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SCIENCE MEDICINES HEALTH

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European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Sales Data and Animal Population Data Reporting Protocol (version 4)

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1. Introduction

1.1. Terms of reference

In 2009 the European Commission requested the European Medicines Agency to take the lead in collating data on the use of antimicrobial agents in animals in the European Union and to manage the database. The European Medicines Agency (hereinafter referred to as the Agency) was asked to develop a harmonised approach for the collection and reporting of data based on national sales figures as well as data on usage in at least major groups of animal species and to ensure comparability with the sales of antimicrobial agents in human medicine.

Current ESVAC activity should be aligned to comply with requirements laid down in the Article 57 of the Regulation (EU) 2019/6 on veterinary medicinal products. Until the new requirements are implemented, it is advised that the antimicrobial consumption data should be reported as outlined in the latest version of the ESVAC sales data and animal population data reporting protocol.

The collection of data on sales of antimicrobial veterinary medicinal products (VMP), both at national and community level, may serve multiple purposes, of which the most important are the following:

- to support the interpretation of patterns and trends of antimicrobial resistance (AMR);
- to inform risk profiling and risk assessments regarding AMR;
- to identify risk management priorities;
- to support the evaluation of the effectiveness of control measures being implemented;
- to quantify the use of specific classes of antimicrobial VMPs such as those included in Category B of the categorisation made by the EMA Antimicrobial Advice ad hoc Expert Group (AMEG) in 2019[1], which also takes into consideration those identified by World Health Organisation (WHO) as critically important for human medicine[2];
- to facilitate comparison of volume of sales of antimicrobial VMPs within and between time periods;
- to identify focused and targeted research and development needs;
- to support the integrated analysis of the consumption of antimicrobial agents and the occurrence of antimicrobial resistance in bacteria from humans and food-producing animals.

This protocol addresses collection of sales data and data on animal population.

The revision of the ESVAC sales and animal population data reporting protocol includes updates to ESVAC conversion factors and the introduction of the following new sections: section 7 with information required in addition to sales data (questionnaire), section 1.3. of Annex 1 on the reporting of qualitative and quantitative composition of antimicrobial VMPs, including examples of recording of the "STRENGTH" variable, and Annex 2 with background information about updated ESVAC conversion factors. The revision also includes several editorial updates to align the terminology used.

[1] EMA/AMEG 2019. Categorisation of antibiotics in the European Union. Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals (https://www.ema. europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific _en.pdf)

[2] WHO Critically important antimicrobials for human medicine, 6th revision (https://www.who.int/foodsafety/publications/antimicrobialssixth/en/)

1.2. Approach

To enable reliable data reporting, as well as comparison within and between time periods, standardisation and harmonization of data is of vital importance. This also applies for the animal demographic data that are used to normalise the sales data for reporting of the antimicrobial sales per each country. In ESVAC, a population correction unit (PCU) is used as the denominator and this represents purely a technical unit of measurement. 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)[3].

In order to obtain reliable and harmonised data in the ESVAC database, all items in the data reporting package must be adhered to:

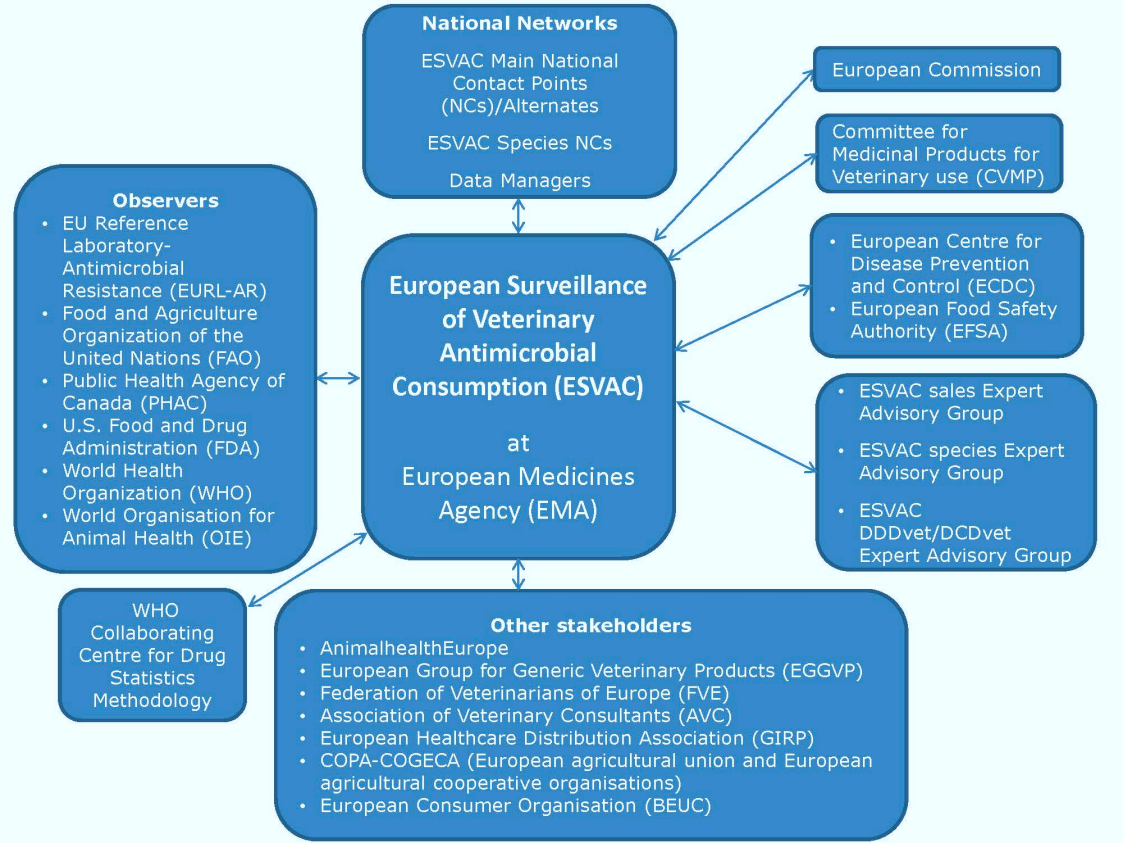
- ESVAC sales and animal population data reporting protocol (ESVAC protocol);
- ESVAC data reporting form (sales template);
- ESVAC animal population reporting form, available on the ESVAC web-based application;
- questionnaire to gather key information such as types of data and data sources, available through the ESVAC web-based application.

1.3. Organization of the project

The ESVAC project is organised into three main work streams: collection of sales data, collection of data on use by animal species and establishment of technical units of measurement. Separate expert groups are established for these three work streams. The organisation of the ESVAC project is illustrated in Figure 1. The ESVAC National Contact Points (NCs) and/or Data Managers (DMs) are responsible for collecting, validating, submitting sales data and for validating the PCU data uploaded by the Agency.

[3] Available from the Agency's website via: Home > Regulatory > Veterinary medicines > Overview > Antimicrobial resistance > European Surveillance of Veterinary Antimicrobial Consumption

Figure 1. Organisation of the ESVAC project



1.4. ESVAC web-based application

Detailed information about the web-based application to report and validate sales and animal population data is described in the document "ESVAC web data collection – user guide". The user guidance describes the process of uploading the sales data via the web-based application, how to correct data sets with errors before submission and finally, how to submit the sales data via the web-based application.

This user guide also includes the reporting of data on animal population by the EMA or by the participating countries when required data are missing in EUROSTAT or TRACES. The document "ESVAC BI validation reports – user guide" also includes the validation of animal population data collected by the Agency by the participating countries.

2. ESVAC sales data

2.1. Selection of data source

The infrastructure of the distribution of antimicrobial VMPs may vary considerably from country to country; such medicinal products can be dispensed to the end-users by marketing authorisation holders, wholesalers, retailers, feed mills, pharmacies, veterinarians or a combination of these. Wholesalers and pharmaceutical industries may also trade between each other and export antimicrobial VMPs to other Member States (MS). The first step in setting up surveillance of antimicrobial VMPs is therefore to identify and describe the distribution system for veterinary medicinal

products. The data source selected should, if possible, provide data on sales to end-users within the country.

2.2. Antimicrobial substances used in veterinary medicine to be included in sales dataset

To obtain harmonised data on sales of antimicrobial VMPs, the Anatomical Therapeutic Chemical classification system for the classification of substances intended for therapeutic use in veterinary medicine (ATCvet) is applied (Table 1) (http://www.whocc.no/atcvet/atcvet_index/). This includes all pharmaceutical forms and medicated feed except dermatological products (ATCvet group QD) and products for sensory organs (ATCvet group QS).

The antimicrobial substances for veterinary use (ATCvet groups) to be reported to the ESVAC database are shown in Table 1.

Table 1. Categories of antimicrobial substances used in veterinary medicine, as included in ESVAC database

Groups of antimicrobial substances	ATCvet codes[4]
Antimicrobial substances for intestinal use	QA07AA; QA07AB
Antimicrobial substances for intrauterine use	QG01AA; QG01AE; QG01BA; QG01BE QG51AA; QG51AG
Antimicrobial substances for systemic use	QJ01
Antimicrobial substances for intramammary use	QJ51
Antimicrobial substances used as antiparasitic agents	QP51AG

2.3. Variables to be collected for each VMP presentation

Table 2. Variables to be collected for each VMP presentation[5]

Variable	Description of variable	Comments
COUNTRY	**ISO Country Code**: 2 letter code (alpha-2 code), according to the International Standard for country codes. (http://www.iso.org/iso/country_codes)	To identify the country for which sales data are reported.
YEAR	**Four-digit number**	To identify the calendar year for reported sales data.

[4] As available in the ATCvet index: http://www.whocc.no/atcvet/atcvet_index/
[5] Of note is that this protocol and 2019 sales data reporting template do not display requirements as outlined in Article 57 of Regulation (EU) 2019/6.

Variable		Description of variable	Comments
PRODUCT INFORMATION	**MA**	**Marketing Authorisation Identification** Number, number and letter combination or name of the marketing authorisation holder. Additional information: For VMPs available through special licence/marketing authorisation or through parallel trade, the field should be marked "Special licence".	To identify the VMP and enable a link with other databases.
	PRESENTATION ID	**Identification Number of Product Presentation** VMP package code (can be a number or number and letter combination) is a unique identifier for each VMP presentation (name, pharmaceutical form, strength and pack size). As a key variable in many databases, identification number should be stable over time, so that medicinal products that are no longer marketed or authorised can still be identified to enable the analysis of historical data.	To enable the identification of all VMP presentations marketed in a country. To enable the validation and analysis of each presentation pack size in which the VMP is sold. To enable the analysis of historical data. To enable the identification of duplicate reporting of sales.
	NAME	**Veterinary Medicinal Product Name (in national language)** Name of medicinal product as per product information (summary of product characteristics, labelling and package leaflet), e.g.: Harmony vet 50 mg tablets 2 x 30; Harmony vet long acting 10 mg/ml suspension for injection.	To identify and validate recorded details.
	FORM	**Pharmaceutical Form/Route of administration** Form should be selected from the standardised defined list: boluses (BOLUS), injectable products (INJ), intramammary products for lactating cow treatment (INTRAMAM), intramammary products for dry cow treatment (INTRAMAM-DC), intrauterine products (INTRAUT), oral pastes (ORAL PASTE), oral solutions (ORAL SOLU), oral powders or granules (ORAL POWD), premixes (PREMIX), capsules and tablets (TABL).	To enable the analysis of data by administration route/ pharmaceutical form.
	LONG ACTING	**Long-acting Injectable Products** This refers to injectable products with long-acting/prolonged release formulation, for which the active(s) substance(s) are released over an extended period of time.	Optional.

Variable		Description of variable	Comments
PRODUCT INFORMATION	**PACKSIZE**	**Content Quantity in Package: Pack size** Numerical value only to indicate the pack size, e.g.: 100 for 100 tablets or 100 intramammary syringes; 10 for 10 ml injection; 2 for a package of 2 kg premix; 300 for a box of 10 blisters of 30 tablets; 12 for a box of 12 intramammary syringes).	To enable the calculation of the quantity of antimicrobial active substance in each product presentation. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI (Business Intelligence) application after data submission.
	PACKSIZEU	**Content Unit of Measurement** e.g.: ML, L, G, KG, PIECE (e.g. tablets, capsules, boluses and intramammary products). The pack size unit should be harmonised with the strength unit, e.g. if the pack size is 1 kg, the strength unit should be per kg.	To enable the calculation of the quantity of antimicrobial active substance in each product presentation. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI application after data submission.
	ATCVET	**ATCvet- 5th level: Anatomic Therapeutic Chemical (Classification) Veterinary** Value to be selected as per the latest version of the ATCvet index.	To standardise the approach for analysis and reporting of data per antimicrobial classes as well as anatomical and therapeutic groups. If an ATCvet code has not been assigned for a substance or for fixed combinations, the Agency has to be contacted.
	SPECIES	**Animal Species** All the animal species for which the VMP is authorised, e.g. cattle (CA), pigs (PIG), poultry (POU), chicken (G*allus gallus)* (GG), turkeys (TU), ducks (DU), geese (GE), sheep (SH), goats (GO), horses (HO), food-producing rabbits (RA), finfish (FI), dogs (DOG), cats (CAT), minks (MI), foxes (FO), other food-producing animals (ZZ), not known (NO), other non-food-producing animals (YY).	Species details are currently used to support data preparation for the JIACRA[6] reports. Completion of this variable is optional for VMPs available through special licence/marketing

[6] Joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) reports present work done by European Medicines Agency, European Food Safety Authority and the European Centre for Disease Prevention and Control to analyse the potential relationship between the consumption of antimicrobials by humans and animals and the occurrence of antimicrobial resistance.

Variable		Description of variable	Comments
			authorisation or through parallel trade.
NO PACKS		**Number of Packages Sold** Numerical value to indicate the number of packages of product presentation sold within the reporting period (year) in the reporting country.	To calculate the mass (in tonnes) of antimicrobial active substance sold for each product presentation. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC web-based application after data submission. For validation purposes by ESVAC BI application after data submission.
ACTIVE SUBSTANCE INFORMATION	**INGR_ID**	**Active Substance Code Value** Automatically attributed identification number of each substance by the macro or the ESVAC web-based application.	Serve as a unique identifier for each active substance per each VMP. For data management purposes.
	INGR	**Antimicrobial Active Substance Name** Name to be selected from the defined list of antimicrobial active substances names as presented according to the latest version of the ATCvet index. In the case of fixed combination products, all the antimicrobial active substances' names must be provided separately.	Important to avoid misinterpretation of a substance name if given in a language other than English. The system only accepts the latest version of names published in the ATCvet index. If a substance name is not published in the ATCvet index, the Agency has to be contacted.
	SALT	**Salt of Antimicrobial Active Substance when Strength is Expressed in International Units (IU)** Name to be selected from the defined list of names of salt of antimicrobial active substances. Currently only applicable to colistin sulfate and colistin methane sulfonate.	Only in cases where the strength of an antimicrobial active substance is given in IU (IU/G, IU/ML or IU/PIECE) and the substance is included in the pre-defined list, to allow for conversion to mass of active substance. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI

Variable		Description of variable	Comments
			application after data submission.
ACTIVE SUBSTANCE INFORMATION	**DERIVATIVE**[7]	**Name of Derivative or Compound of Antimicrobial Active Substance** Name to be selected from the defined list of derivatives/compounds (Table 3), e.g.: for procaine benzylpenicillin this name should be given as the derivative variable and benzylpenicillin as the antimicrobial active substance name variable.	To support the calculation of the mass of antimicrobial active moiety[8] in a standardised manner. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI application after data submission.
	STRENGTH	**Quantity of the Antimicrobial Active Substance** Numerical value of the concentration or quantity of the antimicrobial active substance in mg/g/IU per relevant unit ml/mg/l/g/kg/piece as declared in the product information (e.g. 10 for 10 MG/ML). In the case of fixed combination products, the strengths of all the antimicrobial active substances per presentation must be provided separately.	To enable the calculation of the quantity of antimicrobial active substance in each product presentation and to validate the calculated active substance content. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI application after data submission.
	STRENGTHU	**Unit of Measurement for Strength** Unit of measurement of strength to be chosen from a defined list (e.g.: IU/G, IU/ML, IU/PIECE, G/KG, G/L, G/PIECE, MG/ML, MG/G, MG/PIECE). Should be compatible with the pack size unit. In the case of fixed combination products, the unit of measurement of all antimicrobial active substances per presentation must be provided separately.	To enable the calculation of the quantity of antimicrobial active substance in each product presentation. For validation purposes at country level prior to submission via web-based application. For validation purposes by ESVAC BI application after data submission.

[7] Previously referred to as prodrug
[8] An active substance can have different derivatives with the same therapeutic moiety. In this context, active moiety should be interpreted as the part of the derivative or compound that is responsible for the antimicrobial pharmacological action and not as a synonymous for active substance.

Variable		Description of variable	Comments
ACTIVE SUBSTANCE INFORMATION	**CONV FACT IU**	**Conversion Factor when Strength is given in IU** When strength unit is e.g. IU/ML or IU/PIECE, a conversion factor from the defined list (Table 4) is assigned automatically by the macro or ESVAC web-based application for the harmonised calculation of the mass of the active substance.	To enable the calculation of the mass of antimicrobial active substance per product package. If an antimicrobial active substance with strength given in IU is not listed, the Agency should be contacted.
	CONV FACT DERIV	**Conversion Factor of Certain Derivatives or Compounds** Only when strength of the VMP is given for the listed derivatives/compounds and not for the active moiety (e.g. procaine benzylpenicillin that is a derivative/compound for the active moiety benzylpenicillin), a conversion factor from a defined list (Table 3) is automatically assigned by the macro or ESVAC web-based application, for the harmonised calculation of the mass of the active moiety.	To enable the calculation of the mass of the antimicrobial active moiety per product package. For validation purposes by ESVAC BI application after data submission. If a derivative/ compound is not listed, the Agency should be contacted.
	INGR CONTENT	**Content of Antimicrobial Active Substance in Package** As a clarifying step in the calculation of the sales volume of the antimicrobial active substance, this variable provides the mass (in grams) of antimicrobial active substance per one unit of product package. This value is calculated automatically by the macro or ESVAC web-based application.	To enable the calculation of the sales volume. For validation purposes by ESVAC BI application after data submission.
	CONTENT UNIT	**Unit of Antimicrobial Active Substance in Package** The unit of antimicrobial active substance per product package is given in grams for all antimicrobial substances. This field is filled automatically by the macro or ESVAC web-based application.	To enable the calculation of the sales volume. For validation purposes at country level prior to the submission via web-based application.
TONNES SOLD		**Tonnes of Antimicrobial Active Substance Sold** Based on all the details provided, this represents the volume of the antimicrobial active substance in tonnes per product presentation. This value is calculated automatically by the macro or ESVAC web-based application.	Provides the sales volume of the antimicrobial active substance in tonnes.

2.3.1. Conversion factors when strength is given in IU

When strength is given in IU (e.g. IU/ML) the quantity sold must be converted to present data in mass of active substance. In order to report harmonised data, the conversion factors from IU to mg shown in Table 3. are applied by the ESVAC web-application to calculate the mass of antimicrobial active substance sold.

Note that some conversion factors were updated in the latest version of the ESVAC protocol. More details about these conversion factors, including the derivate form used in the collaborative studies to assign the potency for each active substance, can be found in the Annex 2. of this protocol.

Table 3. Conversion factors for calculation from IU to mg of antimicrobial active substance

Active Substance	IU/MG	Conversion factor (MG/IU)
Apramycin	552	0.0018116
Bacitracin	74	0.013514
Benzylpenicillin[9]	1670	0.0005988
Chlortetracycline	1000	0.001
Colistin sulfate	20500	0.000049
Colistin methane sulfonate	12700	0.000079
Dihydrostreptomycin	777	0.001287
Erythromycin	920	0.001087
Framycetin	706	0.0014172
Gentamicin	620	0.001613
Kanamycin	796	0.001256
Neomycin	762	0.0013123
Oxytetracycline	880	0.0011364
Paromomycin	750	0.0013333
Polymyxin B	8403	0.0001190
Spiramycin	3200	0.000313
Streptomycin	760	0.0013158
Tetracycline	982	0.00101833
Tobramycin	875	0.001142857
Tylosin	1000	0.001

2.3.2. Conversion factors of certain derivatives or compounds

In order to obtain harmonised data, the conversion factors for certain derivatives or compounds of antimicrobials shown in Table 4 are applied to calculate the quantity of antimicrobial active moiety.

Note that some conversion factors were updated in the last version of the ESVAC protocol. More details about these conversion factors can be found in the Annex 2.

[9] Applies to all derivatives/compounds of benzylpenicillin.

Table 4. Name of derivates/compounds for which conversion factors are applied

Derivative or compound[10]	Conversion factor
Benethamine benzylpenicillin	0.61
Benzathine benzylpenicillin	0.68
Cefapirin benzathine	0.78
Cefalexin benzathine	0.74
Cloxacillin benzathine	0.78
Oxacillin benzathine	0.77
Penethamate hydriodide	0.60
Procaine benzylpenicillin	0.57

3. Call for data

Prior to the annual call for data, the Agency updates the lists of ATCvet codes and names of substances as per the ATCvet index. The list of updated ATCvet codes and names of substances are included in the sales template that is provided together with the call.

The sales template contains lists with defined terminology to enable standardised and harmonised data reporting.

3.1. Data submission

Data must be submitted using the ESVAC web-based application. For supporting accuracy check of sales data, the NCs and DMs are also requested to send the final version of the sales template to the Agency - i.e. the version used to create the three CSV files for uploading on the ESVAC web-based application.

4. Filling in the sales template

4.1. General considerations

The sales data should always be recorded in the country specific sales template provided together with the call for data. For new countries a blank sales template should be applied.

In case of fixed combination products, the columns for the INGR variables must be filled in for each active substance in separate columns in the same row.

Enzyme inhibitors such as clavulanic acid, which does not pose any antimicrobial activity by itself and are not included in the latest ATCvet index, are not accepted by the ESVAC web-based application. As it is important to quantify use of e.g. amoxicillin+ clavulanic acid the ATCvet code for the combinations should be given (e.g. QJ01CR02 for amoxicillin+ clavulanic acid).

Other active substances, which are not classified as antibiotics, e.g. anti-inflammatory, fall out of scope of the data reporting protocol and should not be included in the sales template.

[10] Previously referred to as prodrugs.

4.2. Comments on the various fields' components

Presentation identifier (ID) (VMP Package Code Value)

When this information is not available, it is necessary to assign individual value for each VMP presentation.

The use of a standard and stable Presentation ID, e.g. International Article Number (EAN) (originally European Article Number) or national unique presentation ID number, is needed for the traceability of each product presentation as well as for the interaction with other databases (e.g. the EU Veterinary Medicinal Product Database). Furthermore, it enables identification of duplicates.

In case Presentation IDs are not available, these IDs can be derived from other variables. It is recommended to combine the marketing authorisation number (MA), name with the FORM, the PACKSIZE and PACKSIZEU variables. This combination of MA+NAME+FORM+PACKSIZE+PACKSIZEU should be unique per each VMP presentation.

FORM

The VMP form must be selected from the standardised list that combines pharmaceutical form and route of administration: boluses ("BOLUS"), injectable products ("INJ"), intramammary products for lactating cow treatment ("INTRAMAM"), intramammary products for dry cow treatment ("INTRAMAM-DC"), intrauterine products ("INTRAUT"), oral pastes ("ORAL PASTE"), oral solutions ("ORAL SOLU"), oral powders or granules ("ORAL POWD"), premixes ("PREMIX") and capsules and tablets ("TABL").

Form "BOLUS" represents a type of large tablet authorised for use in food-producing animals, and this form should be selected if the product information supports this information.

The option "INTRAUT" should be indicated for any VMP intended for gynaecological and intrauterine use, including different forms of product e.g. as tables, solutions, suspensions for gynaecological or intra-uterine administration.

Form "ORAL SOLU" also captures powders for administration in drinking water, for example, when there are instructions such as "powder for solution" or "powder for administration in drinking water" in the product information, this VMP should be reported as an oral solution.

If in the product information it states that an oral powder can be administered both, with drinking water and in feed, the form should be reported as oral powder ("ORAL POWD").

Premixes ("PREMIX") are VMPs, usually in the form of powders or granules, which are intended to be mixed into animal feed by feed mills.

Form "TABL" includes capsules and tablets, typically authorised for use in cats and dogs.

LONG ACTING

All injectable products with long-acting/prolonged release formulation, for which the active(s) substance(s) are released over an extended period of time, e.g. with indication to long acting duration in the product's name (e.g. LA or L.A.), should be filled-in as "YES" in this column. For those injectable products where information about long acting duration is not possible to obtain from the name or the product information, this field should be left blank.

ATCVET [ATCvet code- 5th LEVEL]

If the ATCvet code has not been assigned for a specific antimicrobial substance for veterinary use or for fixed combinations, please contact the Agency that will ask the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (WHO Centre) to provide a code for such product. The sales template will be updated by the EMA when the codes have been assigned.

The ESVAC web-based application will not allow the upload of a product unless a valid ATCvet code has been assigned (see the document "ESVAC web data collection – user guide" for further information).

SPECIES

All the animal species for which the VMP is authorised should be included in the sales template as per details available in the product information, and should be marked with the following abbreviations: cattle (CA), pigs (PIG), poultry (POU), chicken (*Gallus gallus)* (GG), turkeys (TU), ducks (DU), geese (GE), sheep (SH), goats (GO), horses (HO), food-producing rabbits (RA), finfish (FI), dogs (DOG), cats (CAT), minks (MI), foxes (FO), other food-producing animals (ZZ), not known (NO), other non-food-producing animals (YY)

For VMPs available through special licence/marketing authorisation or through parallel trade the identification for which species these VMPs are authorised in the respective country may be problematic, therefore for such cases "not known (NO)" could be recorded in the sales template, if no detailed information on species is available.

Species details are currently used to support data preparation for the JIACRA reports. Therefore, it is requested detailing the type of species, when the category "others" is applicable, e.g. ZZ (quail, partridges, pheasants) and YY (pet rabbits, ornamental birds, racing pigeons).

INGR _ID [Active Substance Code Value]

If using the macro of the excel template, the INGR_IDs is assigned automatically by the macro.

If either the sales template or the macro is not used, it is recommended to assign the INGR_ID by concatenating the Presentation ID with the order of the active substance in the VMP package separating by a '#', e.g. for a medicinal product package with a presentation ID of "AZE10" containing two substance the first substance will be coded "AZE10#1" and the second one "AZE10#2".

INGR [Antimicrobial Active Substance Name (ATCvet name)]

If an antimicrobial active substance name is not published in the ATCvet index, the Agency has to be informed as soon as possible. Upon receiving your email, the Agency will ask the WHO Centre to provide the ATCvet code and substance name for such active substance. The Agency will provide you a temporary solution or the correct name when the ATCvet codes and substance names have been assigned by the WHO Centre.

CONV FACT IU (Conversion Factor IU) and CONV FACT DERIV (Conversion Factor of certain Derivatives or Compounds)

These will be recorded automatically by use of a macro designed for the ESVAC Sales Template.

If a Conversion Factor IU or Conversion Factor of certain Derivatives or Compounds for the antimicrobial active substance or derivative/compound in question is not included in the sales template, the Agency (via email address: ESVAC@eu.europa.eu) must be contacted.

5. Data quality check

The sales and animal data quality requirements are confirmed by NCs and/or DMs of the ESVAC participating countries and by the Agency at the data entry and data checking phase. NCs and DMs are responsible to ensure that sales data submitted to the Agency fulfil business information demand. Suitable quality control procedures are defined by each country taking into account their individual data collection process. It is strongly advised to establish a procedure for checking data quality, including data coverage prior, during and after data collection and reporting, in order to obtain high quality of data available in the ESVAC database.

Although NCs/DMs validate their data prior to submission via ESVAC web-based application, the Agency in addition gathers essential detailed information via the annual questionnaire. In line with the Agency proposed framework intended to serve as quality indication for data completeness and logical consistency of every approved dataset, the Agency follows up with the responsible NCs/DMs on any potential outlier identified.

A brief overview of the outlier-detection measures taken by the Agency to assist in the identification of possible errors in data submitted to the ESVAC database are included in Annex 1 of this protocol.

For the EU Member States, the ESVAC reference animal data are obtained from the Eurostat and TRACES databases and provided to the NCs and/or DMs for their approval; EEA countries have to fill in these data themselves. Typically, NCs and/or DMs approach suitable institutions in their country to confirm statistics and, when necessary, replace reference values with the data provided from their national statistical offices.

5.1. Validating the sales data prior to the submission to the Agency

The sales data submitted to the ESVAC web-based application should cover all sales of antimicrobial VMPs (according to ATCvet categories defined in Table 1) in the territory of the respective participating country. To attain full data coverage, for all countries where specific VMPs are available through special licence/marketing authorisation or through parallel trade, these antimicrobial VMPs should be included in the sales template for each reporting year. Verification of sales data compliance to the requirements as disclosed in this document from every ESVAC NC and/or DM is expected. Therefore, it is highly recommended to follow the procedures listed below.

Table 5. Processes for validating the sales data prior submission to the Agency

Item	Steps	Comments
Stage 1. Establishing a procedure for checking the data quality, including data coverage, prior to the data collection.	1.1. Identify ALL the actual data providers through the national register of VMPs suppliers – e.g. wholesalers, MAHs, pharmacies, feed mills etc.	• The National Medicines Authority is usually responsible for keeping registers of authorised VMPs and VMPs suppliers; exceptionally no such information may be available of feed mills. • Identify if there are any other data sources of sales data that can be used for comparison or for cross-checking of data.
	1.2. In case sales data are obtained from prescriptions (e.g. from pharmacies, veterinarians), identify all antimicrobial VMPs for which data are to be collected.	
	1.3. Specify the antimicrobial VMPs to be included in the data call/selection[11] – i.e. the ATCvet codes to be covered (see Table 1.).	
Stage 2. Sending a call for sales data of antimicrobial, if applicable.		
Stage 3. Data collection – after a deadline has passed for data to be delivered by the national data providers.	3.1. Check that all data providers have delivered the data.	• In case not all data providers have delivered the data, submit a reminder; ask for a written confirmation in case of no sales of specific VMP. • Alternatively, after entering data into the ESVAC template compare the output with the filled-in national data. • As an additional verification step, data can be cross-checked with other sales sources, if available.
	3.2. Identify/review that all VMP presentations are included in the sales template for the corresponding year.	

[11] It is a responsibility of the National Authority to ensure the collection of other antimicrobial agents, if required for national reporting.

Item	Steps	Comments
Stage 4. When responses received from all identified data providers.	4.1. After entering data in ESVAC template, compare NO PACKS, e.g. number of packages, and TONNES SOLD, e.g. calculated tonnes sold, by ID number with data in template for previous year(s) to identify potential outliers (if applicable).	
	4.2. For the assumed outliers contact corresponding data provider(s) and ask for verification.	
	4.3. Run a validation by using the macro included in the template to identify any inconsistencies in the data and correct any identified mistakes.	
	4.4. Additionally, cross-check ATCvet entries and corresponding active substances per presentation.	
Stage 5. Submitting sales data after the initial validation via the ESVAC web-based application for corresponding year.	5.1. Run validation reports from the ESVAC BI application to identify any outliers (see Annex 1).	• For potential outliers compare latest submitted dataset with dataset approved for previous year by classes of antimicrobial VMPs and by pharmaceutical forms.
	5.2. After receiving validation report, clarify the major differences in sales, if possible.	

Item	Steps	Comments
Stage 6. After sales data are finalised and corrected, sending approval to the Agency to confirm that corresponding sales template can be used for further analysis and for preparation of the next report.	6.1. Upload the final sales template into the ESVAC web-based application, if necessary, and send the final sales template to the Agency.	
	6.2. Review suggestions sent by the Agency, when applicable, and send your approval to use the finalised sales template for further analysis.	

6. Animal population data. Calculation of PCU

6.1. Animal categories included in PCU

Animal categories included in the calculation of the PCU are included in Table 6. The animal population data are obtained from Eurostat, the Statistical Office of the European Union[12], which covers data on numbers and biomass of food-producing animals slaughtered, as well as data on livestock food-producing animals per EU MS. In cases where data are not available in Eurostat (e.g. for rabbits), national statistics is applied. For horses (food-producing species according to the EU legislation), national statistics provided by the NCs and/or DMs are used. As data on population of dogs and cats are not available in all participating countries, these species are not included in the PCU. Therefore, antimicrobial VMPs approved for use in companion animals only, i.e. tablets, are excluded from the datasets prior to the normalisation of the sales by the PCU.

Animals exported for fattening or for slaughter in another Member State are likely to be treated with antimicrobial agents in the country of origin, and therefore it is important to correct this for the major species (chickens, cattle, pigs and sheep). However, the Eurostat data on numbers of animals exported or imported for fattening or slaughter might not be completed, as exports and imports are only reported above a certain number, which implies that the Eurostat data represent an underestimate of these for most species and countries. Such data are therefore obtained from TRACES (DG SANCO, European Commission), as these are based on health certificates, which are obligatory for all animals crossing any border.

Typically each year at the start of September, the Agency provides the reference data for the animal categories shown in Table 6. obtained from Eurostat and TRACES databases. These are the only animal categories that are accepted by the ESVAC web-based application. For categories for which data are not available in Eurostat or TRACES, countries should submit missing values to enable PCU calculation.

EEA countries are requested to upload all animal population data per specified categories as no values may be available through Eurostat and TRACES.

[12] http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes

Table 6. Animal categories included in the calculation of the PCU and data types to be reported

Animal category
Cattle (heads/number of animals)
Slaughtered cows
Slaughtered heifers
Slaughtered bullocks and bulls
Slaughtered calves and young cattle
Slaughtered bovine – Import
Slaughtered bovine – Export
Fattening bovine – Import
Fattening bovine – Export
Living dairy cows
Pigs (heads/number of animals)
Slaughtered pigs
Slaughtered pigs – Import
Slaughtered pigs – Export
Fattening pigs – Import
Fattening pigs – Export
Living sows
Poultry (heads/number of birds)
Slaughtered broilers
Slaughtered turkeys
Slaughtered poultry – Import
Slaughtered poultry – Export
Caprinae (heads/number of animals)
Slaughtered sheep and goats
Slaughtered sheep – Import
Slaughtered sheep – Export
Fattening sheep – Import
Fattening sheep – Export
Living sheep
Slaughtered goat – Import
Slaughtered goat – Export
Fattening goat – Import
Fattening goat – Export
Equidae (heads/number of animals)
Living horses
Rabbits (heads/number of animals)
Slaughtered rabbits
Fish (tonnes)
Biomass of farmed fish produced

6.2. Calculation of PCU

Essentially, the PCU for each animal category is calculated by multiplying numbers of livestock animals (dairy cows, sheep, sows and horses) and slaughtered animals (broilers, cattle, goats, pigs, rabbit, sheep and turkeys) by their theoretical weight at the likely time for treatment. For farmed fish, Eurostat data are given only as live-weight slaughtered, rather than weight of slaughtered farmed fish; thus, for fish biomass live-weight slaughtered is used to calculate the total PCU. In case of animals exported or imported for fattening or slaughter (broilers, cattle, goats, pigs and sheep), the PCU is calculated by multiplying the number of animals with a standardised weight (Table 7.).

The PCU of the animals exported for fattening or for slaughter in another Member State is added to the PCU of livestock and to the PCU of slaughtered animals in the country of origin, because young animals are typically treated more frequently than at other age classes. The PCU for animals imported for fattening or for slaughter in another Member State is subtracted from the total PCU of livestock and slaughtered animals, since it is included in the data of slaughtered animals (Eurostat data) and in order to avoid double counting (both in exporting and importing country).

Table 7. Theoretical weights at the likely time for treatment used to calculate the population correction unit[13]

Animal category	Weight in kg
Slaughtered or livestock (Eurostat)	
Slaughtered cow	425
Slaughtered heifer	200
Slaughtered bullocks and bulls	425
Slaughtered calves and young cattle	140
Living dairy cow	425
Slaughtered pig	65
Living sow	240
Slaughtered broiler	1
Slaughtered turkey	6.5
Slaughtered sheep and goats	20
Living sheep	75
Living horse	400
Slaughtered rabbit	1.4
Imported/exported for fattening or slaughter (TRACES data)	
Slaughtered bovine	425
Fattening bovine	140
Slaughtered pig	65
Fattening pig	25
Slaughtered poultry	1
Slaughtered sheep	20
Fattening sheep	20
Slaughtered goat	20
Fattening goat	20

PCU calculation by species, age class and production type

The PCU is calculated for each species, weight class 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

The total PCU by country is calculated as follows:

$PCU = \text{total } PCU_{Domestic} + \text{total } PCU_{Export} - \text{total } PCU_{Import}$

1 PCU = 1 kg of animal biomass.

[13] The data sources used 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).

7. Information required in addition to sales data

In order to support understanding of the reported data it is important to have access to some key information such as types of data and data sources. Therefore, a set of questions have been included in the ESVAC web-based application under the section "Answer questionnaire".

Questionnaire is split in 5 sections to record necessary information:

1) Data source
    a. to identify the source of the sales data;
    b. to identify total number of data sources or data providers;
2) Data type
    a. to indicate if submitted data present sales, prescriptions or purchase data;
    b. to record the supplementary information on the origin and end-users;
3) Possible double reporting
    a. to indicate if sales between wholesalers or between pharmaceutical companies and wholesalers have been excluded;
    b. in case both wholesalers and feed mills are providing data, to indicate if possible double reporting of sales has been excluded;
4) Products sold on special licence
    a. to indicate if VMPs reported include VMPs available through special licence/marketing authorisation or through parallel trade. In case these VMPs are included in the sales template, the proportion of their sales in comparison to total sales for that year should be indicated.
5) General comments
    a. to note any other useful information for interpretation of the data submitted to the Agency.

The questionnaire must be submitted annually.

8. Indicator for reporting of the sales data

The main indicator to be applied expressing the sales of antimicrobials VMPs is mg of antimicrobial active substance normalised by the population correction unit (mg/PCU):

$$\frac{\text{Quantity sold in metric tonnes} \times 10^9}{\text{PCU in kg}}$$

The data are presented according to the ATCvet hierarchical system. For fixed combination products, each antimicrobial active substance is allocated to the relevant ATCvet code for single substances (e.g. spectinomycin is included in 'Other antibacterials').

9. Confidentiality and security of submitted sales data

During the validation of the submitted data, NCs and/or DMs are requested to inform the Agency on any data which for reasons of commercial confidentiality (or any other grounds) cannot be disclosed either on the ESVAC annual report and/or on the ESVAC Interactive Database.

Data published by the Agency, either on the public web page or as part of scientific or other publication, do not contain, or in any other way disclose, any commercially confidential information on specific veterinary products. Principles for ensuring the confidentiality of data supplied to the ESVAC project (EMA/327935/2010) are published on the Agency web page.

The Agency has dedicated controls that adhere to the three main requirements related to the security of information: availability, confidentiality and integrity.

- Data are stored in a secure location in the Agency premises and backed-up regularly. The Agency IT infrastructure provides high availability of services.
- Data are made publicly available by the Agency at the agreed date of publication (typically the same day when the ESVAC annual report is published). Until this time, only users can see their own datasets (to which they have full access). As no personal data are held in the ESVAC databases, no specific controls are required.
- Networks are segregated so that stored data are filtered with only relevant data being exposed, in a consolidated format, to the public through the ESVAC Interactive Database.

ANNEX 1

1. Additional information for checking data quality

The ESVAC web-based application runs a data accuracy check ensuring that the information provided is in compliance with the requirements, as noted in sections 2.2 of this protocol. In case of inconsistencies, a list of errors for follow-up actions is provided. The system will only allow submission of the sales template once all issues are resolved.

1.1. Validation of data

To facilitate quality and validity checks of the submitted data, confirmation reports are provided via the Oracle Business Intelligence Enterprise Edition (BI) tool, known as ESVAC BI application.

A set of ESVAC BI validation templates are available to each ESVAC representative to run analysis for any uploaded datasets of their own country. Confirmation reports include:

1.1 Substance Sales Report;

1.2 Register Report;

1.3 Product Sales Report;

1.4 PCU Category Report;

1.5 PCU Report;

1.6 Sales Data Compare Report.

Confirmation reports support the comparison of sales, by antimicrobial classes and pharmaceutical forms, and animal population data with previously uploaded values.

1.2. Cross-checking of sales data (supplementary information to section 5)

For supporting cross-checking of sales data, the NCs/DMs are requested to also send to the Agency the sales template – i.e. the final sales template used to create 3 CSV files for uploading on the ESVAC web-based application. To identify any possible errors, e.g. missing active substances, inaccurate strength values, imprecise ATCvet codes, data recorded per each product in the sales template are compared with the details from the publicly available product information by the Agency. All identified potential discrepancies are reported to the NCs/DMs for their attention and confirmation.

Manual checking, run by the Agency, for standardization and harmonization concern the following fields of the sales template:

1. COUNTRY – to confirm if all lines are completed;
2. YEAR – to confirm if all lines include reference to corresponding year;
3. PRESENTATION ID – to confirm if ID is provided in all lines and if there are any possible duplicates;
4. FORM – to filter by form and gradually cross-check with product names and ATCvet codes;
5. LONG ACTING – to confirm if all injectable products with indication to long acting duration (e.g. LA or L.A) or any previously identified VMPs are marked as long acting;

6. ATCvet – to confirm codes with a special attention to intramammary, intrauterine products and penicillins; to confirm if all active substances are reported in the line with ATCvet index indicating fixed combination products;
7. SPECIES – to confirm if species information is provided in the template; to search for corresponding product information to add missing details for NCs and/or DMs consideration;
8. INGR – to cross-check if all active substances are provided as per corresponding product information;
9. SALT – to filter any lines where strength is given in IU and to confirm details as per available product information; to confirm that salts are only provided for colistin;
10. STRENGTH – to confirm if strength is in line with the name of VMP or as per available product information, when applicable; and to identify any peculiar strength values reported;
11. STRENGTHU – filtering by PACK SIZEU, to ensure that strength unit is given in a harmonised manner (e.g. if pack size unit is provided in ML, then strength unit should be given as IU/ML or MG/ML); all strength units should be checked by line for all active substances.

1.3. Rules for reporting of qualitative and quantitative composition of antimicrobial VMPs (variable strength)

The Working Group on Quality Review of Documents (QRD) provides assistance to the Agency's scientific committees and to companies on linguistic aspects of the product information for medicines. The current QRD template [Version 8.2, 01/2021][14], determines that in section 2 of the SPC, full details of the qualitative and quantitative composition in terms of active substances should be provided using their International Nonpropriety Names (INN) or common names.

For salts, esters or other derivatives, the quantity of active moiety, i.e., the part of the derivative/compound which has pharmacological activity, should be clearly expressed in the product information.

According to the latest version of the QRD annotated template[14], qualitative and quantitative composition should include following details:

For salt/ester:	*{quantity of active moiety} as {salt/ester}* *or* *{quantity of active moiety} equivalent to {quantity of salt/ester}*
E.g.:	*5 mg {X} as {Y}* *8 mg {X} equivalent to 10 mg {Y}]*

The QRD also establishes that the strength, as provided in the name of the product, should be consistent with the requirements of section 2 of the SPC.

These requirements are also in line with the "Guideline on the Summary of Product Characteristics for Pharmaceutical Veterinary Medicinal Products – Volume 6C Notice to Applicants"[15].

As many of the antimicrobial presentations included in the sales template may correspond to old VMPs for which the official product information may not be updated in line with the last version of the QRD,

[14] https://www.ema.europa.eu/en/documents/template-form/qrd-veterinary-product-information-annotated-template-english-version-82_en.pdf
[15] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-6/c/spcpharmaceuticals_10-07-2006_en.pdf

ESVAC sales data validation rules should be applied in order to allow the standardised calculation of the mass of the antimicrobial active substances.

For the ESVAC activity, the reporting of the variable strength in the sales template file (Table 2) should follow the following rules:

Rule 1 – if only the quantity of active moiety is indicated in the SPC, the variable strength should be reported as the quantity of active moiety;

Rule 2 – if both the quantity of active moiety and quantity of ester/salt are indicated in the SPC, the variable strength should be reported as the quantity of active moiety;

Rule 3 – if only the quantity of ester/salt is indicated in the SPC, but a conversion factor is available for that specific compound/derivative in the defined list (Table 4.), the variable "strength" should be reported as the quantity of ester/salt or hydrous form, as applicable, and the compound name should be indicated in the column "derivative", to allow the macro in the ESVAC sales template and ESVAC web-based application to calculate automatically the quantity of active moiety;

Rule 4 - if only the quantity of salt/ester is indicated in the SPC, and no conversion factor is available for that compound/derivative in the defined list (Table 4.), the variable strength should be reported as the quantity of salt/ester or as per product's name and the Agency should be informed.

Rule 5 – if the quantity of active moiety is indicated in the SPC both in mg and in IU, the variable strength should be reported as the quantity of active moiety in mg;

Rule 6 – if the quantity of active substance is indicated in the SPC only in IU and a conversion factor is available for that specific antimicrobial active substance in the defined list (Table 3.), the variable strength should be reported as the quantity of active substance in IU, in order to convert the content to mass (in mg). For more details about the form of the active substance applicable to each conversion factor, please refer to Table 11 of the ESVAC protocol;

Rule 7 – if the active substance is colistin and the quantity of salt (colistin sulfate or colistin methane sulfonate) is indicated in the SPC in IU, the variable strength should be reported as the quantity of salt in IU, to enable application of the conversion factor from the defined list (Table 3.), and colistin sulfate or colistin methane sulfonate should be added as variable SALT.

If none of the above rules is applicable, a case-by-case analysis will be performed, and the Agency should be contacted.

Table 8. Examples for reporting the quantity of active substance (variable "strength") in the ESVAC sales template

No	Name of VMP, as available in section 1 of the SPC	Qualitative and quantitative composition, as available in section 2 of the SPC	How to interpret information on section 2 of the SPC	Quantity of active substance to be reported to ESVAC (column STRENGTH)	Additional comments
1.	Amoxicillin, 200 mg, powder for oral solution	Amoxicillin (as amoxicillin trihydrate) 200 mg	Quantity of amoxicillin trihydrate is not indicated in the SPC Quantity of amoxicillin is 200 mg	200	**Rule 1** should be applied.
2.	Amoxicillin 100	100 mg of amoxicillin base as trihydrate	Quantity of amoxicillin is 100 mg	100	**Rule 1** should be applied. In this example, base refers to the active moiety.
3.	*Invented Name* 250 mg	Amoxicillin (as amoxicillin trihydrate) 200 mg Clavulanic acid (as potassium clavulanate) 50 mg	Quantity of amoxicillin is 200 mg	200	**Rule 1** should be applied The ATCvet code QJ01CR02 should be used to indicate the presence of an enzymatic inhibitor (clavulanic acid).
4.	*Invented Name* 48%	Sulfadiazine as sulfadiazine sodium 400 mg Trimethoprim 80 mg	Quantity of sulfadiazine sodium is not indicated in the SPC Quantity of sulfadiazine is 400 mg Quantity of trimethoprim is 80 mg	400 sulfadiazine 80 trimethoprim	**Rule 1** should be applied for both active substances. For a fixed combination product, with 2 or more active substances, each active substance and respective strength should be reported in the sales template as INGR1, INGR2, etc and according with the rules applicable for each active substance.

No	Name of VMP, as available in section 1 of the SPC	Qualitative and quantitative composition, as available in section 2 of the SPC	How to interpret information on section 2 of the SPC	Quantity of active substance to be reported to ESVAC (column STRENGTH)	Additional comments
5.	*Invented Name*, 800 mg/g, oral powder	Amoxicillin trihydrate 800 mg (corresponds to 697 mg of amoxicillin)	Quantity of amoxicillin trihydrate is 800 mg Quantity of amoxicillin is 697 mg	697	**Rule 2** should be applied.
6.	Amoxicillin 20% oral powder	Amoxicillin trihydrate 200 mg (200 mg amoxicillin trihydrate = 174 mg of amoxicillin base).	Quantity of amoxicillin trihydrate is 200 mg Quantity of amoxicillin is 174 mg	174	**Rule 2** should be applied. In this example, base refers to the active moiety.
7.	Doxycycline, 500 mg/g, powder for oral solution	Doxycycline hyclate 500 mg (corresponds to 433 mg doxycycline)	Quantity of doxycycline hyclate is 500 mg Quantity of doxycycline is 433 mg	433	**Rule 2** should be applied.
8.	*Invented Name* 450 mg/g, granules for oral solution	Tiamulin hydrogen fumarate 450 mg (corresponds to 365 mg/g tiamulin)	Quantity of tiamulin hydrogen fumarate is 450 mg Quantity of tiamulin is 365 mg	365	**Rule 2** should be applied.
9.	*Invented Name*, 330 mg/g, intramammary solution	Lincomycin (as lincomycin hydrochloride) 330 mg (359.6 mg)	Quantity of lincomycin hydrochloride is 359.6 mg Quantity of lincomycin is 330 mg	330	**Rule 2** should be applied.

No	Name of VMP, as available in section 1 of the SPC	Qualitative and quantitative composition, as available in section 2 of the SPC	How to interpret information on section 2 of the SPC	Quantity of active substance to be reported to ESVAC (column STRENGTH)	Additional comments
10.	*Invented Name*, 100 mg, intramammary suspension	Procaine benzylpenicillin 100 mg	Quantity of procaine benzylpenicillin is 100 mg Quantity of benzylpenicillin is not indicated in the SPC	100	**Rule 3** should be applied. The quantity of active moiety is calculated automatically by the macro in the sales template and ESVAC web-based application, by indicating benzylpenicillin as INGR and procaine benzylpenicillin as DERIVATIVE.
11.	Amoxicillin 500 mg oral powder	Amoxicillin trihydrate 500 mg	Quantity of amoxicillin trihydrate is 500 mg Quantity of amoxicillin is not indicated in the SPC	500	**Rule 4** should be applied. The quantity of active moiety is not indicated in the SPC and no conversion factor is available, therefore the variable STRENGTH should be reported as the quantity of salt/ester or as per product's name.
12.	*Invented Name*, 200 mg/g, premix	Tylosin 200000 IU	The potency of tylosin is 200000 IU	200	**Rule 5** should be applied. The potency is indicated in section 2 of the SPC in IU and in section 1 in mass unit (mg).
13.	Spiramycin 1500000 IU oral powder	Spiramycin 1500000 IU	The potency of spiramycin is 1500000 IU	1500000 IU	**Rule 6** should be applied. The quantity of active substance is converted from IU to mg automatically by the macro in the sales template and ESVAC web-based through the

No	Name of VMP, as available in section 1 of the SPC	Qualitative and quantitative composition, as available in section 2 of the SPC	How to interpret information on section 2 of the SPC	Quantity of active substance to be reported to ESVAC (column STRENGTH)	Additional comments
					application of the defined conversion factor.
14.	*Invented Name*, 1000 mg/g, Premix	Colistin sulfate 1000 mg (20000000 IU)	The quantity of colistin sulfate is 1000 mg and the potency is 20000000 IU	20000000 IU	**Rule 7** should be applied. The quantity of active substance is converted from IU to mg automatically by the macro in the sales template and ESVAC web-based application, when indicating colistin as variable INGR, colistin sulfate as variable SALT and 20000000 IU/g as variable STRENGTH, through the application of the defined conversion factor.

2

ANNEX 2

2. Background information about ESVAC conversion factors

Two separate lists of conversion factors were established already at the start of the ESVAC activity in 2009 – one for certain derivatives or compounds of antimicrobials and one for antimicrobials for which strength may be given as IU. Conversion factors allow the expression and calculation of specific active substances in a standardised and harmonize manner. Gradually both lists of conversion factors have been revised by adding new examples and updating existing ones.

While the conversion factors to convert from IU to mass (mg) of active substance are mainly based on WHO International Standards for Antibiotics[16], conversion factors used to convert quantity from derivative/compound to quantity of active moiety are calculated based on the proportion of the molecular weight of the antimicrobial active moiety vs the molecular weight of whole compound or derivative.

It must be emphasized that all historical data included in the ESVAC database for all countries have been recalculated to apply the new conversion factors where it is applicable. Therefore, some of the results as presented in versions of the ESVAC annual reports published before 2021, which were in line with the previous versions of the ESVAC protocol, may differ slightly from results to be presented in any further reports. The ESVAC Interactive Database will reflect the new data.

2.1. ESVAC conversion factors when strength is given in IU

The conversion factors established for a list of defined antimicrobial active substances shown in Table 4 are applied to calculate the quantity of antimicrobial active substance when the strength in the SPC is given in IU. The application of these conversion factors allows for the conversion of the quantity from IU to mg and consecutively to calculate the sales volume per active substance in a standardised manner.

IU are used as a measure of the potency of a specific antibiotic, estimated by comparing the inhibition of growth of susceptible micro-organisms produced by known concentrations of the antibiotic to be examined and the corresponding reference standard of the substance, as described in the European Pharmacopeia, chapter 2.7.2.: Microbiological assay of antibiotics[17]. IU are different than mass units and depend on the activity of the substance.

The International Standard for Antibiotic (ISA) are established, prepared and distributed by the European Directorate for the Quality of Medicines (EDQM), through collaborative studies, and approved by WHO. These are considered as the primary standards for antibiotics and therefore are used for the establishment of national/regional secondary standards[18].

Since the ISA is considered the primary standard for antibiotics, it is used as a first choice of reference for ESVAC conversion factors from IU to mg. When the results of collaborative studies assign the potency in IU per mg, 1 is divided by this value to obtain the conversion factor in mg per IU. Where the results are assigned in IU per vial, the potency is first divided by the vial unit quantity indicated in that study and then 1 is divided by this value.

[16] https://www.edqm.eu/en/who-international-standards-antibiotics-isa-purpose-use
[17] European Pharmacopeia 10.5, accessed on 02/02/2021
[18] https://crs.edqm.eu/db/4DCGI/search?vSelectName=4&vContains=1&vtUserName=ISA&OK=Search

For antimicrobial active substances for which no reference to the ISA was available in the EDQM database, other relevant scientific publications were used.

It is important to clarify that, in contrary to the derivative conversion factors, IU conversion factors are not applied to calculate the quantity of active moiety for a specific compound or derivative. They are used solely for the purpose of converting the quantity of active substance from IU to mass and accordingly with the available official study. Depending on the starting material and candidate batch preparation used in the collaborative studies, after applying the IU conversion factors, the mass obtain only refers to the active moiety (referred to as "base" in the studies indicated on Table 11) for few substances (erythromycin, spiramycin, topramycin and tylosin) and to the salt or compound used in the ISA study for all others.

Recently, the references used for these conversion factors were reassessed, confirming if potencies (IU/mg) used to calculate each the conversion factor were still up to date or if new studies, assigning a different potency for that antimicrobial active substance were available. As a result of this exercise, some updates to the list of conversion factors were made as indicated in Table 11. Table 11 also includes detailed information on the derivative form used in the collaborative studies to assign the potency for each active substance and explanation about the necessity to the update the conversion factor, when applicable. The reassessment exercise should be considered for revision every 5 years.

Table 9. Updates and background information about ESVAC conversion factors used to convert from IU to mg of active substance

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Apramycin	556	0.00180	552	0.0018116	Outcome of a procedure under Article 34 of Directive 2001/82/EC (EMEA/V/A/122), Annex II, EMA, 2018 (https://www.ema.europa.eu/en/documents/referral/girolan-article-34-referral-annex-i-ii-iii_en.pdf, accessed on 02/02/2021) **Notes for clarification:** • The potency was assigned to apramycin sulfate. • The former conversion factor has been calculated by dividing the daily administration of apramycin at a dose of 12,500 IU apramycin per kg bw by 22.5 mg of product/kg bw and was updated to the target potency established for the medicinal product used in the study.
Bacitracin	74	0.013514	No updates suggested		ISA_62_003 - The 2nd International Standard for Bacitracin, 1963 (https://crs.edqm.eu/db/4DCGI/View=ISA_62_003, accessed on 02/02/2021) **Note for clarification:** Solutions for assay used in the study were prepared with zinc bacitracin.
Benzylpenicillin	1667	0.00059988	1670	0.0005988	The 2nd International Standard for Penicillin, 1953 (https://apps.who.int/iris/bitstream/handle/10665/265872/PMC2542105.pdf?sequence=1&isAllowed=y, accessed on 02/02/2021) **Notes for clarification:** • A single batch of recrystallized sodium penicillin G was used to prepare the ampoules for the collaborative study. • The former value in IU/mg was a value within the range of the results obtained in the collaborative study. It was decided to update the conversion factor to the final value assigned in the study.

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Chlortetracycline	900	0.00111	1000	0.001	The 2nd International Standard for Chlortetracycline, 1972 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2480840/pdf/bullwho00185-0093.pdf, accessed on 02/02/2021) **Notes for clarification:** • A sample of chlortetracycline hydrochloride was used to prepare the ampoules for the collaborative study. • The conversion factor was updated because previous reference to 900 IU/g was not possible to identify anymore.
Colistin sulfate	20500	0.000049	No updates suggested		ISA_65_062 - The 1st International Standard for Colistin, 1969 (https://crs.edqm.eu/db/4DCGI/View=ISA_65_062, accessed on 02/02/2021) **Note for clarification:** Samples of colistin sulfate were used to prepare the ampoules for the collaborative study.
Colistin methane sulfonate	12700	0.000079	No updates suggested		ISA_66_254 - The 1st International Standard for Colistin Methane Sulfonate, 1967 (https://crs.edqm.eu/db/4DCGI/View=ISA_66_254, accessed on 02/02/2021) **Notes for clarification:** • Colistin Methane Sulfonate is also known as "Colistin Sulphomethate" or as "Colistimethate". • The available study report does not refer if the starting material used to prepare the candidate batch was in the form of sodium (colistimethate sodium) or colistimethate base.

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Dihydrostreptomycin	820	0.00122	777	0.001287	The 3rd International Standard for Dihydrostreptomycin, 2011 (https://crs.edqm.eu/db/4DCGI/View=ISA42688, accessed on 02/02/2021) **Notes for clarification:** • The bulk material used for candidate batch was dihydrostreptomycin sulfate. • The conversion factor was updated from the 2nd International Standard to the 3rd International Standard.
Erythromycin	920	0.001087	No updates suggested		ISA_76_538 - The 2nd International Standard for Erythromycin, 1978 (https://crs.edqm.eu/db/4DCGI/View=ISA_76_538, accessed on 02/02/2021) **Note for clarification:** The ampoules used in the collaborative study contained erythromycin base.
Framycetin	670	0.00149	706	0.0014172	ISA_46104 – 2nd International Standard for Neomycin B, 2012 (https://crs.edqm.eu/db/4DCGI/View=ISA_46104, accessed on 02/02/2021) **Notes for clarification:** • Framycetin is also known as "Neomycin B". • The bulk material used for candidate batch was Neomycin B sulfate. • The conversion factor was updated from the 1st International Standard to the 2nd International Standard.
Gentamicin	620	0.001613	No updates suggested		ISA_92_670 - The 2nd International Standard for Gentamicin, 1968 (https://crs.edqm.eu/db/4DCGI/View=ISA_92_670, accessed on 02/02/2021) **Note for clarification:** The sample used in the collaborative study was gentamicin sulfate.

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Kanamycin	796	0.001256	No updates suggested		ISA_83_521 - The 1st International Standard for Kanamycin, 1986 (https://crs.edqm.eu/db/4DCGI/View=ISA_83_521, accessed on 02/02/2021) **Note for clarification:** The ampoules used in the collaborative study contained kanamycin sulfate.
Neomycin	755	0.00132	762	0.0013123	ISA46707 - The 3rd International Standard for Neomycin, 2012 (https://crs.edqm.eu/db/4DCGI/View=ISA46707, accessed on 02/02/2021) **Notes for clarification:** • The bulk material used for the candidate batch was neomycin sulfate. • The conversion factor was updated from the 2nd International Standard to the 3rd International Standard.
Oxytetracycline	870	0.00115	880	0.0011364	The 2nd International Standard for Oxytetracycline, 1967 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2476364/, accessed on 02/02/2021) **Notes for clarification:** • The ampoules used in the collaborative study were prepared from a sample of oxytetracycline dihydrate. • The conversion factor was updated because previous reference to 870 IU/g was not possible to identify anymore.

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Paromomycin	675	0.00148	750	0.0013333	International Reference Preparation of Paramomycin, 1965 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2480736/, accessed on 02/02/2021) **Notes for clarification:** • The ampoules were prepared from a sample of paromomycin sulfate. • The conversion factor was updated because previous reference to 675 IU/g was not possible to identify anymore.
Polymyxin B	8403	0.000119	No updates suggested		ISA_67_301 - The 2nd International Standard for Polymyxin B, 1970 (https://crs.edqm.eu/db/4DCGI/View=ISA_67_301, accessed on 02/02/2021) **Note for clarification:** The bulk material used to prepare the samples was Polymyxin B sulfate.
Spiramycin	3200	0.000313	No updates suggested		ISA_62_008 - The 1st International Standard for Spiramycin, 1964 (https://crs.edqm.eu/db/4DCGI/View=ISA_62_008, accessed on 02/02/2021) **Note for clarification:** The ampoules used in the collaborative study contained spiramycin base.
Streptomycin	785	0.00127	760	0.0013158	ISA_55821 - The 4th International standard for Streptomycin, 2015 (https://crs.edqm.eu/db/4DCGI/View=ISA_55821, accessed on 02/02/2021) **Notes for clarification:** • The bulk material used to prepare the candidate batch was streptomycin sulfate. • The conversion factor was updated from the 3rd International Standard to the 4th International Standard.

Active substance	Previous conversion factor		New conversion factor (updated in 2021)		References and notes for clarification
	IU/MG	MG/IU	IU/MG	MG/IU	
Tetracycline	982	0.00101833	No updates suggested		The 2nd International Standard for Tetracycline, 1973 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2481037/, accessed on 02/02/2021) **Note for clarification:** The ampoules used in the study where prepared from a sample of tetracycline hydrochloride.
Tobramycin	875	0.001142857	No updates suggested		ISA_82_510 - The 2nd International Standard for Tobramycin, 1985 (https://crs.edqm.eu/db/4DCGI/View=ISA_82_510, accessed on 02/02/2021) **Note for clarification:** The ampoules used in the collaborative study contained tobramycin base.
Tylosin	1000	0.00100	No updates suggested		ISA_TYN - The 1st International Standard for Tylosin, 1966 (https://crs.edqm.eu/db/4DCGI/View=ISA_TYN, accessed on 02/02/2021) **Note for clarification:** The preparation used to establish the international standard was tylosin base.

2.2. ESVAC derivative conversion factors

Previously, the term derivative has been referred to as prodrug. With this revision, the calculation of the conversion factors has been reassessed, in order to confirm and align the approach used for calculating the conversion factors from derivatives/compounds to respective active moieties. Some errors in the previous calculations of conversion factors were identified, mainly related with benzathine derivatives (calculation was being made considering 1 instead of 2 molecules of active moiety per one molecule of benzathine) and benzylpenicillin (benzylpenicillin sodium, instead of anhydrous benzylpenicillin was being considered as the active moiety), therefore some updates to the list of conversion factors were made in 2021 as indicated in Table 10.

The conversion factors for certain derivatives or compounds of antimicrobials shown in **Error! Reference source not found.** are applied to calculate the mass of antimicrobial active moiety content, through the multiplication of the concentration of derivative/compound indicated as STRENGTH in the sales template by a defined factor. The value of such conversion factor is between 0 and 1.

Each of the derivative/compound conversion factors is calculated by dividing the antimicrobial active moiety molecular weight by the derivative or compound molecular weight, taken into consideration the molecular formula and structure of the antimicrobial active substance.

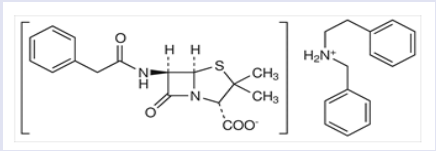
For benzathine benzylpenicillin and procaine benzylpenicillin, the hydrate forms where used to calculate the conversion factors, since they commonly exist in the hydrate form in the finished product and to align with European Pharmacopeia (Ph. Eur.) monographs for these substances.

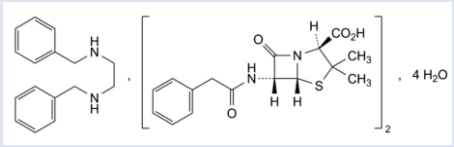
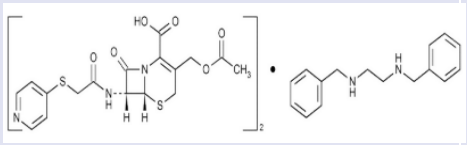
Table 10. Updates made to the list of conversion factors of derivatives or compounds

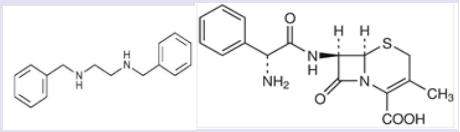
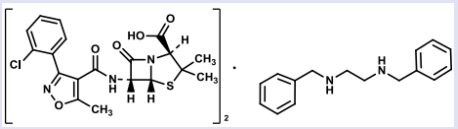
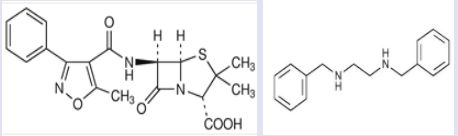
Derivative or compound	**Previous conversion factor**	**New conversion factor** (updated in 2021)
Benethamine benzylpenicillin	0.65	0.61
Benzathine benzylpenicillin tetrahydrate	0.74	0.68
Cefapirin benzathine	0.41	0.78
Cefalexin benzathine	0.36	0.74
Cloxacillin benzathine	0.43	0.78
Oxacillin benzathine	0.69	0.77
Penethamate hydriodide	0.63	0.60
Procaine benzylpenicillin monohydrate	0.61	0.57

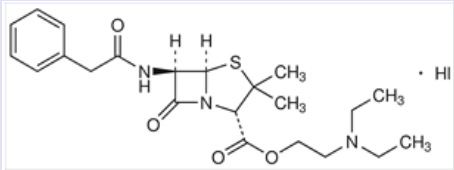
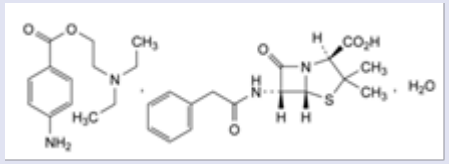
Table 11 includes a summary of all background details of relevance for calculation of currently applied conversion factors of the list of derivatives or compounds.

Table 11. Background information about conversion factors used to convert from derivates or compounds to content of active moiety

Derivative or compound	**Chemical structure**	**Derivative or compound molecular weight (in g/ml)**	**Active moiety molecular weight (in g/mol)**	**Conversion factor**	**References**
Benethamine benzylpenicillin		$C_{31}H_{35}N_3O_4S$ 545.7	$C_{16}H_{18}N_2O_4S$ 334.4	334.4/545.7 = **0.61**	Martindale: The Complete Drug Reference, CAS No.: 751-84-8, accessed on 01/02/2021

Derivative or compound	Chemical structure	Derivative or compound molecular weight (in g/ml)	Active moiety molecular weight (in g/mol)	Conversion factor	References
Benzathine benzylpenicillin tetrahydrate		$C_{48}H_{64}N_6O_{12}S_2$ 981.2	2[$C_{16}H_{18}N_2O_4S$] 2[334.4]	(2*334.4)/981.2 = **0.68**	US Pharmacopeia, CAS No.: 41372-02-5, accessed on 04/03/2021 and image is obtained from Ph. Eur., version 10.5, monograph 01/2019:0373 (Benzylpenicillin benzathine tetrahydrate), accessed on 08/02/2021
Cefapirin benzathine		$C_{50}H_{54}N_8O_{12}S_4$ 1087.3	2[$C_{17}H_{17}N_3O_6S_2$] 2[423.5]	(2*423.5)/1087.3 = **0.78**	US Pharmacopeia, CAS No.: 97468-37-6, accessed on 01/02/2021

Derivative or compound	Chemical structure	Derivative or compound molecular weight (in g/ml)	Active moiety molecular weight (in g/mol)	Conversion factor	References
Cefalexin benzathine		$C_{48}H_{54}N_8O_4S$ 935.1	2[$C_{16}H_{17}N_3O_4S$] 2[347.4]	(2*347.4)/935.1 = **0.74**	Individual information regarding each part of the compound was obtained from Martindale: The Complete Drug CAS No.: 15686-71-2 (anhydrous cefalexin) and PubChem, CAS No.: 140-28-3 (N,N'-Dibenzylethylenediamine), both accessed on 01/02/2021
Cloxacillin benzathine		$C_{54}H_{56}Cl_2N_8O_{10}S_2$ 1112.1	2[$C_{19}H_{18}ClN_3O_5S$] 2[435.9]	(2*435.9)/1112.1 = **0.78**	Details obtained from Martindale: The Complete Drug Reference, CAS No.: 23736-58-5; 32222-55-2, and image from US Pharmacopeia, both accessed on 01/02/2021
Oxacillin benzathine		$C_{54}H_{58}N_8O_{10}S_2$ 1043.3	2[$C_{19}H_{19}N_3O_5S$] 2[401.4]	(2*401.4)/1043.3 = **0.77**	Individual information regarding each part of the compound was obtained from Martindale: The Complete Drug Reference CAS No.: 66-79-5 (oxacillin) and PubChem,

Derivative or compound	Chemical structure	Derivative or compound molecular weight (in g/ml)	Active moiety molecular weight (in g/mol)	Conversion factor	References
					CAS No.: 916-96-1 (oxacillin benzathine compound), both accessed on 01/02/2021
Penethamate hydriodide		$C_{22}H_{32}IN_3O_4S$ 561.5	$C_{16}H_{18}N_2O_4S$ 334.4	334.4/561.5 = **0.60**	Martindale: The Complete Drug Reference, CAS No.: 3689-73-4 (penethamate), accessed on 01/02/2021
Procaine benzylpenicillin monohydrate		$C_{29}H_{40}N_4O_7S$ 588.7	$C_{16}H_{18}N_2O_4S$ 334.4	334.4/588.7 = **0.57**	Ph. Eur., version 10.5, monograph 04/2021:0115 (Benzylpenicillinum procainum monohydricum) accessed on 01/02/2021