on antimicrobial use between animal species/categories and between MSs. For the interpretation and communication/reporting of data on use of antimicrobials by animal species/category, identification and reporting of the main characteristics of the data collection system is important. Therefore, the provision of data to EMA should be accompanied by a completed questionnaire on the characteristics of the national data collection system, which includes items on the data collection approach, animal production coverage, data sources used, etc. See Annex 3 for the (preliminary) questionnaire.

3.3. Data protection and confidentiality

EMA would only collate and report data of VMPs presentations aggregated at national animal species/category level and therefore individual farms or prescribers, pharmacies and other data suppliers would not be recognisable in any publication by EMA. Data which are processed by EMA would be handled in accordance with the 'Principles for ensuring the confidentiality of data supplied to the European Surveillance of Veterinary Antimicrobial Agent Consumption (ESVAC) project (EMA/327935/2010-Rev.1)'.

Data provided to EMA should be anonymised and aggregated. However, for e.g. validation purposes or data quality control it is necessary that the authorities providing data to EMA would have access to the collected raw (detailed) data that may include personal identifiers, or would be able to work with the

raw data holders. Arrangements and provisions would have to be made between authorities and data holders to ensure for example the protection of (commercially) confidential information.

4. Terms and abbreviations

- ATCvet: Anatomical Therapeutic Chemical classification system for veterinary medicinal products
- BI: Oracle Business Intelligence
- Census: data collection model (often continuous and automated) involving all antimicrobial use during the collection period covering practically the whole animal production for the animal species/category or practically all farms in the country
- CID: Commission Implementing Decision
- DCDvet: Defined Course Dose for animals
- DDDvet: Defined Daily Dose for animals
- EC: European Commission
- ESVAC: European Surveillance of Veterinary Antimicrobial Consumption
- EU/EEA: European Union/European Economic Area
- Farm: holding where farm animals are kept, including small-holdings
- MS: EU/EEA Member State
- PCU: ESVAC sales Population Correction Unit (used in the ESVAC reports on overall sales), a composite variable representing the animal demographics in a country in the form of the total estimated weight at treatment of livestock and slaughtered animals in a country, taking into account import and export of animals for fattening or slaughter in another MS. The species PCU refers to the PCU calculated for one specific animal species/category.
- (VMP) Presentation: product name, form, strength and pack size with which a VMP is marketed; one VMP can be marketed in several presentations, or pack sizes
- Raw data: actual data collected and recorded from treatment log books/health records, delivery notes, invoices or veterinary practice records/prescriptions representing the number of packages per VMP presentation, the total quantity/volume of a VMP or medicated feed or the dosing regimen for a treatment with a VMP or medicated feed
- Sample survey: data collection model involving all antimicrobial use during the collection period from a representative sample of farms or the animal production in the country
- SPC: Summary of Product Characteristics of a VMP
- Use: prescribed, administered, purchased or delivered amount of antimicrobials to certain animal species on a farm/holding
- VMP: Veterinary Medicinal Product

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Annex 1 – Use and benefits of antimicrobial use data by species

This annex introduces potential use and benefits of collecting and reporting antimicrobial use data by animal species/category at EU/EEA and national level, respectively. Although not covered in this annex, interpreting data at a local level would also provide valuable additional insights.

Collecting data by species would enable, among other things, the reporting of use in more refined units of measurements such as defined daily doses or defined course doses. These units take the differences in dosing between active substances, formulations and species into account, which provides for a more refined measure of exposure of animals to antimicrobials. Furthermore, use data collected by species (at farm level) would allow for recognising certain off label use of VMPs, which cannot be identified by means of analysing (stratified) sales data.

At EU/EEA level

Collecting data by animal species/category to be reported at an EU/EEA level would provide trends in use patterns across the years for defined animal species/categories. It would also allow certain verification of the overall sales data, especially for those MSs with complete (or near complete) data coverage. Moreover, it could allow for substantiation of data on for example estimates of use in certain animal species/categories currently provided by the pharmaceutical industry within the Periodic Safety Update Reports.

Direct comparison of antimicrobial use between the MSs should be done with caution; available data should be analysed taking into account e.g. differences in husbandry types (size, technologies, management, etc.) and prevalence of resistance (targeting veterinary pathogens as well as zoonotic, commensal and indicator bacteria), and could serve to analyse the impact of risk management measures and to analyse proposals of measures to be implemented at national level.

Data by species can provide insight into the species or animal category where exposure of animals to antimicrobials is high, which may influence selection pressure for antimicrobial resistance. It would be possible to identify where to focus efforts on reducing antimicrobial use (e.g. identifying groups with high antimicrobial use, or in which groups critically important antimicrobials for human medicine are used). The amount of antimicrobials used in specific species could also be considered from the perspective of environmental loading and could lead to proposing mitigation measures for handling of for example manure according to technologies specifically for certain species of animals and certain antimicrobials. Finally, data collected by species at EU/EEA level could allow for identification of the areas of concern for further research in a specific species.

At national level

When data on antimicrobial use have been collected at the animal sector level for provision to EMA, they could also be used for a range of other purposes at national level. Whilst data provided to EMA would be provided anonymised, data at national level might identify the source of the data, allowing for a more detailed analysis of the results. The data could provide policy makers with insight into the effect of implemented measures, such as those prescribed in responsible use and treatment guidelines, which are produced nationally. The data collection could also provide risk managers with data to identify risk factors and tools for risk assessment as well as risk management at a national, animal sector or even farm level depending on the data collection system implemented by each country. The possible analysis would depend on the data that would be collected in addition to antimicrobial use data, e.g.:

- collection of data by species could enable identification of some off label use of antimicrobials e.g. treatments with products that are used for species for which they have not been authorised, identifying the need for extension of authorisation of some of those products. Off label use with regard to the amount to be administered (e.g. underdosing/overdosing) or duration (e.g. prolongation) of the treatment could provide a signal of insufficient efficacy of authorised dosing schedules or provide signals of wrong farmer/veterinarian practices (e.g. rough estimation of weight of animals of certain categories and under/overdosing);
- if use data were collected for a number of farms, description of antimicrobial use at farm level would be possible and give insight into the variation in use between farms;
- if use data were recorded for specific age categories of animals (e.g. sows/piglets, weaning pigs, finisher pigs), use per age category could be calculated, not only in terms of total use (e.g. in DDDvet/DCDvet), but also broken down by e.g. antimicrobial class or type of application (oral, other). This information could become of greater interest when also differences between farms for the different age categories could be explored;
- if use data were collected for several years, trends could be monitored. These trends could in principle be related to antimicrobial resistance data of relevance to animal and public health (e.g. coming from surveillance of zoonotic, indicator and/or commensal pathogens) when available from the farms and collected at the same time as the use data. In addition, data on veterinary pathogens could be collected with regard to AMR.

In particular in case of availability of use data with complete coverage of an animal category, these data could be used for a range of additional purposes. However, for any specific purpose, potentially more information might have to be collected (see for suggestions Table 4). Examples include:

- all the above mentioned examples (collection per farm, collection per age category, evaluation of trends) apply here as well. An additional approach could be calculation of the use per veterinary practice or even veterinarian. The differences in e.g. total number of DDDvet/DCDvet between veterinarians give an impression of variation in prescription patterns between veterinarians. Approaches for comparing prescription patterns between veterinarians are available[4];
- when distribution of e.g. numbers of DDDvet/DCDvet by farm and veterinarian are available, these data could be used for inter-colleague comparisons and discussion within professional groups, and benchmarking of farms and veterinarians. Experience with benchmarking exists in a few MSs with full or high level of coverage (e.g. Belgium, Denmark, the Netherlands). It is beyond the scope of this document to present and discuss all details on benchmarking approaches, but these can be found in various reports of national authorities in these MSs and in peer-reviewed literature;
- in many animal production sectors all kinds of data are collected, for instance from disease monitoring programs, and data are often available on farm structure, size, presence of biosecurity measures, etc. These data are more and more often used for analyses that can be of use for development of management approaches at sector level and evaluation of intervention measures. A particular example is when animal disease data have been collected; antimicrobial use data could then be related to disease occurrence. In many cases, this is done in dedicated studies, with tailor-made data collection strategies, but more and more 'big data' type of analyses are seen in MSs

[4] Bos, M. E. H., Mevius, D. J., Wagenaar, J. A., van Geijlswijk, I. M., Mouton, J. W., & Heederik, D. J. J. (2015). Antimicrobial prescription patterns of veterinarians: introduction of a benchmarking approach. Journal of Antimicrobial Chemotherapy, 70(8): 2423-5.

where there is full coverage of antimicrobial use data collection and disease or other meta-data is collected routinely.

Data on the use of other products that may have an effect on antimicrobial resistance in animals, but which are not included in Table 1, could also provide useful insights. These may include for example topical preparations for skin or sensory organs, ionophores and/or products authorised for human use administered in accordance with Article 11 of Directive 2001/82/EC.

Furthermore, in some MSs food-producing animals other than pigs, broilers, turkeys and cattle are of importance, such as rabbits, sheep, goats or farmed fish. In such MSs it could be adequate to include these species into the animal sector specific national data collection systems on use of antimicrobials in addition to those species/categories for which data could be provided to EMA. Collecting data on antimicrobial use in companion animals (e.g. cats and dogs) could also be considered.

Table 4. Additional variables that could be collected for national purposes

Variable	Examples	Justification
Treatment type	• Therapeutic/metaphylactic/prophylactic • Group/individual	To help monitor prudent use and risk mitigating measures
Treatment indication	• Digestive/respiratory/urinary/ reproductive/etc. • Acute urinary-tract infections caused by susceptible strains of *Escherichia coli*/Treatment of swine respiratory disease	To help identify reasons for animal treatment and possible risk mitigation measures
Administration as "off-label use"	• Yes/no • *Cascade* use	To help identify need for products authorised for other target species and risk mitigation measures
Stage at treatment	• Weaner/sow/etc.	To help identify risk mitigation measures
Date of event		To identify seasonal influence; link to disease incidence; enable reactive monitoring of use and impact of (un)planned events
Variables on farm identification and farm characteristics	• Livestock production system (e.g. calf rearer, farrow-to-finish)	To enable benchmarking and identifying risk mitigation measures
Herd health management practices	• Vaccination (e.g. against *E. coli* (F4 or F18)) • Use of coccidiostats	To help identify impact of risk mitigation measures

Annex 2 – Data collection at national level

This Annex is intended to give additional information: an explanation of the proposed data collection models, detailed information on the required data and suggestions for how to collect those data.

Table of contents of Annex 2

1. Animal species or categories included in data collection

Following Commission Implementing Decision 2013/652/EU, AMR data collection is mandatory for the following animal species/categories:

- broilers;
- fattening turkeys (where production of turkey meat is more than 10,000 tonnes per year);
- fattening pigs;
- bovine animals slaughtered under one year of age (where production of meat of those bovine animals is more than 10,000 tonnes per year).

MSs wanting to provide data to EMA may decide to prioritise certain species or collect data from all species. A phased approach could also be applied, starting with for example data collection in pigs followed by data collection in pigs and broilers for the subsequent year, etc.

MSs where the production of meat of bovine animals < 1 year and/or turkeys falls below the threshold may want to collect data on those animal categories in case these species are considered to be priority species in terms of antimicrobial use or resistance in their country.

MSs may also want to collect data on antimicrobial use in dairy production, for example to monitor the implementation of prudent use guidelines and/or the use of those antimicrobial agents identified by the World Health Organization as high priority critically important antimicrobials for human medicine or those categorized by the Antimicrobial Advice ad hoc Expert group (AMEG)[5] as level 2. Furthermore, MSs may want to collect data on antimicrobial use in beef production, especially those MSs where antimicrobial use in calves and young cattle is considered to be high but where bovine animals generally are not slaughtered under one year of age, and thus would not be included in the AMR monitoring.

For those MSs where data on resistance in target pathogens are also available, it would be useful to include such data in the abovementioned integrated analysis on antimicrobial resistance and use.

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

2. Approach for collection of data

Figure 1 (see below) presents a flow chart of the major steps identified for the development of a (national) system for the collection of data on antimicrobial use by species:

- definition of the objectives of the data collection (such as the provision of data to EMA; see for further examples Annex 1) in order to understand which data need to be collected to achieve those objectives;
- identification and characterization of:
  - the animal production sector;
  - the distribution of veterinary medicinal products.
- identification and confirmation of availability of data/variables that need to be collected;
- decision on the data collection model;
- identification of the data sources;
- definition of the data collection protocol and logistics (including the templates and software needed);
- testing of the data collection system.

Several parts of the flow chart are further detailed in the following paragraphs.

It is recommended to identify and involve stakeholders as soon as possible in the process, and when possible also involve (veterinary) pharmacists, (veterinary) epidemiologists, data managers, etc. Additional steps may be needed in a country, and other aspects may need to be taken into account, such as the resources needed and available, and additional objectives for data collection in future legislation either at EU/EEA or national level.

All farm types should be covered in the data collection, regardless of the structure of the animal population on the particular farm. This means that for example in the case of a pig farm specialized in weaners, antimicrobial use data is to be collected for that farm, even though the animal population on that farm (consisting of only weaners) may not contribute to the denominator (which could for example be based on numbers of living sows and slaughtered pigs). Furthermore, to establish the collection of complete, reliable data on all events of antimicrobial use per animal species/category in a country, it should be ensured that data on any use of medicated feed/water/milk replacer containing an antimicrobial agent is included in the data collection as well. It should be clarified therefore if medicated feed containing antimicrobials is used in an animal sector and from which source the data can be obtained, whilst ensuring there is no overlap between data collected on medicated feed and on antimicrobial VMPs.

2.1. Data collection model

Two major models for collecting data by animal species/category are identified here:

1. 'census' model: a continuous – often (semi-)automated – data collection model covering (practically) the whole animal production for a specified animal species/category;

2. ‘sample survey’ model: a data collection model through which data are collected from a representative sample of farms or the animal production, using a well-designed random selection procedure, for a specified animal species/category.

A data collection model that can collect or extract the required data in a practical and automated way, with a limited need for additional manual data entry, may be preferred. In the case of a census model, most often electronically stored records are used to facilitate the collection of large numbers of such records. However, electronic record collection can also be applied in a sample survey. For automatic, continuous data collection of the electronic records, the use of the internet with connections between computer systems from farmers, veterinarians or pharmacies, data transfer hubs, software solutions to facilitate data retrieval and transfer and control of data integrity would be necessary, as well as uniform formats to avoid data quality issues and transfer problems. Such continuous systems require a high initial investment in terms of human and financial resources, but once established produce high quality antimicrobial use information and the costs of running such systems are expected to decrease over time. The resources associated with setting up a sample survey may be less, but especially when data have to be collected manually such a survey can still be highly labour demanding which would lead to high recurring labour costs.

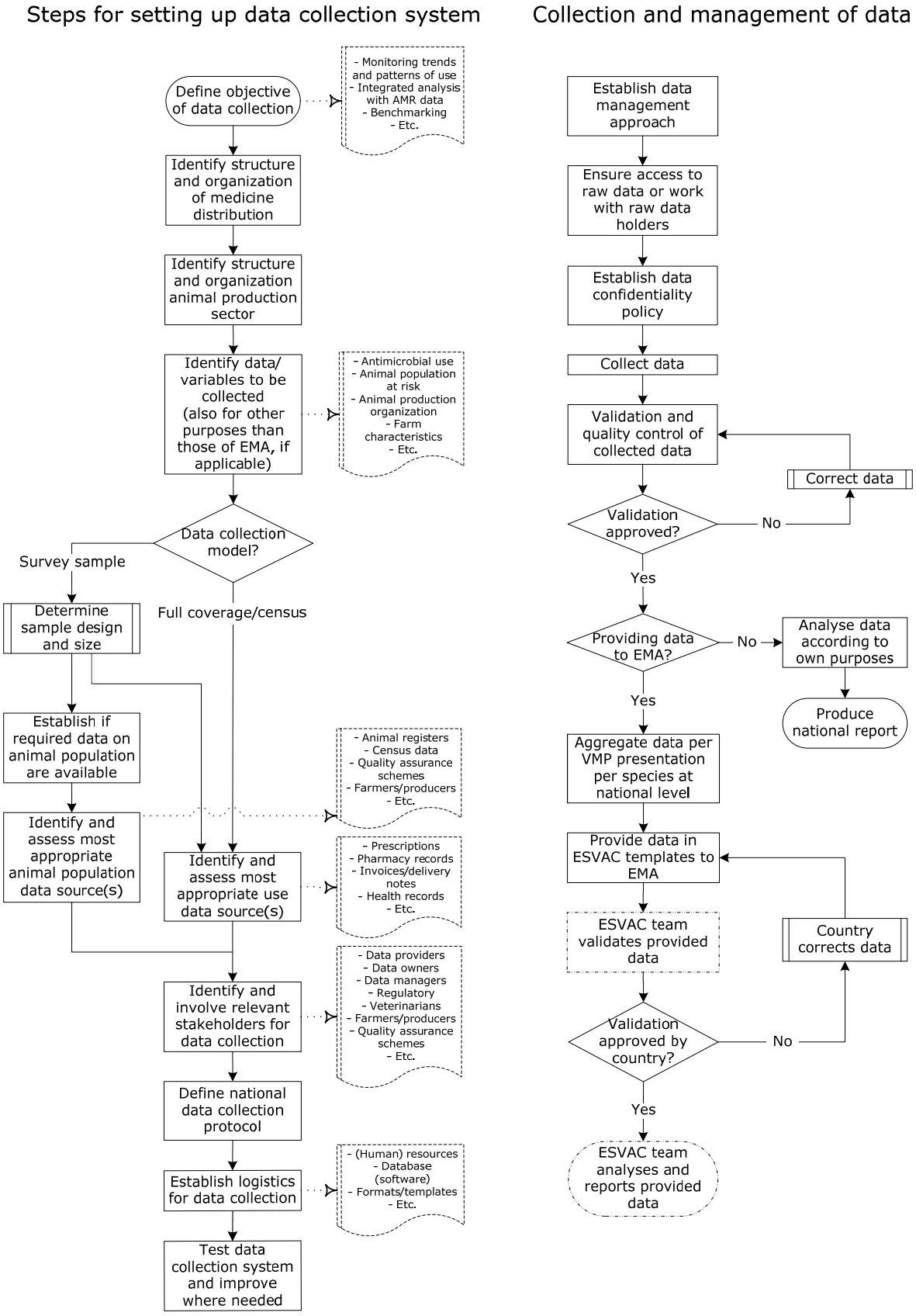

Figure 1. Flow charts of major steps involved in setting up a system for the collection of data on antimicrobial use by species/category and the animal population at risk of being treated, and the collection and management of those data

2.2. Possible data sources and raw data

The data sources, or combination of data sources, which provide the exhaustive, required data on the use of VMPs by animal species/category and those on the animal population may vary between MSs. Once the data collection model is decided, the optimum data sources should be identified and selected.

2.2.1. Use data

The sources for use data can be:

- health records, treatment log books, delivery notes and invoices from the farms;
- prescriptions or pharmacy records;
- veterinary practice records.

If data are collected from more than one data source there is a risk of having multiple observations on the same treatment, i.e. duplicate data or (partial) overlap. Therefore, data collection should be planned carefully to avoid any double counting. In other words, care should be taken that when data are collected from e.g. both prescriptions and delivery notes, any treatment with antimicrobials administered on the farm is only included once in the data collection. The application of data verification/validation is therefore recommended.

It is highly recommended to use electronic data whenever possible. This will reduce the risk of errors and consume less resources than manual data collection (i.e. manually copying data from the source to the data collection system).

The form of raw data can depend on the data source. For instance, data from delivery notes and invoices are typically number of packages and data from prescriptions and health records can be the treatment schedule or weight/volume of VMP.

Depending on the source used, the so-called 'raw data' on antimicrobial use by animal species/category can be collected in the form of:

- the treatment schedule applied or prescribed, including the number and weight of animals treated, for a VMP or medicated feed[6];
- the number of packages per VMP presentation used for the treatment/observation;
- the total quantity of a VMP (premix) mixed into medicated feed.

Antimicrobial use calculated from the administered treatment schedule (dose, frequency and duration) will generally be the most accurate, whereas the number of packages may lead to overestimation of the actual use if not all the total contents are administered.

If data are not collected in the form of number of packages, the raw data may need to be converted to the number of packages, before providing the data by web-based delivery to EMA. The use of a unique identifier for each VMP presentation is recommended to simplify the data collection process.

As calculations of the quantity of the VMP into the quantity of active substance need to be harmonised and standardised, this would be performed by EMA and therefore data could not be provided in the form of quantity of active substance. Exceptionally the data could be provided as the total weight or

[6] It is highly recommended to collect or establish the actual weight at treatment in order for the use data to reflect as close as possible actual use. If these weights are not available, standardised weights can be applied, such as the standardised average weights at treatment as used for the calculation of the denominator, see Table 5.

volume of the VMP.

Calculations would be performed automatically during the web-based delivery and conversion factors as shown in the ESVAC Sales reports (e.g. Tables A11 and A12, Annex 2 of the ESVAC sales report[7]) would be applied.

2.2.2. Animal population data

EMA would report use data by animal species/category adjusted by a standardised denominator for that species/category. This denominator, the species PCU, represents the animal population at risk of being treated with antimicrobials in the country or on the sample farms during the data collection period.

The species PCU would be calculated for each animal species/category separately by multiplying the number of animals in each category by the standardised, average weight at treatment for each category (see Table 5). Subsequently, the PCU for each species/category will be calculated by summing the PCU for each separate category included in that species denominator. For example, the species PCU for broilers in a country slaughtering 12 million chickens, exporting 100,000 chickens for slaughter and importing 500,000 chickens for slaughter would be calculated as follows: (12,000,000 * 1 kg) + (100,000 * 1 kg) - (500,000 * 1 kg) = 11,600,000 kg (see also Appendix 2 of the first ESVAC sales report[8]). The standardised weights are derived from EMA guidance[9], as already established for the calculation of the ESVAC sales PCU.

Table 5. Animal species and categories with definition and standardised average weight at treatment

Animal species and category	Definition	Standardised weight (kg)
Pigs		
Breeding sows	Live breeding sows with a live weight of 50 kg and over[10]	240
Slaughtered pigs	Slaughtered domestic animals of the species *Sus scrofa domestica* (no breakdown into categories)[10]	65
Pigs imported/exported for slaughter	Live swine (no breakdown into categories)[11]	65
Pigs imported/exported for fattening	Live swine (no breakdown into categories)[11]	25
Broilers		
Slaughtered chickens	Slaughtered domestic birds of the species *Gallus gallus* – (Eurostat data include broilers and boiling hens – i.e. cull animals slaughtered for human consumption)[10]	1
Chickens imported/ exported for slaughter	Live domestic fowls of the species *Gallus domesticus* (no breakdown into categories)[11]	1

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236750.pdf
[8] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf
[9] EMA guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guidance/2009/10/WC500004386.pdf; which is based on Montforts (2006): https://rivm.openrepository.com/rivm/bitstream/10029/8374/1/montforts.pdf

Animal species and category	Definition	Standardised weight (kg)
Turkeys		
Slaughtered turkeys	Slaughtered domestic birds of the species *Meleagris* spp.[10]	6.5
Turkeys imported/ exported for slaughter	Live domestic turkeys (no breakdown into categories)[11]	6.5
Bovine animals (domestic animals of the species *Bos taurus* and *Bubalus bubalis*)		
Dairy cows (live)	Live female bovine animals that have calved and are kept exclusively or principally for the production of milk for human consumption and/or for processing into dairy products, including living dairy cows destined to become cull cows – whether fattened or not between last lactation and slaughter[10]	425
Slaughtered cows	Slaughtered female bovine animals that have calved[10] (over 2 years of age)	425
Slaughtered heifers	Slaughtered female bovine animals that have not yet calved and which are not included under calves and young cattle[10] (between 1 and 2 years of age)	200
Slaughtered bullocks and bulls	Slaughtered castrated/non-castrated male bovine animals not included under calves and young cattle[10]	425
Slaughtered young cattle	Bovine animals slaughtered aged over 8 but not over 12 months[10]	140
Slaughtered calves	Bovine animals slaughtered at age 8 months or under[10]	140
Bovine animals imported/ exported for slaughter	Live bovine animals (no breakdown into categories)[11]	425
Bovine animals imported/ exported for fattening	Live bovine animals (no breakdown into categories)[11]	140

For MSs operating data collection systems that provide full coverage of the animal production (i.e. census model), the total number of live and slaughtered animals (including, where appropriate, those imported from and exported to other MSs for fattening and/or slaughter) in the country over the year of data collection for the animal categories listed in Table 5 would be used to calculate the PCU per species/animal production sector for the country. The data would be collected by EMA from Eurostat and TRACES, as these data sources are transparent, validated, robust and publicly available in the case of Eurostat.

When collecting data from a sample survey the data on the animal population may usually be available from sources such as animal registers, quality assurance scheme census data and/or from the animal keeper or farmer.

[10] Source: Art. 2 and Annexes I, II and IV of the Regulation (EC) 1165/2008
[11] Source: Section I of Part two of the Commission implementing Regulation (EU) 2016/1821

3. Data integrity and quality control

National data quality control is recommended to start by communicating a standardized format to e.g. veterinarians, pharmacies or farmers who have to deliver data. It may be considered by the national authorities setting up the data collection to visit the site(s) where the data are collected. This national format should contain variables that are required for calculating antimicrobial use and the animal population at risk of being treated with antimicrobials present at a farm and describing relevant farm characteristics. It should also describe the units in which the data have to be expressed and, if applicable, the range within which values should fall. Variables should be defined explicitly and uniquely. This national format should also describe the software package and format of the files delivered to the national authority.

Data may require additional handling to change the structure of the file, values of variables etc. Processes like these can be automated to a large extent. Even transfer of data can be automated through the internet. Once set up, this generally reduces error rates. Automated or manual transfer of data should allow for checking completeness of the data. For instance, when files are being transferred, descriptive information about the file should be communicated separately (e.g. number of variables, number of records, ranges for variables).

Data collection might require manual data entry of e.g. prescriptions or delivery notes into electronic files. In those cases, development of specific data entry modules using software like Microsoft Access, EpiData or other similar software packages may be advised. The fields for the different variables can be predefined in these packages, which implies that for instance data formats can only have a certain structure or value for a specific variable (numeric or alphanumeric, number of decimals, value range, etc.). This reduces error rates during data entry.

Data collected and received should be checked in a structured way. First, completeness of the data should be checked which means that individual records should be complete and have values for all required variables. Software can facilitate these checks before records can be stored. Second, value ranges should be checked for each variable or values of certain variables should be checked by comparisons with existing databases (international article number, etc.). Any changes made to values of variables should be recorded in a log file that contains information about who made changes to the original data at what time and the exact nature of the modification. The log file, the original data as well as the modified data should be kept in a directory. Reconstruction of final datasets after quality control and modification from source datasets should always be possible. It is recommended to perform data evaluation by using database software or statistical software which requires steering files or programming that can be used as (a series of) log files.

Annex 3 – Questionnaire on national data collection system

When data are provided according to the guidance, harmonisation and standardization are ensured to the extent possible. However, different data collection systems using different data sources can be applied by the MSs, which may lead to systematic differences between animal species and MSs. The amount of antimicrobials administered, documented through health records and treatment log books, can be affected by errors, approximations and omissions. The amount of antimicrobials prescribed or delivered can be larger than the actual use, if not all the prescriptions are dispensed or if not all the product is administered. Also the systems collecting the data from representative samples and collecting the data from the whole sector in the respective country may also lead to systematic differences between MSs. Husbandry systems, production characteristics (such as breed types, animal weight at slaughter and life span), climate (influencing also e.g. prevalence of diseases), trading/transferring (intra-national) of animals and biosecurity context may also differ between species and MSs. All these elements should be considered when interpreting and communicating the reported outcomes.

A questionnaire including the variables listed below would be sent to reporting MSs to collect information about the national data collection system from which the provided data have been collected. This is needed to account for underlying systematic differences between species and/or MSs. In line with the ESVAC sales reports, MSs providing data would be able to comment on the use by species in their country as reported by the ESVAC activity, clarifying potential underlying reasons for in- or decrease.

Variable	Description
Country	Country providing the data
Species	Species for which data are provided
National data provider to EMA	Name of institute/agency/authority/etc. providing the data to EMA
Year of first implementation of data collection by species	The first year in which a data collection system was fully functional for each species included in the data collection (if applicable)
Legal basis for collection of use data by species	• Mandatory • Voluntary
Data collection structure	• Census (involving the use during a year on (practically) all farms or in (practically) the whole animal population in an animal species/sector in the country), specifying – Passive (collecting already existing data from other purposes) – Active (data collected specifically for EMA purposes) • Representative sample survey (involving the use during a year in a sample of the animal population in an animal species/sector in the country), specifying the sampling strategy
Coverage of farms/production per animal species/category	• Number of farms in the country • Number of farms from which data were collected • Annual production in a country (tonnes slaughtered) • Production covered by the farms from which data were collected (tonnes slaughtered)

Variable	Description
Are exclusion criteria or thresholds applied for the farms/animals included in the data collection (e.g. farms with less than x animals, back yard flocks, parents, petting zoos)?	• No • Yes (specify which criteria or threshold and what proportion is excluded)
Are VMPs marketed solely for use in companion animals included?	• Yes • No
Are human medicinal products included?	• Yes • No
Type of use data records	• Prescriptions/veterinary practice records • Health records/treatment log books • Invoices/Delivery notes • Combination of above (specify)
Source of records containing use data	• Farmers • Pharmacies • Veterinarians • Combination of above (specify)
Type of use data collected	The data represent • Dosage and treatment schedule (including number of animals treated) • Number of packages used • Total quantity of VMP used per treatment • Combination of above (specify)
What is the data source for medicated feed	• Feed mills • Same as for VMPs • Combination of above
Source for animal population data	• Farm data • Eurostat • TRACES • National database (specify) • Other (specify)
Are quality controls in place for data collected at farm level	• Yes, describe • No
Are quality controls in place for data aggregated at national level	• Yes, describe • No
Additional comments	• Other comments useful for interpretation of the provided data or to provide additional information that a MS would like to make publicly available

Annex 4 – Sample survey

In cases where it is not possible to apply a census model for collecting antimicrobial use data by species, another possible approach is a sample survey. The objective of this sample survey is to have a proper estimation of the antimicrobial use at species level by taking information from a representative subset of the farms (the sample) belonging to the animal population under study.

The elements of the sample survey that must be established in order for the collected data to be representative of the animal population under study are the sampling frame, the sampling strategy (selection plan) and the sample size. These are discussed in this Annex.

Sampling frame

The sampling frame is a complete list of all units (farms) of the population which can be sampled (EFSA definition[12]). For the sake of simplicity, some practical criteria could be established to differentiate commercial farms from those only devoted to own-farmer consumption (which could be excluded from the sampling frame).

To be able to use the sampling frame, there needs to be available a minimum set of data on the units of sampling, such as contact information (name of owner, full address of location of farm, phone number, etc.) and information enabling farm characterization (type, size, geographical location). Especially, information on the farm animal population is needed, also in terms of which categories are present on the farm (live animals and slaughtered animals).

Separate sampling frames should be established per animal species/category (pigs, broilers, turkeys, cattle – veal, dairy cattle and beef cattle). If a cluster sampling would be the preferred option (see below) the sampling frame should be composed of cluster units (mainly regions or other administrative/geographical units) and the same minimum set of data must be known at this level.

Sampling strategy (selection plan)

A variable but probably high level of heterogeneity is to be expected among farms in some animal production sectors. In these cases it is suggested to apply sampling strategies like clustering and/or stratification procedures to improve the sampling efficiency without increasing sampling size. Clusters are useful for large MSs, mainly for reducing the cost, and are usually existing administrative units. Strata are homogeneous groups regarding the topic of interest where a low internal variability but high external variability (between strata) can be expected.

For instance, the Farm Accountancy Data Network sampling model employs three criteria for stratification at farm level (region, economic size and type of farming[13]) that could also be used for antimicrobial use data, although farm size should be expressed in terms of the animal population at risk. Nevertheless, depending on the country and the animal sector, some of these criteria would not be needed; for instance, small MSs might not need stratification by region, or broiler and turkey sectors might not need stratification by farm type. Accordingly, stratification criteria should be defined per country and animal sector.

[12] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3686.pdf
[13] http://ec.europa.eu/agriculture/rica/methodology2_en.cfm#strat

In addition, from a sampling perspective in some cases the region will not be a stratum but a cluster, if for those regions variation is low in farm antimicrobial use among regions. For bigger MSs, the sampling strategy could be improved by applying cluster sampling and then performing stratification in a subset of clusters (regions) before selecting the farms to be sampled. Accordingly, different examples of sampling strategies for different scenarios are proposed, which are explained in more detail below and for which an overview is presented in Table 6.

Scenario A: *Expected homogeneity among farms (e.g. one farm type and one main farm animal population component on each farm, e.g. only slaughter animals on broiler farms) in a small country.*

In this scenario only the size of the farm (in terms of animal population) would have to be taken into account for sampling, so the preferred option would be a systematic[14] random sampling, taking sample units from a list of farms ranked by size (in terms of animal population).

Table 6. Overview sampling strategies for four scenario's based on heterogeneity among farms within a country and size of country

Scenario	Expected heterogeneity farms	Country size	Preferred sampling strategy
A	Homogeneous	Small	Systematic random sampling by randomly selecting farms from list of farms ranked by size[a]
B	Homogeneous	Large	Two-step sampling: • Random sampling by randomly selecting regions from a list of regions (clusters) • Systematic random sampling by randomly selecting farms from list of farms ranked by size in each selected region[a]
C	Heterogeneous	Small	Stratified sampling: • Stratification of sampling frame based on farm type • Systematic random sampling by randomly selecting farms from list of farms ranked by size[a] within each stratum
D	Heterogeneous	Large	Stratified, two-step sampling: • Random sampling by randomly selecting regions from list of regions (cluster) • Stratification of sampling frame based on farm type within each selected region • Systematic random sampling by randomly selecting farms from list of farms ranked by size[a] within each stratum

[a] If a skewed distribution of farms according size is expected, use a simple random sampling

[14] Systematic random sampling: random sampling performed by 1) determining sampling interval named *k* (N/n), 2) choosing a random number "j" between 1 and *k*, and 3) selecting units labelled "j", "j+*k*", "j+2*k*", etc. (Paul S. Levy and Stanley Lemeshow (1999) Sampling of Populations: Methods and Applications, Third Edition. John Wiley & Sons, New York, New York) When units are ranked by farm size this procedure guarantees a balanced sample covering all farm sizes in a population.

Scenario B: *Expected homogeneity among farms (e.g. one farm type and one main farm animal population component on each farm, e.g. only slaughter animals on turkey farms) in a larger country.*

In this scenario a two-step sampling would be the preferred option in order to reduce the cost of the data collection, taking the region (or another administrative unit) as the first level (clusters) followed by the systematic random sampling explained under scenario A as the second step.

Scenario C: *Expected heterogeneity among farms (different farm types and farm animal population components per farm type) in a small country (e.g. slaughter and live animals on pig farms).*

In this complex scenario a more elaborated sampling strategy would be needed, based on stratification of the sampling frame according to the distribution of the farm animal population components among the different farm types. To adequately perform this procedure, complete information on each farm regarding numbers of animals according to the farm animal population components should be available (preferably from national husbandry registers[15]), which should enable categorisation of all farms into the various farm types present in a country and their relative weight in the respective animal sector. In each stratum (farm type), systematic random sampling for taking units from a list of farms ranked by size should be applied, as explained under scenario A.

Scenario D: *Expected heterogeneity among farms (different farm types and different farm animal population components on each farm type) in a larger size country (e.g. slaughter and live animals on pig farms).*

In this scenario a two-step sampling could be applied, taking the region (or another administrative unit) as the first level (clusters) and the stratification procedure explained under scenario C as the second step.

Sample size allocation

Since the sampling strategies recommended for scenarios "B", "C" and "D" are based on cluster sampling and/or stratification, a procedure should be established for allocation of sample size.

Scenario "B": The sample size should be distributed among the clusters identified in the population. Under the cluster structure it is not compulsory that all clusters are sampled, so it is allowed to apply a sampling of clusters. Software is available[16] that performs simultaneously sampling of clusters based on their size and allocation of the number of sampling units per cluster (according to cluster size or other criterion). For an example of the sample size allocation see Table 7.

Scenario "C": The sample size should be distributed among the strata identified in the population. Under the strata structure it is compulsory that all strata are sampled. Software is available that performs allocation of the number of units per strata based on their size or other features. For an example of the sample size allocation see Table 7.

Scenario "D": The sample size should first be distributed among the clusters identified in the population (according to cluster size or other criterion) and then among all strata in each cluster. Software is available for performing this two-step allocation. For an example of the sample size allocation see Table 7.

[15] As an alternate source, other data providing a good national picture of these contributions could be employed.
[16] For an example see CSurvey sofware at http://www.ph.ucla.edu/epi/csurvey.html.

Table 7. Examples for sample size (n at least 385) allocation under scenarios "B", "C" and "D"

Scenario	Nº of clusters/strata in the country	Nº of clusters/strata in the sample	Nº of strata per cluster	Nº of samples per cluster[a]/stratum	Total sample size
B	20 clusters	5 clusters 7 clusters 11 clusters		77 per cluster 55 per cluster 35 per cluster	77*5= 385 55*7= 385 35*11= 385
C	20 strata	20 strata		20 per stratum	20*20= 400
D	20 clusters	5 clusters 7 clusters 11 clusters	3 strata 3 strata 3 strata	26 per cluster 19 per cluster 12 per cluster	26*3*5= 390 19*3*7= 399 12*3*11= 396

[a] The number of samples per cluster could be allocated according to cluster size or other criterion

Sample size[17]

In most cases populations involved in sampling surveys will be large, diverse and probably unequally distributed. These features necessitate that both accuracy and cost criteria are considered for establishing the most appropriate sample size. In addition, accuracy depends on the variability of the parameter to be estimated. In the antimicrobial use 'landscape' for sampling at farm level, the parameter that should be estimated should be the same indicator as listed in chapter 3.1. which is expected to have a wide distribution among farms.

Under a simple random sampling scenario, without clustering or stratification, the sample size is calculated using classical formulae available in many books on Epidemiology or Statistics. These sample size calculations use the population standard deviation in antimicrobial use across farms included in the sample as starting point. Some examples using public domain software are included below. However, the formulae for the calculation of sample size for cluster and stratified random sampling designs need more input parameters which are not easily estimated or determined, but in most cases produce figures for sample size in the same order of magnitude.

For informative purposes, the approach used by EFSA[18] is summarized as follows: *"The following assumptions were used for the calculations: (1) infinite population size for the number of bacteria isolates in each study population and Member State; (2) a confidence level of 95% and a power of 80%; (3) perfect sensitivity and specificity of the diagnostic test (susceptibility testing)".*

EFSA defines four objectives, with the following objective being the most similar to that of this guidance document: *"Precision of proportion of resistance estimate."* The "worst case scenario" under this model (50% proportion of resistance) shows, for a precision of 5%, the same sample size as 385. Probably practical considerations led to reduction of the sample size to 170 for EFSA monitoring.

Examples for sample size calculations were performed under a simple random sampling scenario using basic information for national data from the 2015 ESVAC report on the 2013 sales data[19] (in mg/PCU). The parameter values used for the calculations and the results are listed in Table 8. All calculations

[17] To explain the contributions of sampling strategy and sampling size we add a short paragraph from Levy and Lemeshow, Sampling of populations, 3rd Edition, p 75: "*… In general, the larger the sample, the greater will be the reliability of the resulting estimates. Validity, on the other hand, is a function of the measurement process rather than the sample size and will not, in general, be improved with an increase in sampling size. An improvement in validity requires an improvement in the measuring process*".

[18] The EFSA Journal (2007), 96, 1-46, "*Report including a proposal for a harmonized monitoring scheme of antimicrobial resistance in Salmonella in fowl (Gallus gallus), turkeys, and pigs and Campylobacter jejuni and C. coli in broilers*"

[19] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf.

were performed assuming a coefficient of variation (CV) of 100%[20], expected relative error of 10%, confidence level of 95% and infinite and finite (n =300 to 5000) population sizes[21]. Due to lack of available data on antimicrobial use on the country level, for multiple countries, to establish the standard deviation (SD), an assumed CV will be used. The following formulas were used:

*SD = CV * mg/PCU*

*Expected absolute error = 0.1 * mg/PCU*

Table 8. Examples for calculated sample size based on different scenarios for the average national antimicrobial use and population size

Example	A	B	C	D	E	F	G
Average national consumption (overall sales; mg/PCU)	3.7	425.8	3.7	3.7	425.8	3.7	425.8
Population size	Unknown	Unknown	5000	500	500	300	300
Expected standard deviation	3.7	425.8	3.7	3.7	425.8	3.7	425.8
Accepted absolute error	0.37	42.58	0.37	0.37	42.58	0.37	42.58
Exact sample size	-	-	357	218	218	169	169
Exact sampling fraction	-	-	7.1%	43.6%	43.6%	56.3%	56.3%
Approximated sample size	385	385					

Note that the different sample sizes (from 169 to 385 farms per species/animal category) proposed in this Annex are tentative, suggested sample sizes. The aim is to reach a certain precision for the estimated antimicrobial use in the sample; this level of precision for EMA purposes would be set at a later stage and would be based on key parameters such as the standard error and the required confidence level. However, EMA would receive aggregated data on antimicrobial use at species level and therefore would have no insight into use patterns on the individual farm level. As a result, EMA would not be able to calculate measures of precision for use by animal species in a certain country, such as a confidence interval around the total. To address this issue, the following approach is proposed:

- in the first year of sampling, participating MSs using a sample survey would be asked to include a fixed number of farms or percentage production per species. Further information would be provided on those at a later stage. Examples are included in this Annex;
- on the basis of this sample, the local participating authority or holder of the farm level data would, where possible, be asked to calculate antimicrobial use for each individual farm, the population standard deviation in use across farms and the average use;
- the confidence interval around the total could then be calculated on the basis of the population standard deviation and the number of farms in the sample using conventional Gaussian statistics;
- for subsequent surveys, EMA would define a required level of precision, which would be similar for each country. The number of farms and percentage production per species required to reach this level of precision would, where possible, be calculated using power calculations on the basis of the earlier obtained population standard deviation for each country. The number of farms or percentage production included should not be lower than a predefined minimum number of farms

[20] CV = (Standard Deviation (σ) / Mean (μ)) multiplied by 100.
[21] http://www.winepi.net/uk/index.htm.

or percentage production per species, irrespective of the outcomes of the power calculations. The details of this approach will be defined at a later stage;

- each year, the national authorities or holders of the farm level data would, where possible, be asked to rerun these calculations to evaluate whether the sample size for a particular species has to be modified because of changes in the distribution of average use across farms.

Annex 5 – Data/variables to be eventually provided to EMA

For data management purposes the data to be provided to EMA by the MSs have to be standardized. To ensure this and to ensure that all variables are collected, templates with which data should be provided to EMA would be provided by EMA at the time of a call for data. The variables proposed to be included in those templates are shown in this Annex.

Antimicrobial use data

The template for use data would be based on the ESVAC national sales register used to collect the sales figures. Similar to the sales register the template would be country-specific and include information on all antimicrobial VMPs marketed in a country and belonging to the ATCvet groups in chapter 2.2. of this guidance document. However, if a VMP (or VMP presentation) would be identified which has not been included in the template (e.g. for products on special licence), the variables as indicated in Table 9 would need to be filled in for that VMP (or presentation) by the national data provider. In case of combination VMPs, the SUBSTANCE variables would have to be filled in for each substance in separate columns. In addition to the variables included in the sales register the template would contain a variable on the animal species/categories for which the data are provided.

Animal population data

For data obtained from sample survey, data on the animal population covered by the survey have to be provided to EMA by use of a separate template which would be supplied by EMA. Variables proposed to be included in this template are listed in Table 10.

Table 9. Data/variables on antimicrobial use to be provided to EMA per country and year, per animal species/category. Variables in cursive text are only needed when data are provided as the number of packages.

Variable	Description of variable	Comments
COUNTRY	Two-letter ISO country code (alpha-2) (http://www.iso.org/iso/country_codes)	To identify country
YEAR		To identify data collection period
SPECIES	**Species Code** Character code being a unique identifier for each animal species and category where applicable E.g. Broilers (BR), Dairy cattle (DC), Beef cattle (BC), Pigs (PI), Turkeys (TU), Veal calves (VC)	To identify species (and category where applicable) for which data are collected
MA	**Marketing Authorisation Number**	To enable link with other databases
PRESENTATION ID	***Medicinal Product Package Code Value*** *Digit code being a unique identifier for each package size, strength and formulation of the VMP presentation. A key variable in many databases so it has to be stable over time so that VMP presentations no longer available on the market or no longer registered can still be identified, allowing*	*To allow a unique identification of the Veterinary Medicinal Product (VMP) presentation* *To identify and correct duplicates when uploading data to web*

Variable	Description of variable	Comments
	for analysis of historical data	
NAME	**Medicinal Product Name (in national language)** E.g.: Harmony vet 50 mg tablets 2 x 30; Harmony vet long acting 10 mg/ml injection 10 ml	For validation purposes • At country level prior to submission to web • By EMA after data submission
SPECIES_AUTH	**Authorised species** Character code that identifies the species for which the VMP is authorised, according to the SPC.	To enable identification on off label use
FORM	**Pharmaceutical Form** Bolus (BOLUS), Injection (INJ), Intramammary (INTRAMAM), Intramammary dry cow treatment (INTRAMAM-DC), Oral solution and oral powder for water administration (ORAL SOLU), Oral paste (ORAL PASTE), Oral powder (ORAL POWD), Premix (PREMIX), Capsules and Tablets etc. (TABL), Intrauterine preparation (INTRAUT)	
LONG ACTING	**Long-acting injectable preparations** It refers to injectable preparations that maintain its antimicrobial activity over a long period of time once injected	
PACKSIZE	***Content Quantity in Package: Pack size (numerical only)*** *E.g.: 100 tablets or 100 intramammaries: 100; 10 ml injection: 10; Package of 2 kg premix: 2; Box of 10 blisters of 30 tablets: 300; Box of 12 injectors: 12*	*To allow for calculation of the amount of active substance in each VMP presentation* • *For validation at country level prior to submission in web* • *Validation by BI after submission of data*
PACKSIZEU	***Content Unit of Measurement*** *E.g.: ML, L, G, KG, PIECE (for e.g. tablets, capsules, bolus and intramammary preparations)* *To be harmonised with strength unit – e.g. if pack size is 1 KG then strength unit should be per KG; if pack size is 12 PIECES the strength unit should be per PIECE*	*To enable calculation of amount active substance in each VMP presentation* • *For validation at country level prior to submission in web* • *Validation by BI after submission of data*
ATCVET	**ATCvet – 5th level: Anatomic Therapeutic Chemical (Classification) Veterinary**	Only last version of ATCvet codes will be accepted by the system If an ATCvet code has not been assigned for an substance EMA has to be contacted

Variable	Description of variable	Comments
NO PACKS	***Number of Packages Used Per Species (category)/Year/Country*** *Numeric value indicating the number of packages used (i.e. prescribed/administered/sold/delivered); can include two decimals – e.g. 210 for 210 packages used in pigs or 3.33 for 3.33 packages used in poultry*	*To calculate weight of active substance sold for each VMP presentation* • *For validation at country level prior to submission on web* • *Validation by BI after submission of data* • *For validation by EMA after data submission*
QUANTITY_VMP	**Weight or Volume of VMP Used Per Species (category)/Year/Country** Numeric value indicating the quantity of VMP used (i.e. prescribed/administered/sold/delivered); can include two decimals – e.g. 210 for 210 ml used in pigs or 3.33 for 3.33 kg used in poultry	To calculate weight of active substance used for each VMP • For validation at country level prior to submission on web • Validation by BI after submission of data • For validation by EMA after data submission
QUANTITY_U	**Quantity Unit of Measurement** E.g.: ML, L, G, KG, PIECE (for e.g. tablets, capsules, bolus and intramammary preparations) e.g. ML for 210 ml used in pigs or KG for 3.33 kg used in poultry	To enable calculation of quantity of active substance for each VMP • For validation at country level prior to submission in web • Validation by BI after submission of data
INGR_ID	**Substance Code Value**	Serve as a unique identifier for each substance for each product Needed for data management purposes
INGR	**Active Substance Name (ATCvet name)**	Only last version of ATCvet names will be accepted by the system If an ATCvet name has not been assigned for an substance EMA has to be contacted For combination VMPs the ATCvet name of all the substances has to be given but in separate columns
SALT	**Salt of Active Substance**	**Only** in cases when the strength is given in international units (IU), e.g. IU/ML or IU/UNIT, **and when** different salts exists Currently only applicable for colistin sulphate and colistin methane sulphonate To enable conversion to weight of active substance • For validation at country level prior to submission in web • Validation by BI after submission of data

Variable	Description of variable	Comments
PRODRUG	**Prodrug name (ATCvet name)** E.g.: Procaine penicillin, which is the prodrug for benzylpenicillin	Names of prodrugs are listed in Annex 3 To allow for calculating the weight of the active substance • For validation at country level prior to submission in web • Validation by BI after submission of data
STRENGTH	**Quantity of the Active Substance in Each Unit as declared in name (if not in name as in SPC): Strength (numerical only)** E.g. 10 for 10 MG/TABLET, 10 IU/TABLET, 10 MG/ML, 10 IU/ML, 10 MG/PIECE or 10 IU/PIECE In case of a combination VMP strengths have to be given for each substance in separate columns	For validation purposes To enable calculation of the amount of active substance in each package/product • For validation at country level prior to submission in web • Validation by BI after submission of data
STRENGTHU	**Unit of Measurement for Strength** E.g.: IU, IU/G, IU/ML, IU/PIECE, G, G/KG, G/L, MG, MG/ML, MG/PIECE In case of a combination VMP unit of measurement strength has to be given for each substance in separate columns To be harmonised with pack size – e.g. if pack size is 1 KG then strength unit should be per KG; if pack size is 12 PIECES the strength unit should be per PIECE	To enable calculation of the amount of active substance in each package/product • For validation at country level prior to submission in web • Validation by BI after submission of data
CONV FACT IU	**Conversion Factor IU** When strength is given in IU (e.g. IU/ML, IU/PIECE)	**In ESVAC template conversion factor IU will be recorded by use of a macro** Conversion factors are listed in Annex 3 To allow for calculation of the weight of the active substance in each package by MS for validation of data prior to upload in web If an substance with strength given in IU is not listed, EMA should be contacted
CONV FACT PRODR	**Conversion Factor Prodrug** Only when strength is given for the prodrug and not for the active substance (e.g. for procaine penicillin (prodrug for benzylpenicillin))	**In ESVAC template it will be recorded by use of a macro** Conversion factors are listed in Annex 3 To enable for the calculation of the weight of the active substance in package • For validation at country level prior to submission in web

Variable	Description of variable	Comments
		• Validation by BI after submission of data If a prodrug is not listed EMA should be contacted
CONTENT	**Content of Active Substance in Package** Numeric value indicating the quantity of the active substance in one package – e.g. 450 for 450 G; to be given in gram (G) for all substances In case of combination VMP the content in the package has to be given separately for each substance in separate columns	For validation of data by MS prior to upload in web • For validation at country level prior to upload and submission in web • Validation by BI after submission of data
CONTENTU	**Unit of Active Substance in Package** To be given in gram (G) for all substances In case of combination VMP the content unit has to be given separately for each substance in separate columns	For validation at country level prior to upload and submission in web
TONNES	**Tonnes of Active Substance** Calculated automatically if all variables are filled in	• For validation at country level prior to upload and submission in web • For validation by EMA after data submission

Table 10. Data/variables on animal population at risk of being treated with antimicrobials, covered by the sample survey, to be eventually provided to EMA by country and year, for each animal species/category

Species/category	Variable	Description of variable
Pigs		
	SOWS_LIVE	Number of live breeding sows in sample
	PIGS_SL	Number of pigs sent to slaughter in sample
Broilers		
	BROIL_SL	Number of broilers sent to slaughter in sample
Turkeys		
	TURKEY_SL	Number of turkeys sent to slaughter in sample
Bovine animals		
Bovine animals slaughtered below 1 year of age		
	CALF_SL	Number of calves (less than 8 months) sent to slaughter in sample
	YOUNG_CAT_SL	Number of young cattle (between 8 and 12 months) sent to slaughter in sample
Dairy cattle		
	DAIRY_LIVE	Number of live dairy cows present in sample
Beef cattle		
	BULL_SL	Number of bulls and bullocks sent to slaughter in sample
	HEIFER_SL	Number of heifers sent to slaughter in sample
	COWS_SL	Number of cows sent to slaughter in sample

Annex 6 – Reports and guidelines on antimicrobial use data (by species)

The table below contains links to websites where (inter)national reports on antimicrobial use by species can be found for those EU/EEA Member States that have made the reports available at the time of publication of this guidance. The table further contains links and references to guidelines and manuals developed by national or global institutes on the collection of antimicrobial use data in food-producing animals[22].

Country/institute	Link to reports or guidances
Belgium (Sanitel-Med)	Manual: http://www.afmps.be/sites/default/files/smed_usrman_sanitel-med_usermanual_nl.pdf (Dutch)
Denmark (DANMAP)	National reports: http://www.danmap.org/downloads/reports.aspx (English)
Germany (HI-Tier)	Manual: https://www4.hi-tier.de/infoTA.html (German)
Netherlands (SDa)	National reports: http://www.autoriteitdiergeneesmiddelen.nl/en/publications (English) http://www.autoriteitdiergeneesmiddelen.nl/nl/publicaties (Dutch) Standard operating procedure: http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/pdf/sda-standard-operating-procedure-(sop)-juni-2013-def.pdf (Dutch)
OIE	Terrestrial Animal Health Code – Chapter 6.8. "Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals" (2016) http://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/current/chapitre_antibio_monitoring.pdf (English) International reports: http://www.oie.int/our-scientific-expertise/veterinary-products/antimicrobials/ (English)
WHO (AGISAR)	Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria - Application of a One Health Approach – Chapter 2.3. "Surveillance of use of antimicrobials in animals" (2017) http://apps.who.int/iris/bitstream/10665/255747/1/9789241512411-eng.pdf?ua=1 (English)

[22] The AACTING (Network on quantification of veterinary Antimicrobial usage at herd level and Analysis, CommunicaTion and benchmarkING to improve responsible usage) project has published and overview of farm-level antimicrobial use monitoring systems http://www.aacting.org/monitoring-systems/

Annex 7 – ESVAC species Expert Advisory Group members

Name	Address	Country
Claire Chauvin (chair)	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail BP 53 Zoopole F-22440 Ploufragan FRANCE E-mail: claire.chauvin@anses.fr	France
Henriette Helin-Soilevaara	Department of Food and Health EVIRA Virology, Animal Diseases and Food Safety Mustialankatu 3 00790 Helsinki FINLAND E-mail: henriette.helin-soilevaara@evira.fi	Finland
Dick Heederik	Utrecht Universiteit Institute for Risk Assessment Sciences PO Box 80 178 3508 TD Utrecht NETHERLANDS E-mail: d.heederik@uu.nl	Netherlands
Miguel A. Moreno	Complutense University of Madrid Veterinary Faculty Animal Health Department Av Puerta de Hierro s/n 28040 Madrid SPAIN E-mail: mamoreno@ucm.es	Spain
Lucie Pokludová	Ústav pro státní kontrolu veterinárních biopreparátů a léčiv Hudcova 56a 621 00 Brno - Medlánky CZECH REPUBLIC E-mail: pokludova@uskvbl.cz	Czech Republic
Fraser Broadfoot	Veterinary Medicines Directorate Woodham Lane New Haw Addlestone Surrey KT15 3LS UNITED KINGDOM E-mail: f.broadfoot@vmd.defra.gsi.gov.uk	United Kingdom