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Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet)

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1. Summary

The main aim of establishing defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet) for antimicrobial veterinary medicinal products (VMP) is to provide standardised fixed units of measurement for the reporting of data on consumption by species that take into account differences in dosing. In order to facilitate comparison between countries, ideally, the ESVAC DDDvet and DCDvet system should also be used to report data at national level.

The terms DDDvet and DCDvet should preferably be reserved for the ESVAC units in order to avoid confusion about which units have been used when others than ESVAC report data on consumption of antimicrobials for animals.

These principles describe the approach suggested for the assignment of DDDvet and DCDvet for antimicrobial veterinary medicinal products (VMP) and for the principles themselves. The principles aim to guide the European Medicines Agency (EMA) on the assignment of DDDvet and DCDvet. A summary of the suggested principles is included in Chapter 2.

These principles may be subjected to exceptions that will be clearly identified in the list of DDDvet and DCDvet values.

The definitions and units to be applied are described in Chapter 7 and the general principles in Chapter 8. These principles are based on the aim of assignment of DDDvet and DCDvet (Chapter 6). Impact analyses as well as other assessments and considerations are outlined in Appendix 1. This Appendix also includes some examples of reporting of data by use of DDDvet and DCDvet.

The development of the principles has been assisted by an ad hoc working group on technical units of measurement that also participated in the development of the “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/ESVAC, 2013b).

The principles for assigning DDDvet for veterinary medicinal products have, to the extent possible, been harmonised with principles for human medicinal products.

Although the principles are developed based on data for antimicrobial agents, they are in general considered to be applicable in the future for other veterinary therapeutic agents. For some therapeutic agents, such as antiparasitics with an intermittent dosing schedule, the approach would have to be further explored.

Antimicrobial growth promoters (AGPs) are not authorised in the European Union and European Economic Area (EU/EEA) countries and thus the principles do not address AGPs; the DDDvet and DCDvet should not be used to analyse and report consumption of AGPs since dosing of these is generally much lower than the therapeutic dosing.

Data on dosing (daily dose and number of days of treatment) obtained from Summaries of Product Characteristics (SPCs) for antimicrobial veterinary medicinal products were provided for broilers, cattle and pigs by nine EU-countries: Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and United Kingdom, using a predesigned template. These nine countries covered approximately 65% of the food-producing animals in the EU in 2012. The data cover the following administration routes/forms: bolus, tablets, oral paste, oral powder, oral solution and premix, (long-acting) injectables, intramammary and intrauterine products. Seven countries delivered data on dosing for intramammary products (for lactating cows (LC) and dry cow treatment (DC)); of these, six

countries also delivered data on dosing for intrauterine products as the seventh country did not have intrauterine products marketed.

The data obtained on dosing were validated in terms of quality and harmonisation across the nine countries and preliminary DDDvet and DCDvet were assigned following exclusion of outliers. The final data sets on oral and injectable products consisted of 2,228 unique records containing information on daily dose and number of treatment days for single substance VMPs indicated for either broiler, cattle or pig; for VMPs containing active substances in combination (with the majority containing 2 ingredients) the data sets consisted of 662 unique records for each substance in a combination VMP.

Numbers of observations for intramammary LC, intramammary DC and intrauterine products included from the data sets were 134, 116 and 45, respectively; these represented both single substance and combination VMPs.

Preliminary DDDvet and DCDvet for the administration routes/forms mentioned above and the sales data for 26 EU/EEA countries and specific Member States (MSs) in 2012 were used for various impact analyses and other assessments, and the outputs of these as well as general considerations served as the basis for the development of the principles.

The data on dosing provided by the nine MSs will be used to assign the DDDvet and DCDvet. In cases where the SPC information on dosing is insufficient, e.g. when duration of effect is not clear, information obtained from scientific publications and/or text books will be consulted.

The DDDvet and DCDvet will be assigned per kg animal for oral and injectable products, providing a basis for calculation and reporting of DDDvet and DCDvet by weight group. For intramammary products for lactating cows the DDDvet and DCDvet will be assigned by teat; for intramammary products for dry cow treatment by udder and for intrauterine products the DDDvet and DCDvet will be assigned by animal.

Separate DDDvet will be assigned for injectables, intramammary products for lactating cows, intramammary products for dry cow treatment, intrauterine and oral products.

DDDvet and DCDvet will be assigned at single substance level for oral and injectable products; for intramammary and intrauterine products these is suggested to be assigned by ATCvet code.

The impact analyses (Appendix 1) have shown that similar approaches and principles can be applied to derive DDDvet and DCDvet for antimicrobials used in veterinary medicine as are applied to derive DDD in human medicine. However, there are differences in the type of products sold, such as much greater sales of combination antimicrobial products in veterinary medicine, and the way in which products are used, such as a much greater range of oral dosage forms in veterinary medicines. These differences mean that different assumptions are sometimes necessary when deciding how particular DDDvet and DCDvet are assigned.

Overall, there is a much larger number of ‘use cases’ for antimicrobials in veterinary medicine than human medicine due to both the need to treat different species and the need for a wider range of dose forms to be able to treat animals of different species and animals of the same species kept under different husbandry conditions.

In defining DDDvet and DCDvet a degree of pragmatism is therefore required to reach the right balance between having a highly complex but accurate system in which a DDDvet/DCDvet is defined for every possible ‘use case’ and having a more simple system in which similar ‘use cases’ are combined requiring fewer DDDvet/DCDvet to be defined.

Based on analyses of actual data on consumption, these principles have been able to show those situations where 'use cases' can, and cannot, be combined without having a major impact on the outcome in terms of estimated DDDvet or DCDvet. Taking into account that DDDvet and DCDvet are technical units of measurement and not measurements of actual consumption, the principles and methods put forward in this document are considered to represent the optimum balance between accuracy and practicability.

Note that in this document DDDvet and DCDvet always refer to the value assigned per kg animal unless otherwise indicated, such as for intramammary and intrauterine products.

It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDvet and DCDvet values will nearly always be a compromise. Established DDDvet or DCDvet are not applicable for commercial use such as pricing and analyses of drug costs.

2. Summary – principles

Table 1 summarizes the general principles recommended for the assignment of DDDvet and DCDvet for oral and injectable VMPs. In the general principles (Chapter 8) and Appendix 1 exceptions from these rules are described. Exception to the principles will be explained in the lists of DDDvet and DCDvet. The DDDvet and DCDvet for oral products and injectables will be assigned by kg animal.

Table 1. Summary of the calculation of DDDvet and DCDvet and the general principles for the assignment of DDDvet and DCDvet for each combination of substance and species for oral and injectable preparations. Single equals to VMPs with one active substance; combinations equals to VMPs with two (or more) active substances

Unit of measurement	Calculation	Oral single	Oral combinations	Injectable single	Injectable combinations
• DDDvet	• Calculated as average of all observations on daily dose by species, substance and form.	• Assign the same DDDvet for all oral forms.	• Assign the same DDDvet as for oral single forms.	• Assign the same DDDvet for injectables and long-acting injectables. • Prodrugs will be assigned separate DDDvet.	• Assign the same DDDvet as for single injectables, long-acting injectables and prodrugs.
• DCDvet	• Calculated as average of all observations – daily dose multiplied by number treatment days – by species, substance and form.	• Assign the same DCDvet for all oral forms.	• Assign the same DCDvet as for oral single forms.	• Assign the same DCDvet for injectables and long-acting injectables. • Prodrugs will be assigned separate DCDvet.	• Assign the same DCDvet as for single injectables, long-acting injectables and prodrugs.

The DDDvet and DCDvet for oral products and injectables will usually be assigned with one decimal.

For LC and DC intramammary products and intrauterine products the DCDvet and DCDvet will be assigned using the mode of all observations and will be assigned by teat, udder (dry cow products) and animal, respectively. Exceptions will be given in the lists of DDDvet and DCDvet values.

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4. Terms and abbreviations

- Average = weighted arithmetic mean
- ATC = Anatomical Therapeutic Chemical classification system
- ATCvet = Anatomical Therapeutic Chemical classification system for veterinary medicinal products
- Broilers = slaughter chicken
- CIA = critically important antimicrobials
- Combination VMP = veterinary medicinal product that contains more than one antimicrobial active substance
- DCDvet = defined course dose for animals
- DDD = defined daily dose (human)
- DDDvet = defined daily dose for animals
- Dosing = daily dose and number of treatment days
- DC = dry cow (period) = period between the end of lactation and calving
- Duration of effect = time period during which a VMP is active in the treated animal; longer than 24 hours for long-acting products
- Injectables long-acting (LA) = duration of effect of one dose > 24 hours
- EC = European Commission
- ESAC-Net = European Surveillance of Antimicrobial Consumption Network
- ESVAC = European Surveillance of Veterinary Antimicrobial Consumption
- ESVAC national sales register = register of antimicrobial VMPs: name, form, pack size, active ingredient(s) and strength(s)
- EU/EEA = European Union and European Economic Area
- LC = lactating cow
- Mode = the most frequent value
- Median = middle value in a sorted list of all observations
- MS = Member State
- Observation = one record containing information on daily dose and number of treatment days for one substance in a VMP for one species
- PDD = prescribed daily doses
- Prodrug = inactive or less than fully active chemical form, which is converted to its active chemical form through a normal metabolic process, such as hydrolysis of an ester, after administration
- Single substance VMP = veterinary medicinal product that contains one antimicrobial active substance
- SD = standard deviation
- Treatment duration = number of treatment days
- UD = unit dose
- VMP = veterinary medicinal product
- WHO = World Health Organization
- WHO CC = WHO Collaborating Centre for Drug Statistic Methodology

5. Introduction

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched in September 2009, following a request form the European Commission (EC) to develop an approach for the harmonised collection and reporting of data on the use of antimicrobial agents in animals in the MSs [SANCO/E2/KDS/rz D(2008) 520915]. Through the terms of reference from the EC, the Agency was requested, among other activities:

- To develop a harmonised approach for the collection and reporting of data based on national sales figures, combined with estimations of usage in at least major groups of species (poultry, pigs, veal calves, other ruminants, pets and fish);
- To collect the data from Member States and manage the database;
- To draft and publish a summary annual report with the data from Member States.

With regard to the data collection:

- Comparability with the sale/use of antimicrobials in humans should be ensured.

As a first step existing data from nine European countries (2005-2009) were collected and published in a harmonised manner (EMA/ESVAC, 2011). Furthermore, ESVAC has implemented a system for the collection of harmonised and validated data on national sales figures of veterinary antimicrobial agents detailed at package level. Such data have been published annually for the years 2010-2012. (EMA/ESVAC, 2011; EMA/ESVAC, 2012; EMA/ESVAC, 2013a; EMA/ESVAC, 2014). These data provide information on overall sales, sales by antimicrobial class/subclass and sales by pharmaceutical form.

In order to develop a harmonised approach for collecting data by species, an "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" was developed and published on 10 October 2013 (EMA/ESVAC, 2013b). It suggests collecting data on consumption for cattle, pigs and poultry (broilers and turkey).

Priority has been given to assignment of DDDvet and DCDvet for broiler, cattle and pigs.

The reflection paper further suggests applying DDDvet and DCDvet for the analysis of consumption data by species in order to take into account differences in dosing (daily dosing and length of treatment) for the various antimicrobials when reporting data. Furthermore, it is proposed to apply information on dosing (daily dose and number of days of treatment) obtained from SPCs as the basis for establishing the same DDDvet and DCDvet for similar products – i.e. active substance and pharmaceutical form by species – as these are available for all MSs and the information is generally available on the websites of the national medicines agencies (see Appendix 3), thus ensuring transparency.

This document provides the principles for the assignment of DDDvet and DCDvet for veterinary antimicrobial agents. The impact analyses, other assessments and considerations supporting the principles are described in Appendix 1.

These principles are in general thought to be applicable if in the future DDDvet and DCDvet will be assigned for other veterinary therapeutic agents; however, for some therapeutic agents such as for antiparasitic medicines with an intermittent dosing schedule, this has to be further explored and the principles revised if required.

The list of DDDvet and DCDvet will be used to analyse and report data on consumption by species collated by ESVAC.

Reporting consumption of antimicrobials in animals using DDDvet or DCDvet represents a substantial improvement over reporting consumption by weight (mass) of active substance. DDDvet and DCDvet take into account that the number of animals that can be treated with a fixed weight of an antimicrobial varies greatly depending on the dose (in terms of mass) that is required for each treatment.

6. Aim of assignment of DDDvet and DCDvet in the context of AMR

In human medicine the defined daily dose (DDD) was established in the mid-1970s for the purpose of drug consumption studies, mainly in order to follow therapeutic trends. This aim is reflected in the Guidelines for ATC classification and DDD assignment published by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHO CC) (WHO, 2015b). The WHO CC was established in Oslo in 1982 and is responsible for maintaining the guidelines as well as maintaining the list of DDDs.

The aim of surveillance of antimicrobial consumption in animals is multiple as described in the Appendix of the request from the EC to the Agency to take the lead in collecting data on the use of antimicrobials in animals:

1. To aid interpretation of patterns and trends regarding antibacterial resistance;
2. As a basis for risk profiling and risk assessment regarding antibacterial drug resistance;
3. As a basis for setting risk management priorities;
4. As a basis for evaluation of the effectiveness of control measures being implemented;
5. To identify emerging use of antibacterial drugs, e.g. of specific drug classes such as critically important antibiotics;
6. To aid comparison of usage of antibacterial drugs between and within countries and between time periods etc.;
7. To assess the spread and effect of antibacterial drug pollution of the environment;
8. As a basis for focused and targeted research and development.

The WHO guidelines (WHO, 2015b) emphasize that the DDD is nearly always a compromise based on review of the available information on dosing; furthermore, it underlines that the DDD is a technical unit of measurement solely intended for drug consumption studies and therefore cannot be assumed to represent the real daily doses applied. This is also applicable for veterinary medicines.

Through the terms of reference from the EC, the Agency was requested, among other, to ensure comparability with human medicine.

The principles for assignment of DDDvet (and DCDvet) are harmonized with the principles for assignment of DDDs in human medicine to the greatest extent possible. It should be noted that in human medicine only DDDs have been assigned.

6.1. Antimicrobial agents and animal species for which DDDvet and DCDvet will be assigned

DDDvet and DCDvet will be assigned for antimicrobial agents belonging to the ATCvet groups shown in Table 2 for oral, injectable, intramammary injectors and intrauterine products.

DDDvet and DCDvet will not be assigned for topical pharmaceutical forms (dermatological products, those for eye and ear and cutaneous spray) as it is complex to establish the dose. This is in line with the approach applied for human medicine (WHO, 2015b). It should be noted that ESVAC data from five EU/EEA countries show that sales of topical forms for animals accounted for between 0.002% and 0.49% of total sales in 2012 (EMA/ESVAC, 2014).

DDDvet and DCDvet are intended to be assigned for broilers, cattle and pigs.

Table 2. ATCvet class of veterinary antimicrobial agents for which DDDvet and DCDvet will be assigned (WHO, 2015a)

Groups of antimicrobial agents	ATCvet codes
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	QP51AG

7. Definitions and units

7.1. Definitions DDDvet and DCDvet

The basic definitions of the units are:

- The DDDvet is the assumed average dose per kg animal per species per day;
- The DCDvet is the assumed average dose per kg animal per species per treatment course.

7.2. Definitions of administration routes/forms for list of DDDvet and DCDvet

- Parenteral (P) = injectables and long-acting injectables;
- Oral (O) = bolus, tablet, oral powder, oral paste, oral solution and premix;
- Intramammary dry cow (IM-DC);
- Intramammary lactating cow (IM-LC);
- Intrauterine products (IUP).

7.3. DDDvet and DCDvet units

The units used for DDDvet and DCDvet are

- Oral and injectable products = mg/kg animal;
- Intramammary products lactating cow = Units (UD)/teat (dairy cow);
- Intramammary products dry cow = Units (UD)/udder (dairy cow);
- Intrauterine products = Units (IUP)/animal.

8. General principles

The DDDvet and DCDvet will usually be assigned according to the declared strength (content) given in the label/name or SPC of the product.

Various salts of a substance will usually be assigned the same DDDvet and DCDvet. Exceptions will be explained in the list of DDDvet and DCDvet.

DDDvet and DCDvet will usually be assigned by species and kg animal. Exceptions are intramammary and intrauterine products.

The assignment of DDDvet and DCDvet will usually be based on the average (arithmetic mean) of all observations of veterinary medicinal products for each species, substance and administration route/form in question given by the SPCs.

$$\text{Average} = (a_1 + a_2 + a_3 \ldots + a_n)/n$$

For each observation of long-acting injectables the dose per day for the substance and species will be calculated by dividing the (single) dose by the number of days of duration of the therapeutic effect of the substance. The same approach will be applied for substances for oral use that are long-acting due to their long biological half-life.

For intramammary products for lactating cows and for intrauterine products the DDDvet and DCDvet will be assigned using the mode values for all observations of the two pharmaceutical forms, respectively.

Generally, in cases where the SPC information on dosing is insufficient, e.g. when duration of effect is not clear, information obtained from scientific publications and/or text books will be consulted.

Review of a DDDvet or DCDvet should be considered if the dosing changes substantially from the one identified, in e.g. the Summary of Product Characteristics (SPC), for a substance, pharmaceutical form and/or species. As changes of DDDvet or DCDvet can have major implications for long-term studies on consumption of veterinary medicinal products these should be kept to a minimum.

The principles will be used to assign new DDDvet or DCDvet and when existing DDDvet or DCDvet need to be revised.

8.1. Assignment of DDDvet

8.1.1. Single substance products – oral products and injectables

Oral and injectable products will be assigned separate DDDvet.

Oral products

For each combination of species and substance for oral VMPs containing a single substance, the DDDvet will usually be assigned based on the average dose (arithmetic mean) of the daily doses given in the SPCs per species and substance – e.g. pigs/colistin/oral products and cattle/flumequine/oral products. Exceptions to these rules will be given in the list of DDDvet.

Injectables

Injectables and long-acting injectables will usually be given the same DDDvet for each combination of species and substance and will be based on the average dose (arithmetic mean) of all observations of injectables and long-acting injectables on daily dose given for each combination of species and substance – e.g. cattle/oxytetracycline/injectables. Exceptions will be described in the list of DDDvet.

Separate DDDvet will be assigned for injectable prodrugs and their active substance - e.g. for procaine benzylpenicillin and benzylpenicillin.

8.1.2. Combinations – oral products and injectables

Substances in combination products (2nd and 3rd ingredient) will be assigned the same DDDvet as assigned for the single substance product for the same administration route (oral products and injectables) and species. Exceptions will be described in the list of DDDvet (e.g. synergistic combinations).

For substances that are only included in combination VMPs the DDDvet will be assigned as the average of the observations by species, substance and administration route.

8.1.3. Intramammary products

8.1.3.1. Intramammary – lactating cow

The DDDvet for VMPs used to treat lactating cows will be assigned as the mode of all observations on the number of intramammary injectors per teat per day. Exceptions will be explained in the list of DDDvet.

8.1.3.2. Intramammary – dry cow

For VMPs used in the dry cow period no DDDvet will be assigned (see 8.2.3.2.).

8.1.4. Intrauterine products

The DDDvet will be assigned as the mode of all observations on the number of intrauterine products per animal per day. Exceptions will be explained in the list of DDDvet.

8.2. Assignment of DCDvet

8.2.1. Single substance products - oral products and injectables

Oral products

For each combination of species and substance for oral products containing a single substance, the DCDvet will be assigned based on the average of course doses given by the SPCs (dose multiplied with number of treatment days for each observation). Exceptions to these principles will be explained in the list of DCDvet (e.g. premixes for pigs).

Injectables

Injectables and long-acting injectables will be assigned the same DCDvet - e.g. pigs/oxytetracycline/injectable. Exceptions to these rules will be explained in the list of DCDvet.

Injectable prodrugs will be given separate DCDvet – e.g. procaine benzylpenicillin and benzylpenicillin.

8.2.2. Combinations – oral products and injectables

Oral products

Substances in oral combination products will usually be assigned the same DCDvet as the one assigned for the single substance product. For substances that are only included in combination VMPs the DCDvet will be assigned as the average of the observations by species, substance and administration route.

Exceptions will be explained in the list of DCDvet (e.g. synergistic combinations).

Injectables

Substances in injectable combination products will be assigned the same DCDvet as the substance in single substance products. For substances that are only included in combination VMPs the DCDvet will be assigned as the average of the observations by species, substance and administration route. This principle will also apply for injectable prodrugs. Exceptions will be explained in the list of DCDvet (e.g. synergistic combinations).

8.2.3. Intramammary products

8.2.3.1. Intramammary – lactating cow

The DCDvet for lactating cows will be assigned as the mode of all observations on the number of intramammary injectors (UD) per udder per treatment course. Exceptions will be explained in the list of DCDvet.

8.2.3.2. Intramammary – dry cow

DCDvet will be assigned as 1 DCDvet = 4 intramammary injectors (4 UD).

8.2.4. Intrauterine products

DCDvet will be assigned as the mode of all observations on numbers of units (UD) per animal per treatment course. Exceptions will be explained in the list of DCDvet.

Appendix 1

This appendix provides general considerations and impact analyses supporting the principles for assignment of DDDvet and DCDvet. First, the data that produce the basis for the impact analyses and considerations are described. The DDDvet and DCDvet used for the various impact analysis and considerations represent mg/kg animal unless otherwise indicated.

1. Assignment of DDDvet and DCDvet

1.1. Collection and analysis of data on dosing

With the aim to assist the development of the general principles for the assignment of DDDvet and DCDvet as well as for their actual assignment, data sourced from SPCs on dosing (daily dose and number of days of treatment) of antimicrobial VMPs were provided by nine volunteer EU countries in 2014: Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and United Kingdom. These countries cover approximately 65% of the food-producing animals of the EU MSs in 2012.

A template was developed to collect the SPC information on dosing (SPC template). The main reasons for using a template for collection of dosing information were to ensure that all data required for assignment of DDDvet and DCDvet were provided for all products marketed for broilers, cattle and pigs and to obtain standardized data for the purpose of further quality check and analysis of the data. The ESVAC sales template[1] was used as a basis for the development of the SPC template, which was country specific and based on the national ESVAC sales register. The final SPC template included the following administration routes/forms: bolus/tablets, injection, injection long-acting, intramammary products, intrauterine products, oral paste, oral powder, oral solution and premix.

In human medicine a DDD is usually established according to the declared content (strength) of the product (WHO, 2015b). Various salts of a substance are usually not given different DDDs. Exceptions are described in the guidelines for the different ATC groups. For example, the DDDs for anti-malarias are expressed as the base. This uniformity principle is applicable for veterinary medicine as well and therefore data on dosing were provided according to the declared strength/label of the VMP.

Prior to the call for data the SPC template was tested by four countries (France, the Netherlands, Sweden and Switzerland) and training on how to fill in the template was provided for the nine volunteer MSs.

Based on the experience from testing of the template and the feedback from the training, instructions on how to fill in the template in a harmonised/standardized manner were developed assisted by the ad hoc working group on technical units of measurement (see Appendix 2).

1.2. Quality check, validation and management of the data

Each national data set was initially subjected to quality check, including identification of missing information and whether the data were harmonised and standardized across the nine MSs. The individual data sets were further validated in terms of identification of extreme values. In case of

[1] Available from
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp&mid=WC0b01ac0580153a00&jsenabled=true

missing information, extreme values or non-compliance in terms of harmonization and standardization, the MS in question was asked to revise the data.

In cases where a country provided dosing information for different pack sizes of the same antimicrobial VMP (name, strength and form) only one pack size was included in the final data set for the country in question.

After aggregating the data sets from the nine MSs, the data were further validated in terms of identification of outliers for dosing or treatment duration for by use of R (R open source software version 3.1.0; R foundation for Statistical Computing, Vienna, Austria). For oral forms and injectables outliers (extreme values) were defined as values greater/smaller than the average dose (or duration) ±2 Standard Deviation (SD) within the group of observations for each antimicrobial, species and administration route/forms combination. For observations (for definition see Chapter 4.) identified as outliers in the aggregated data sets, the SPC information on dosing for the particular VMP was revisited; if the original values were correct, these were excluded from the data (96 observations were outlier for dose; 93 observations were outlier for treatment duration; 18 observations were outlier for both).

For intramammary products for lactating cows 11 products were excluded because the dosing schemes did not allow for calculation of daily dose or treatment dose.

Note that several DDDvet and DCDvet values given in Appendix 1 of the document subjected to consultation have changed slightly in the revised principles; this is due to further validation and revision of the data.

1.3. Numbers of observations - species, administration routes/forms and antimicrobial agents for assignment of preliminary DDDvet and DCDvet

Following the quality check, validation of the data and exclusion of outliers the data sets from the nine countries consisted of a total of 2,890 observations for oral forms and injectables: for single substance oral and injectable VMPs the data sets from the volunteer MSs consisted of 2,228 observations for antimicrobial, species and administration route/forms for which the data were collected and for combination VMPs of 662 observations for antimicrobials (almost solely 2nd ingredient), species and administration route/form (Table 3, Table 4). These data were applied to assign the preliminary DDDvet and DCDvet.

Table 3. Number of observations per species per administration route/form (oral forms and injectables) for single substance products in the data sets from 9 MSs used to calculate preliminary DDDvet and DCDvet

Species	Bolus/ tablet	Injection	Injection long–acting	Oral paste	Oral powder	Oral solution	Premix	Total
Broilers					101	253	50	404
Cattle	18	330	104	2	55	94	15	618
Pigs	3	417	93	3	192	292	206	1,206
Total	**21**	**747**	**197**	**5**	**348**	**639**	**271**	**2,228**

Table 4. Number of observations per species per administration route/form (oral forms and injectables) for combination products in the data sets from nine MSs used to calculate preliminary DDDvet and DCDvet

Species	Bolus/ tablet	Injection	Injection long-acting	Oral paste	Oral powder	Oral solution	Premix	Total
Broilers					15	43	20	78
Cattle	12	95	9		22	17	14	169
Pigs		196	3	2	57	81	76	415
Total	**12**	**291**	**12**	**2**	**94**	**141**	**110**	**662**

For intramammary products for lactating cows the data sets consist of 134 observations (54 for single and 80 for combination products), for dry cow treatment 116 observations (35 for single and 81 for combination products) and for intrauterine products this figure was 45 (36 for single and 9 for combination products).

1.4. Calculation of DDDvet and DCDvet

1.4.1. Oral forms and injectables

An example of dosing information given for two different amoxicillin oral solution VMPs is shown in Table 5. When the dosing was given as a range for an observation – i.e. for one VMP presentation – the “fixed” daily dose and "fixed" number of treatment days was calculated for each observation as the mean of the range.

Table 5. Example of dosing information provided by the nine MSs for two observations: amoxicillin VMPs (oral solution) and pigs

Range daily dose given		Fixed daily dose given	Daily dose	Range number of treatment days given		Fixed number of treatment days given	Number of treatment days	Course dose
Daily dose mg/kg min	Daily dose mg/kg max	Daily dose mg/kg	Daily dose mg/kg	Treatment days min	Treatment days max	Treatment days	Treatment days	Course dose mg/kg
10	20		15*			5	5	75**
		20	20	3	5		4*	80**

*Daily dose/number treatment days calculated by ESVAC; **Course dose calculated by ESVAC

When daily dose was given as e.g. 200 g Premix X/1,000 kg feed or 200 g Oral solution Y/1,000 l water, the daily dose per kg animal for each observation was calculated by use of a standardized feed and water intake per kg body weight, respectively (Appendix 3). When the daily dosing was given in IU/kg, the dose was calculated to provide the dose in mg/kg by use of the conversion factors applied for the ESVAC sales data (EMA/ESVAC, 2014).

The course dose for each observation for oral forms and injectables was calculated by multiplying the daily dose by the number of treatment days (Table 5).

For long-acting injectables the daily dose for each observation was calculated as shown in the following example:

- 20 mg/kg oxytetracycline injection with a duration of effect of 2 days = daily dose 10 mg/kg

In human medicine, the DDDs are calculated as the average of the daily doses given for the substance and administration route in question. This is also the case for the defined daily dose animal (DDDA) as assigned by Postma, Sjolund et al. (2015).

As a general rule for establishing DDDvet and DCDvet using the mode is not applicable for oral and injectable preparations as for several of the substance, form and species combinations no mode could be assigned – e.g. when there are four observations of which two give 20 mg/kg per day and two give 25 mg/kg per day. Furthermore, for the data given in Table 6 the mode would be 7 mg/kg (9 observations), which would disregard that for 12 of the 21 observations, the daily dose is higher.

Table 6. Number of observations and the dose given for injectable amoxicillin single substance VMP for cattle included in the data sets from the nine MSs

Number of observations	Daily dose in single substance VMP
9	7 mg/kg
8	8.75 mg/kg
2	15 mg/kg
1	9.25 mg/kg
1	10 mg/kg

Also mode cannot be established when all the observed values are different (Table 7).

Table 7. Example of daily doses given in the data sets from the nine MSs for oxytetracycline oral powder for cattle

<table>
<tr><th>DDDvet calculation</th><th>Daily dose</th></tr>
<tr><td rowspan="6">Mode?
Median = 20
Average = 25</td><td>13.5</td></tr>
<tr><td>15</td></tr>
<tr><td>17.5</td></tr>
<tr><td>22.5</td></tr>
<tr><td>30</td></tr>
<tr><td>50</td></tr>
</table>

Therefore, the average (arithmetic mean) of all observations for each combination of species, antimicrobial substance and administration route/form for oral and injectable preparations included in the data sets is chosen to assign DDDvet – e.g. pig/colistin/oral forms calculated by use of the following formula:

$$\text{Average} = (a_1 + a_2 + a_3 .... + a_n)/n$$

To obtain the course dose for each observation for a combination of species, antimicrobial substance and administration route/form for oral and injectable preparations included in the data sets, the daily dose is multiplied by the number of treatment days (Table 5). DCDvet were calculated as the average of all observations on course dose for each substance, form and species.

1.4.2. Intramammary products for lactating cow; intrauterine products

For each observation for intramammary (IM) lactating cow (LC) products the course dose was calculated as the number of pieces per teat and day multiplied by the number of days of treatment. When the dosing was given in range for intramammary LC VMPs the same approach for calculating daily dose and treatment dose for each observation applied for oral forms and injectables was used (Table 5).

A similar approach as for the intramammary LC products was used for intrauterine products.

Calculating the average per ATCvet code for intramammary LC products and intrauterine products resulted in DDDvet and DCDvet values with decimals for several observations both for single and combination VMPs. Due to the characteristics of their use - the entire piece (injector) is administered - the average is not applicable for assigning DDDvet and DCDvet for intramammary products and intrauterine products.

For intramammary LC products 92 observations were included in the final data sets from the seven MSs that delivered data. For 50 observations the daily dose was 1 intramammary (IM)/teat per day and for 42 it was 2 IM/teat per day; thus the mode DDDvet is 1 IM/teat. For 45 observations the number of treatment days was 3; thus the mode DCDvet is 3 IM/teat. The average DDDvet is 1.5 IM/teat and the average DCDvet is 3.1 IM/teat. For pirlimycin (N=6) the number of treatment days was 8 for all observations.

It was assessed if mode could be applied to assign DDDvet and DCDvet by ATCvet code 5th level but this was not applicable for e.g. ATCvet code QJ51RC23 (Table 8) as no mode can be established for DCDvet.

Table 8. Daily doses and course doses (as number of injectors) given for intramammary LC products in the data sets from the seven MSs

ATCvet code	1 ingredient	2 ingredients	3 ingredients	4 ingredients	Daily dose	Course dose
QJ51RC23	Procaine penicillin	Dihydrostreptomycin			1	1
QJ51RC23	Procaine penicillin	Dihydrostreptomycin			1	2
QJ51RC23	Procaine penicillin	Streptomycin	Neomycin		2	3
QJ51RC23	Procaine penicillin	Streptomycin	Neomycin		2	3
QJ51RC23	Procaine penicillin	Dihydrostreptomycin	Nafcillin		1	1
QJ51RC23	Procaine penicillin	Dihydrostreptomycin	Nafcillin		1	3
QJ51RC23	Procaine penicillin	Novobiocin	Dihydrostreptomycin	Neomycin	1	1
QJ51RC23	Procaine penicillin	Novobiocin	Dihydrostreptomycin	Neomycin	1	2

DDDvet and DCDvet for intramammary LC products will be assigned as the mode of all the observations for intramammary LC products. Exceptions will be given in the lists of DDDvet and DCDvet – e.g. pirlimycin will be assigned a separate DCDvet.

The calculations and considerations given for intramammary LC products are also applicable for intrauterine products. The DDDvet and DCDvet for intrauterine products will be assigned as the mode of all observations. Exceptions will be given in the lists of DDDvet and DCDvet.

2. Definition of DDDvet and DCDvet

In human medicine DDDs are assigned by the WHO International Working Group for Drug Statistics Methodology and the unit is defined as follows: “The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults” (WHO, 2015b). The DDDs are assigned for a person of 70 kg.

For many antimicrobial VMPs, in particular old products, the information given in the SPC on the indication might be very general – e.g. "to treat bacterial infections". In the instructions on how to fill in the SPC data (Appendix 2) it reads that if the main indication is clear, dosing should always be entered for this. The MSs providing SPC information on dosing were not requested to indicate if it was given for the main indication therefore the number of observations for which the dosing was given for the main indication is not known. It can only be assumed that the dosing is given for the main indication when available, and that the assigned preliminary DDDvet and DCDvet to a certain extent reflect the dosing for the main indication.

The instructions for filling the SPC information in the predesigned template guided the recording of information for various difficult cases such as when a different dose is given for preventive and therapeutic use or for young versus adult animals (Appendix 2).

Since data on consumption of antimicrobials in animals will typically be collected and reported by various weight groups (e.g. finisher pigs) the DDDvet and DCDvet will be assigned by kg animal, allowing for further calculations of numbers of DDDvet and DCDvet consumed by weight group.

DDDvet and DCDvet will generally be assigned by kg animal based on the following definitions:

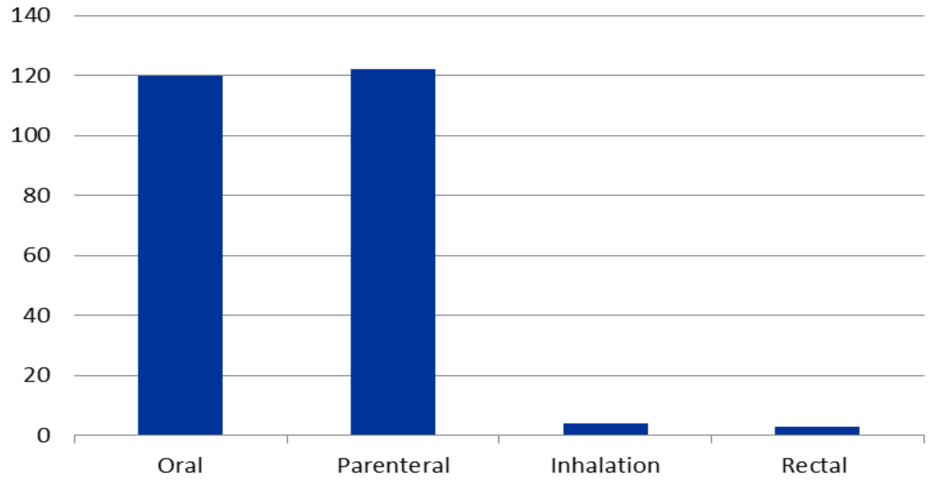
- The DDDvet is the assumed average dose per kg animal per species per day;
- The DCDvet is the assumed average dose per kg animal per species per treatment.

Exceptions are for intramammary LC products and intrauterine products for which the DDDvet and DCDvet are defined as the assumed number of pieces per teat or animal per day and treatment, respectively, and for intramammary DC products number of pieces per udder per treatment.

3. Administration routes/forms and combination VMPs

In human medicine, DDDs are assigned for four administration routes/forms (Figure 1) and the number of DDDs assigned for single substance products is 249. In addition DDDs have been assigned for 20 combination products.

Figure 1. Numbers of DDDs assigned for single substance human medicinal products containing antimicrobial agents



In order to have detailed data available for impact analyses, SPC information on dosing for antimicrobial VMPs was collected for the following administration routes/forms: bolus, tablets, injection, injection long-acting, intramammary, intrauterine, oral paste, oral powder, oral solution and premix. If DDDvet and DCDvet were to be assigned separately for each of these administration routes/forms for single substance VMPs for broilers, cattle and pigs, estimations based on the data on dosing obtained from the nine MSs show that the total number would be approximately 530 (Figure 2). Assignment of DDDvet and DCDvet for substances in combination VMPs would add to the number by 272 (Figure 3).

Figure 2. Numbers of DDDvet to be assigned for single substance products of antimicrobial agents for oral and injectable veterinary medicinal products (N =265), estimated from data provided by nine EU MSs. Note that the data represent preliminary numbers

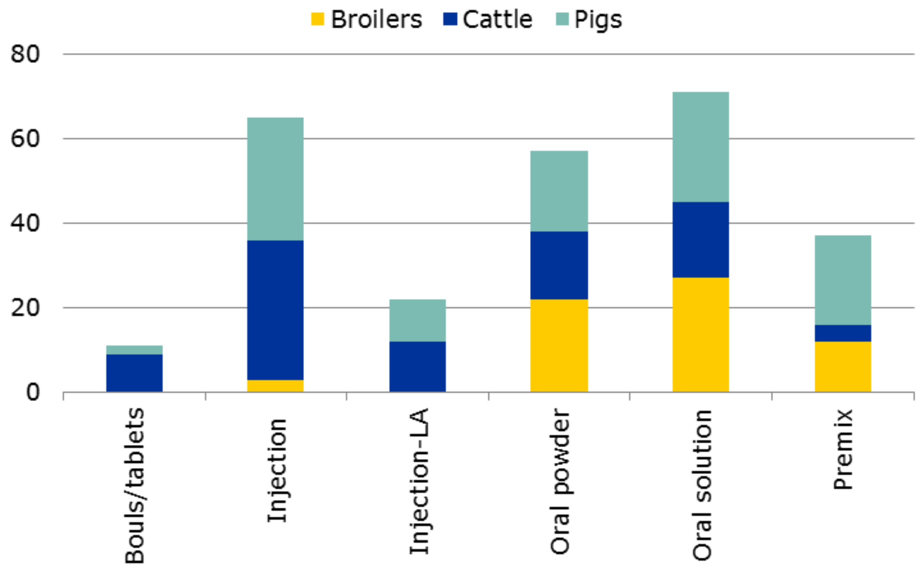
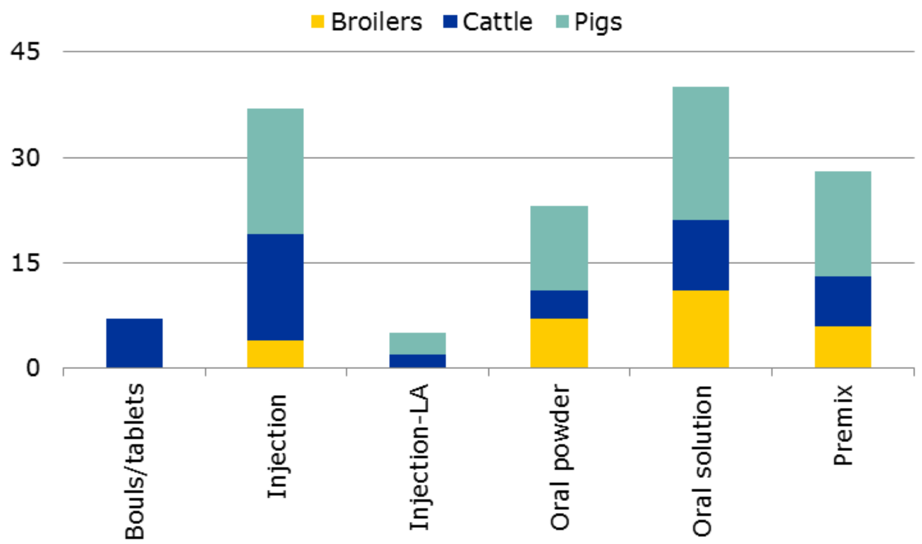


Figure 3. Numbers of DDDvet to be assigned for substances in combination VMPs of antimicrobial agents for oral and injectable veterinary medicinal products (N =136), estimated from data provided by nine EU MSs. Note that the data represent preliminary numbers



In total, more than 800 DDDvet and DCDvet would have to be assigned if they are assigned by species and separately for each oral form, injectables and long-acting injectables and for single substance VMPs as well as for combination VMPs. In addition, DDDvet and DCDvet for intramammary and intrauterine products would still add to that number.

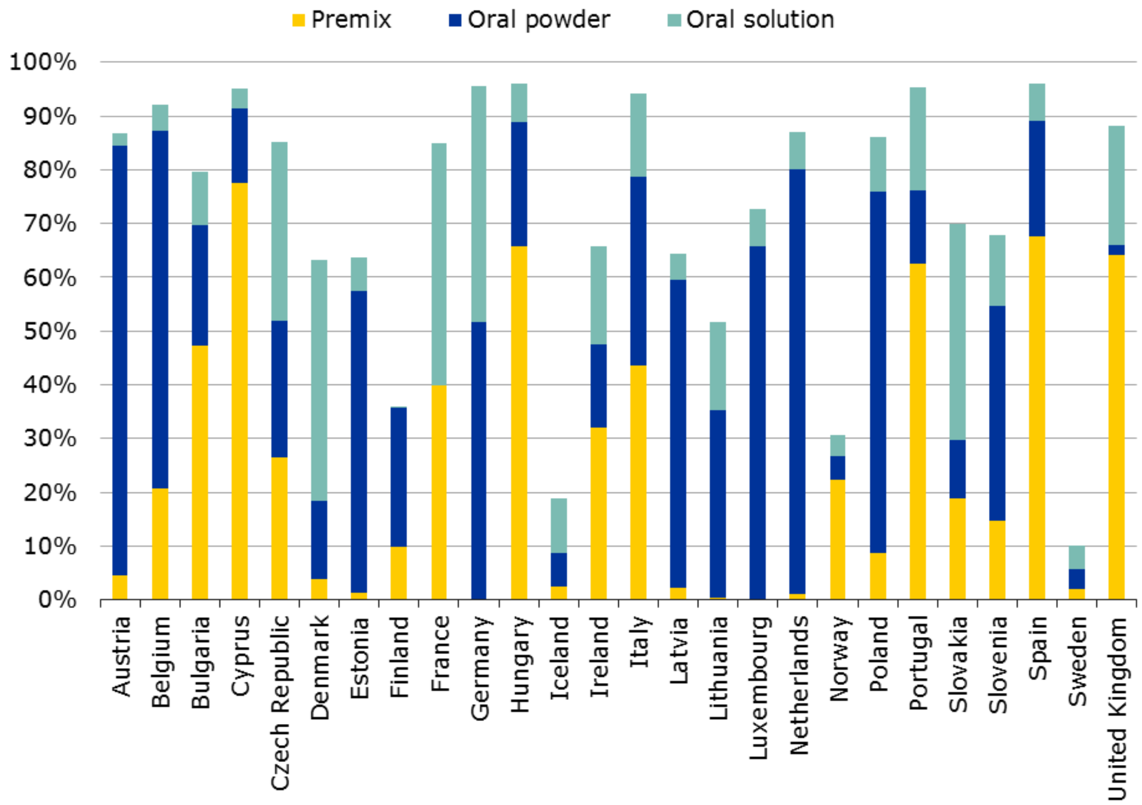
In order to make the list of DDDvet and DCDvet manageable for analysis and reporting of data the impact of e.g. assigning the same DDDvet and DCDvet for each unique combination of antimicrobial, species and oral forms was assessed.

3.1. Administration routes/forms

3.1.1. Oral forms

The proportion of sales, in mg per population correction unit (mg/PCU), accounted for by the main oral forms (oral powder, oral solution and premix) varies substantially between the 26 EU/EEA countries that provided data for ESVAC in 2012 (Figure 4).

Figure 4. Premixes, oral powders and oral solutions, as percentages of total sales, in mg/PCU, of veterinary antimicrobial agents for food-producing animals (including horses), by country, for 2012 (EMA/ESVAC, 2014)



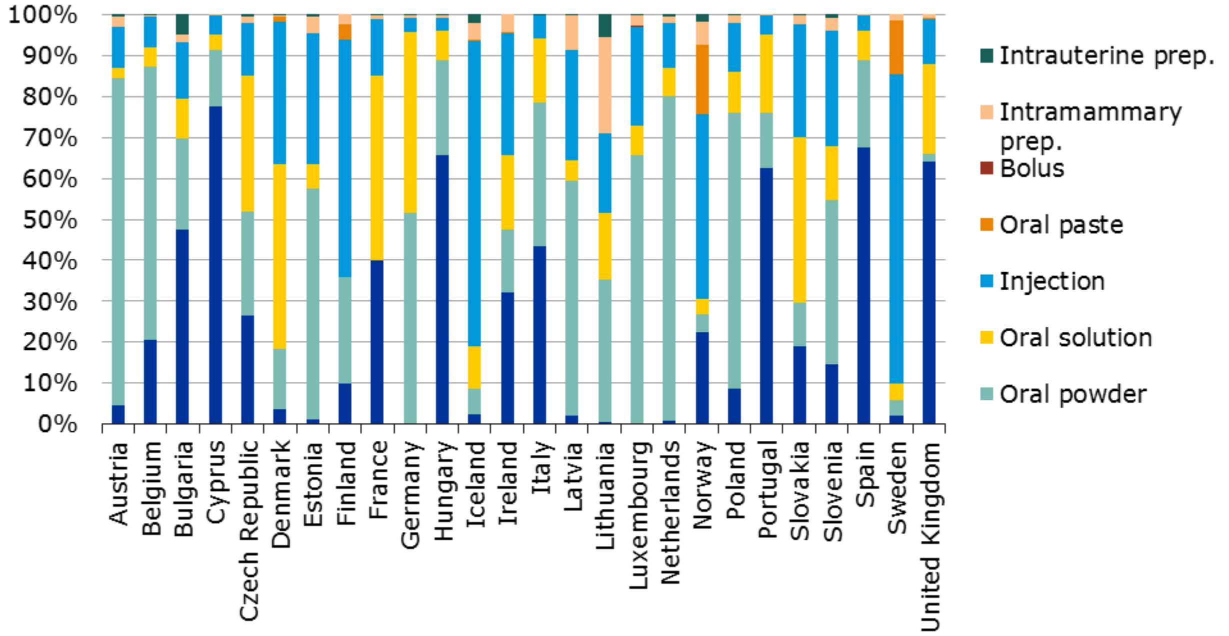
If the daily dose and number of treatment days varies substantially between these forms, this could have an impact on the reported output in terms of numbers of DDDvet and DCDvet.

3.1.2. Injectables

In human medicine assignment of the same DDD for oral and parenteral forms of antibiotics is common, since parenteral formulations are often only used initially in the treatment course. In the current Guidelines for ATC classification and DDD assignment (WHO, 2015b) in human medicine, it reads (page 24): *"The DDD is often identical for various dosage forms of the same drug. Different DDDs may be established when the bioavailability is substantially different for various routes of administration (e.g. oral and parenteral administration of morphine) or if the dosage forms are used for different indications. When the use of parenteral formulations represents only a minor fraction of the total use for a specific indication, these products do not receive a separate DDD even if the bioavailability of the oral form is substantially different."*

In veterinary medicine, the proportion of antimicrobial agents sold as injectable antimicrobial VMPs in some countries in the EU/EEA area is high, in particular in the Nordic countries (Figure 5), and injections are frequently used as the only administration route for treatment of the food producing animals.

Figure 5. Distribution of sales of veterinary antimicrobial agents for food-producing animals (including horses), in mg/PCU, by pharmaceutical form, by country, for 2012



Of the sales of injectable antimicrobial agents for food-producing animals in 26 EU/EEA countries in 2012, the most sold substances (in weight of active substance) were benzylpenicillin (as prodrugs), dihydrostreptomycin (almost solely in combination VMPs), amoxicillin, oxytetracycline and florfenicol. Preliminary data show that the DDDvet for e.g. injectable amoxicillin and oxytetracycline are about 2 and 4 times higher than for the oral forms, respectively. Therefore, DDDvet and DCDvet will be assigned separately for injectables and oral forms.

3.1.2.1. Long-acting injectables

In human medicine the only long-acting substances for injectables specified as such are some sulfonamides and a macrolide (azithromycin) which indicates that the number of long-acting antimicrobials in human medicine is low (WHO, 2015b).

In veterinary medicine, the consumption of long-acting injectable VMPs is considerable higher than in human medicine and some substances have a much longer biological half-life than the sulfonamides previously mentioned. Therefore it was assessed whether DDDvet and DCDvet should be assigned separately for long-acting injectables.

3.1.2.2. Injectables - prodrugs

In human medicine, DDDs are always linked to the ATC code and prodrugs are usually assigned a separate ATC code and DDD if the doses used are different and/or the non-proprietary name of the prodrug and the active drugs are different. Depot formulations (e.g. sustained release formulations) are usually assigned the same DDDs as the ordinary dosage forms.

In the EU/EEA area injectable benzylpenicillin prodrugs account for the major proportion of sales expressed as benzylpenicillin and is almost solely accounted for by procaine benzylpenicillin (ESVAC, unpublished data). Separate DDDvet and DCDvet will be assigned for injectable prodrugs and its active substance.

3.1.3. Intramammary and intrauterine products

Most of the intramammary VMPs sold in the EU/EEA are combination products. In the human ATC/DDD system DDDs for e.g. vaginal creams containing more than one active ingredient are given in UDs. That means that for vaginal creams (applied with a dose applicator) 1 application equals 1 UD (WHO, 2015b).

A similar approach will be used for intramammary and intrauterine VMPs.

The units for reporting of e.g. intramammary products are:

- Intramammary products lactating cow = Units (UD)/teat (dairy cow);
- Intramammary products dry cow = Units (UD)/udder (dairy cow)

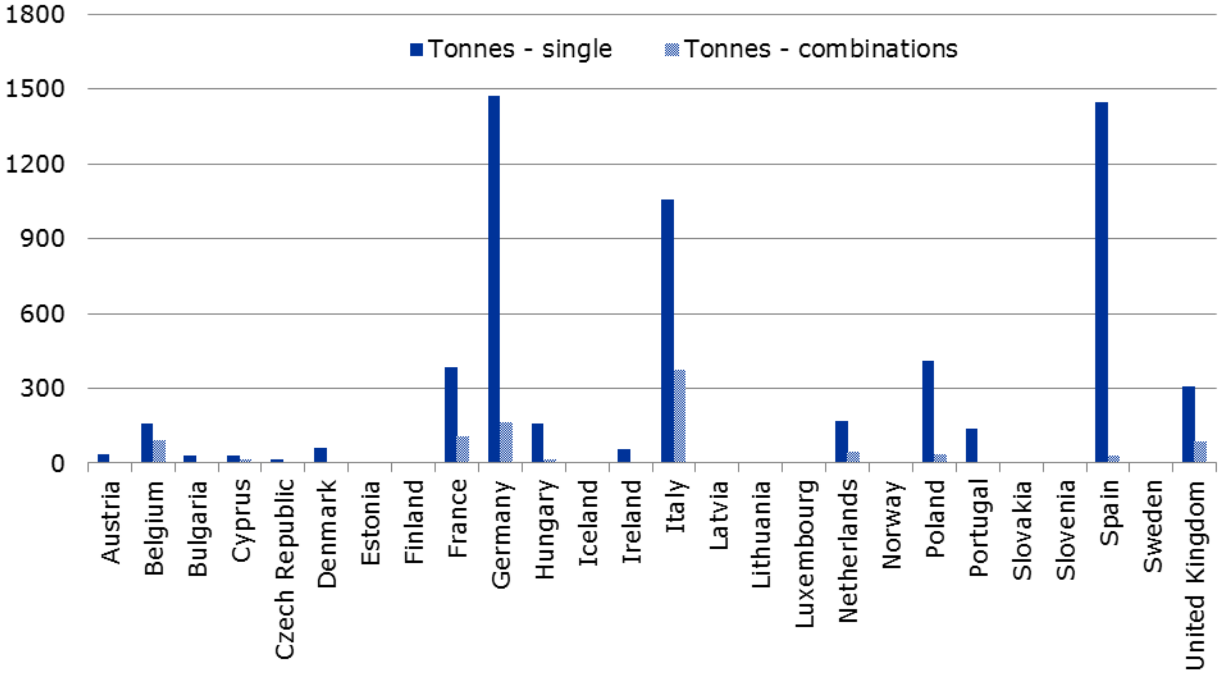
3.2. Combination VMPs – oral and injectable products

In human medicine the DDDs assigned for combination products are based on the main principle of counting the combination as one daily dose (main indication), regardless of the number of active ingredients included in the combination: *"If a treatment schedule for a patient includes e.g. two single ingredient products, then the consumption will be measured by counting the DDDs of each single ingredient product separately"* (WHO, 2015b).

In the EU/EEA countries the type/number of combination antimicrobial products in human medicine is negligible compared to veterinary medicine and consists mainly of sulfonamide-trimethoprim combinations and antibiotics combined with an enzyme inhibitor.

The sales of antimicrobial VMP combinations applicable for group treatment (oral powder, oral solution and premix) were shown to represent 14.2% of the sales of these pharmaceutical forms in 26 EU/EEA countries in 2012 (EMA/ESVAC, 2014) (Figure 6). Of these, a large proportion consists of combinations that in principle could be regarded as treatment with two different antimicrobial VMPs.

Figure 6. Sales, in tonnes of active ingredient, of premixes, oral powders and oral solutions as single and combination antimicrobial VMPs in 26 EU/EEA countries in 2012



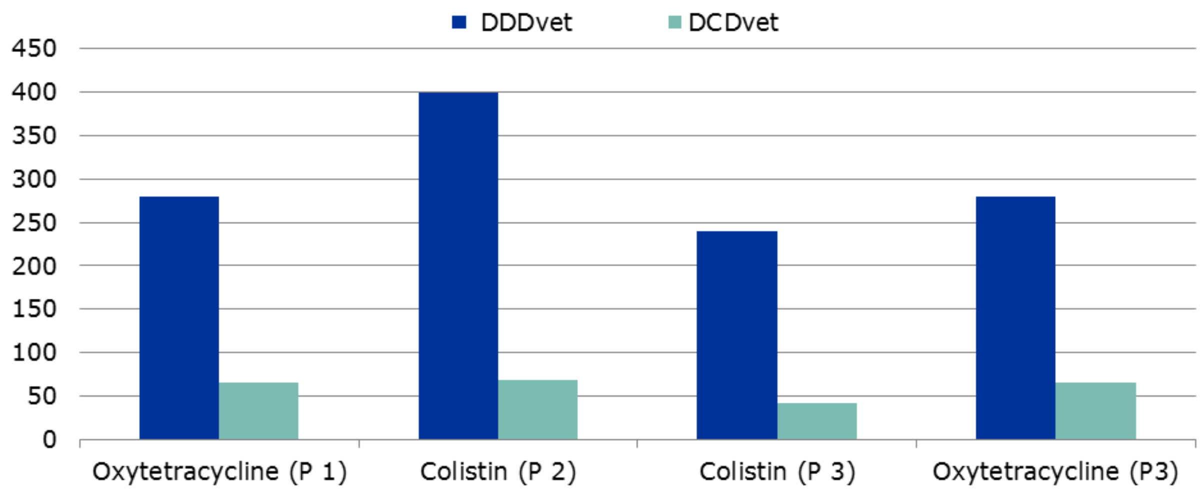
In particular for the analysis of data on prevalence of antimicrobial resistance by species together with data on consumption in the same species, it is important to assess the consumption of each substance in a combination VMP.

An example on output, in numbers of DDDvet calculated by use of invented figures of consumption of colistin and oxytetracycline in single and combination VMPs as oral powders (real products) is shown in Table 9 and Figure 7.

Table 9. Calculated numbers of DDDvet (thousands) and DCDvet (thousands) per kg pig of three different products consumed in pigs

	Substance	Pack size	Strength	No. sold	DDDvet (thousands)	DCDvet (thousands)
Prod 1	Oxytetracycline	1,000 g	70 mg/g	100	280	65
Prod 2	Colistin	1,000 g	20 mg/g	100	400	69
Prod 3	Colistin	1,000 g	12 mg/g	100	240	41
	Oxytetracycline	1,000 g	70 mg/g	100	280	65

Figure 7. Calculated numbers of DDDvet and DCDvet (thousands) per kg pig of three different products authorised for use in pigs (data from Table 9)



In case the 2nd ingredient for product 3 (oxytetracycline) is not included in the analyses only half of the consumption (selection pressure) of oxytetracycline would have been identified. Note that the same DDDvet and DCDvet have been used for single and combination VMP in this analysis. DDDvet and DCDvet will be assigned also for the 2nd (and 3rd) ingredient in combination VMPs.

4. Impact analyses and other assessments

In order to make the list of DDDvet and DCDvet manageable for the analysis and reporting of data on consumption by animal species – i.e. to limit the numbers to be assigned - various impact and other assessments were performed. The impact analyses address the major administration forms – i.e. oral and injectable products, and assess:

1. Whether the same DDDvet could be assigned for each antimicrobial and species for all oral forms and injectables, respectively;

2. Whether the DDDvet assigned for single antimicrobial VMPs could be applied for the same antimicrobial, species and oral forms and injectables, respectively, in combinations products;
3. Whether the same DCDvet could be assigned for each antimicrobial and species for all oral forms and injectables, respectively;
4. Whether the DCDvet assigned for single antimicrobial products could be applied for same antimicrobial, species and oral forms and injectables, respectively, in combinations products.

Sales data for 2012 in 26 EU/EEA countries were used as a basis for selecting the antimicrobials for the impact analyses (Figure 8). Since the oral forms account for the major proportion of the sales (Figure 9), these forms as well as injectables were addressed for the impact analyses.

Figure 8. Sales of antimicrobial agents by antimicrobial class as percentage of the total sales for food-producing species (including horses), in mg/PCU, aggregated by 26 countries, for 2012

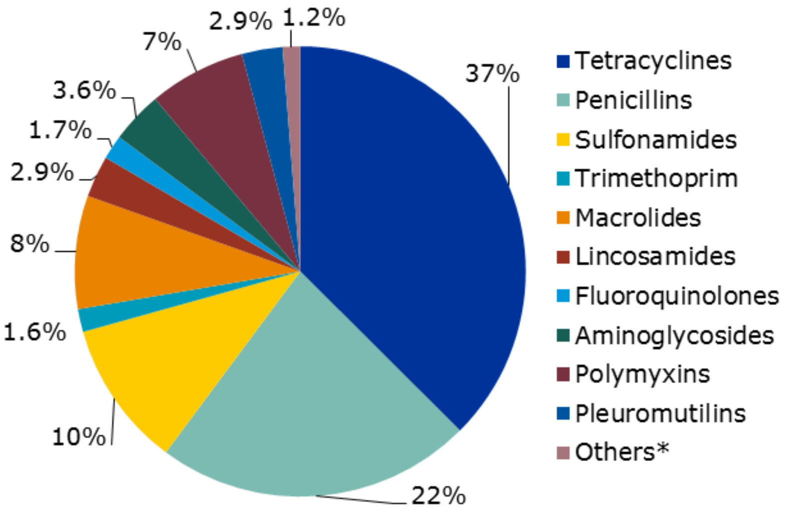
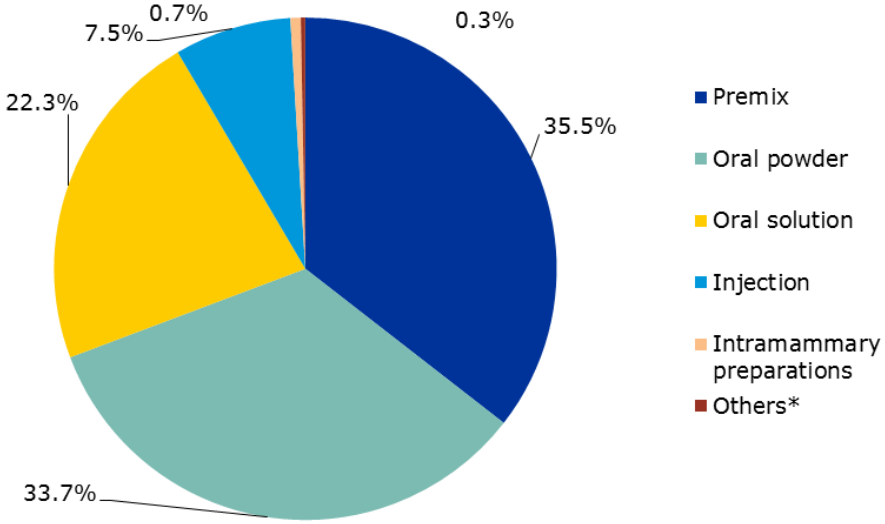


Figure 9. Distribution of sales, in mg/PCU, of the various pharmaceutical forms of veterinary antimicrobial agents for food-producing animals (including horses) aggregated by 26 EU/EEA countries for 2012



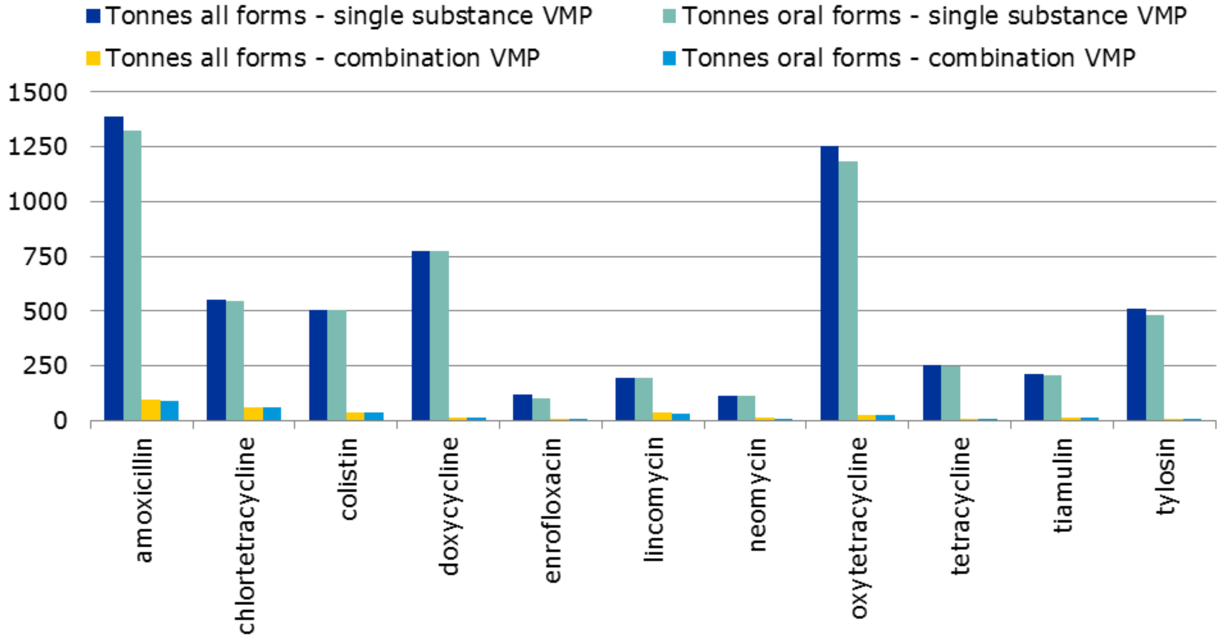
* Oral paste, bolus and intrauterine products.

4.1. DDDvet - single substance products

4.1.1. Oral forms

In a study by Postma, Sjolund et al. (2015) on assigning defined daily dose animals (DDDA) by use of SPC data from four EU MSs, oral forms were aggregated; it was however suggested to consider assigning a separate DDDA for oral solution and for oral powder and premix. An impact analysis was performed by ESVAC to identify the influence of assigning DDDvet separately for oral solutions compared to applying the same DDDvet for all oral forms.

Figure 10. Total sales (tonnes) of the most-selling single antimicrobial VMPs (sales of more than 100 tonnes) for all pharmaceutical forms and for all oral forms; total sales of the same substances as combination VMPs of all pharmaceutical forms and for oral forms in 26 EU/EEA countries in 2012



Amoxicillin and oxytetracycline were selected for the analyses as these substances were the overall most-selling antimicrobial agents, in tonnes, in the 26 countries providing data to ESVAC for 2012 (Figure 10). The tonnes sold of oral powder, oral solution and premix of amoxicillin and oxytetracycline in 26 EU/EEA countries in 2012 as well as in two specifically chosen MSs as provided to ESVAC 2012 were used for the impact analyses. The complete amount was considered as sold for one animal species (pigs). The aim of analysing “DDDvet average oral powder and premix/DDDvet oral solution” was to identify the impact of assessing consumption of oral solution separately from the other oral forms.

Explanation of the labels of the axis shown in Figure 11, Figure 12, Figure 13 and Figure 14:

- DDDvet by oral form = (tonnes oral powder sold substance X/DDDvet oral powder) + (tonnes oral solution sold substance X/DDDvet oral solution) + (tonnes premix sold substance X/DDDvet premix)
- DDDvet average oral powder and premix/DDDvet oral solution = (tonnes oral powder + premix sold of substance X)/(average DDDvet of oral powder + premix) + (tonnes oral solution sold of substance X/DDDvet oral solution)
- DDDvet average oral forms = (tonnes oral powder + oral solution + premix sold of substance X)/(average DDDvet of all oral forms).

4.1.1.1. Amoxicillin

Preliminary DDDvet for single substance VMPs of amoxicillin for pigs for oral solution, oral powder and premix shown in Table 10 were used for the various impact analyses.

Table 10. Preliminary DDDvet (mg/kg) for amoxicillin single substance VMPs for pigs for the major oral forms and DDDvet average of oral powder and premix)

	Oral powder	Oral solution	Premix	Average oral powder and premix	Average all oral forms
Pigs	18	16	17	17.5	17

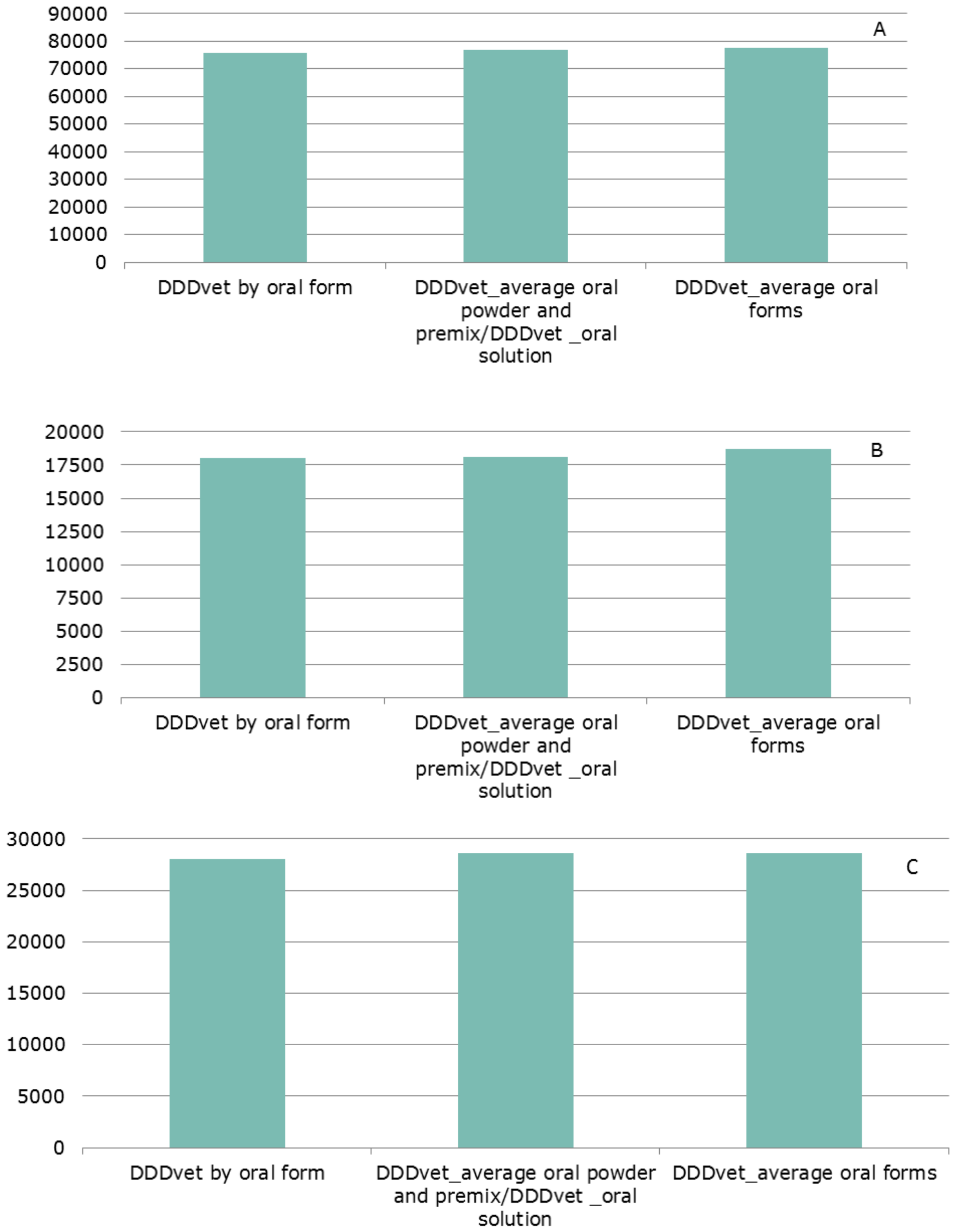
Annual outputs

The preliminary DDDvet and sales data shown in Table 10 and Table 11, respectively, were applied for the impact analyses on annual output.

Table 11. Sales (tonnes) of amoxicillin in single substance VMPs oral solution, oral powder and premix in 2012 in 26 EU/EEA countries (A) and two different MSs (B and C). It was assumed that all sales were used for pigs

	Oral powder	Oral solution	Premix
A. Sales 26 EU/EEA countries	863	265	194
B. Sales MS 1	198	<0.5	120
C. Sales MS 2	333	153	<0.5

Figure 11. Calculated numbers of DDDvet (millions) sold of single amoxicillin VMPs as oral powder, oral solution and premix in 26 EU/EEA countries (A) and two different MSs (B and C) in 2012 assuming that the total amounts sold were used for pigs



The numbers of DDDvet amoxicillin calculated by application of DDDvet for each oral form was 1%, 1% and 2% lower for A, B and C, respectively, compared to the output when oral solution was calculated separately (Figure 11).

The numbers of DDDvet calculated by application of DDDvet for each oral from was 2%, 4% and 2% lower for A, B and C, respectively, compared to the output when average DDDvet were applied.

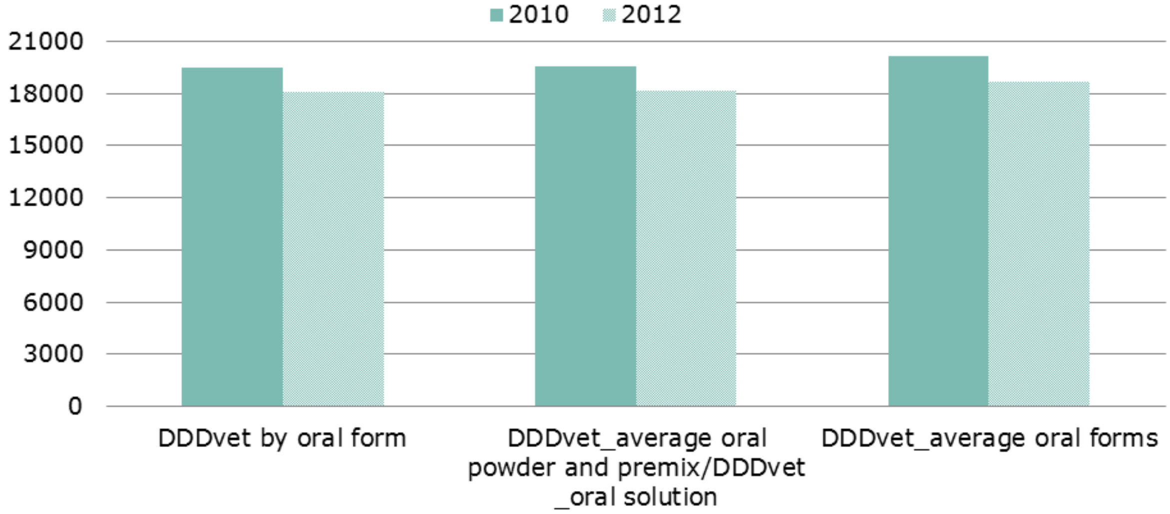
Changes across time

In order to assess the impact of applying DDDvet as average of oral forms compared to applying DDDvet by the various oral forms on identifying changes in consumption across time, sales data for amoxicillin single substance VMPs from one specific MS for 2010 and 2012 were applied (Table 12).

Table 12. Sales (tonnes) of amoxicillin in single substance VMPs oral solution, oral powder and premix in 2010 and 2012 in one specific MS

	Oral powder	Oral solution	Premix
2010	207	<0.5	135
2012	198	<0.5	120

Figure 12. Calculated numbers of DDDvet (millions) sold of single amoxicillin VMPs as oral powder, oral solution and premix. Sales data for one EU MS in 2010 and 2012 were applied for the calculation and it was assumed that the total amounts sold were used for pigs



The difference in the output was small and a 7.4% reduction in consumption from 2010 to 2012 was observed when DDDvet for the three oral forms were applied to analyse sales by these forms. When using average DDDvet for these forms the estimated decline was 7.3% (Figure 12).

Preliminary DDDvet for single substance VMPs of oxytetracycline for pigs for oral solution, oral powder and premix shown in Table 13 were used for the impact analyses.

Table 13. Preliminary DDDvet (mg/kg) for oxytetracycline for the major oral forms for pigs

	Oral powder	Oral solution	Premix	Average oral powder and premix	Average all oral forms
Pigs	25	20	32	28.5	26

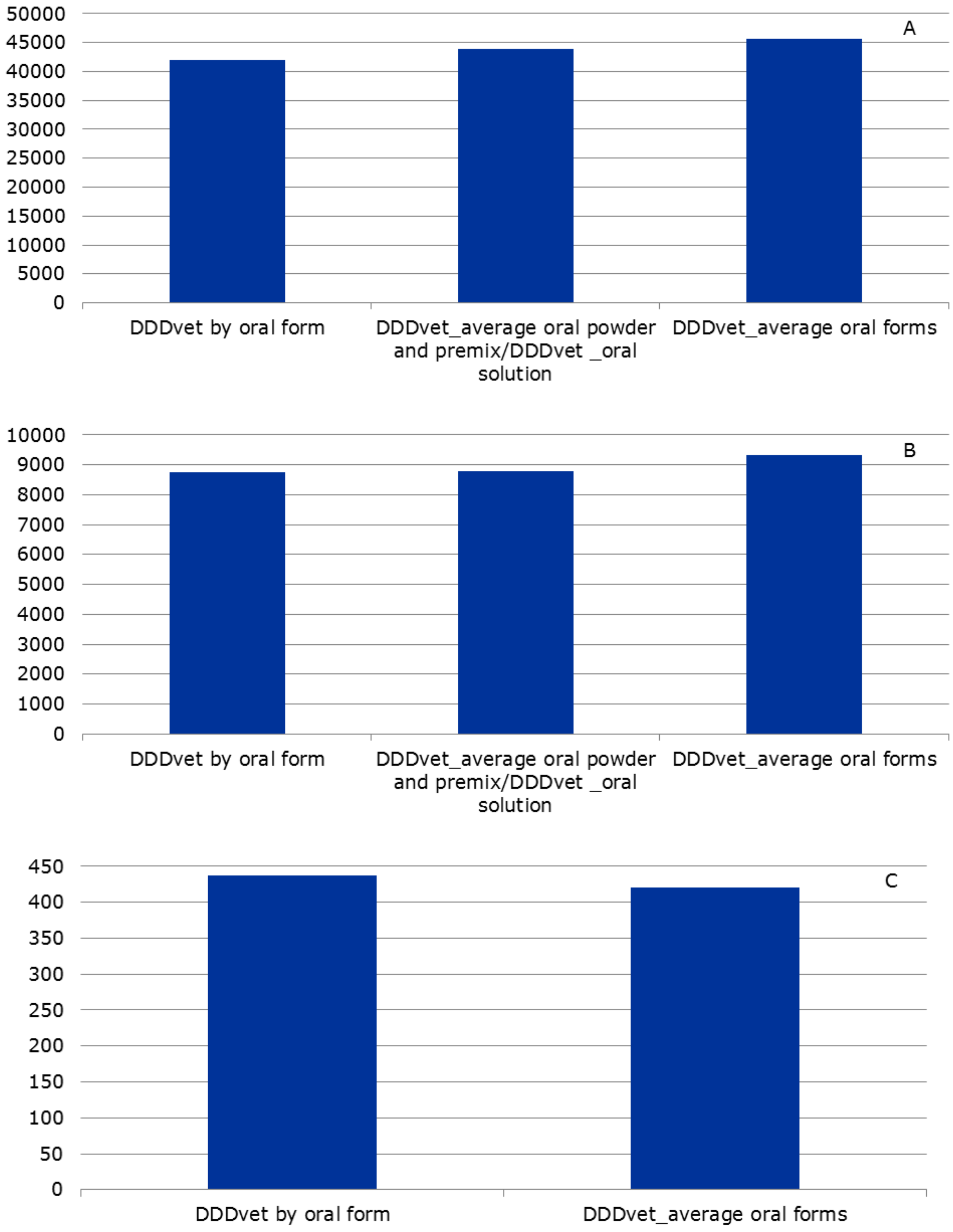
Annual output

The sales data shown in Table 14 were used for the impact analyses.

Table 14. Sales (tonnes) of oxytetracycline in single substance VMPs for oral solution, oral powder and premix in 26 EU/EEA countries (A) in 2012 and in two different MSs (B and C). It was assumed that all sales were for use in pigs

	Oral powder	Oral solution	Premix
A. Sales 26 EU/EEA countries	227	161	797
B. Sales MS 1	97	19	127
C. Sales MS 2	11	0	0

Figure 13. Calculated numbers of DDDvet (millions) sold of single oxytetracycline VMPs as oral powder, oral solution and premix in 26 EU/EEA countries (A) and two different MSs (B and C) in assuming that the total amounts sold were used in pigs



*Represent sales of oral powder (see Table 14)

The numbers of DDDvet oxytetracycline calculated by application of DDDvet for each oral form was 5% and 0.1% lower for A and B, respectively, compared to the output when oral solution was calculated separately (Figure 13). The numbers of DDDvet calculated by using DDDvet for each oral form was 8%, 6% and 4% lower for A, B and C, respectively, compared to the output when average DDDvet were applied.

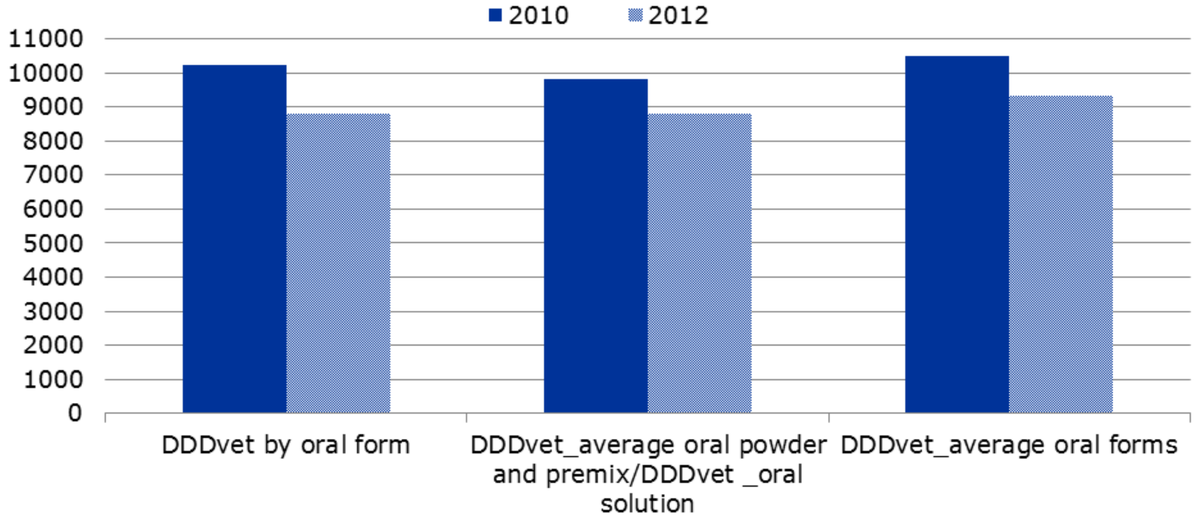
Changes across time

In order to assess the impact of using DDDvet as average for all oral forms compared to applying DDDvet for each form and to identify changes in consumption across time sales data for oxytetracycline single substance VMPs from one MS for 2010 and 2012 were used (Table 15).

Table 15. Sales (tonnes) of oxytetracycline in single substance VMPs of oral solution, oral powder and premix in 2010 and 2012 in one specific MS

	Oral powder	Oral solution	Premix
2010	158	33	198
2012	97	19	127

Figure 14. Calculated numbers of DDDvet (millions) sold of single oxytetracycline VMPs as oral powder, oral solution and premix. Sales data for one specific EU MS in 2010 and 2012 were used for the calculation and it was assumed that the total amounts sold were used for pigs



The difference in the output was small as a 14.2% reduction in sales from 2010 to 2012 was observed when specific DDDvet for the three oral forms were applied to analyse sales; when the average DDDvet of these forms were applied the estimated reduction was 11.2% (Figure 14).

It is generally acknowledged that the main arena for implementing management measures for the containment of AMR is at national/local level and thus valid measures to identify changes across years within a country/locally are important. Applying the average DDDvet oral forms for the estimation on changes across years at country level had almost no impact compared to when the “form”-specific DDDvet were used to analyse sales of oral powder, oral solution and premix.

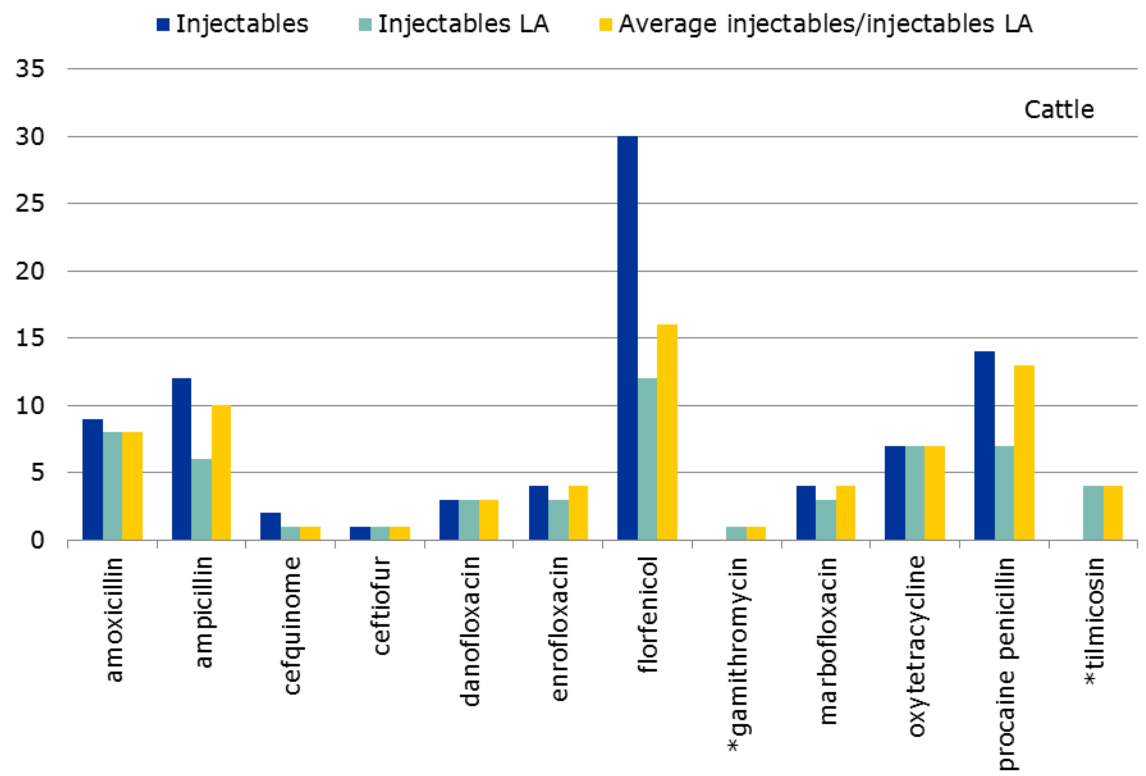
The same DDDvet will be assigned for an antimicrobial substance and species for all oral forms.

4.1.2. Injectables

The data sets provided by the nine MSs comprise information on dosing for injectables and for long-acting injectables by antimicrobial and species. For the collection of data on dosing from the nine MSs (Chapter 1) injectables were defined as long-acting when the duration of effect is more than 24 hours. An antimicrobial VMP may be long-acting either because of its long biological half-life, its formulation or sometimes because of both – e.g. procaine-penicillin can be "short-acting" because of an intermediate half-life (<24 hours) and long-acting because of the formulation. The substances identified with long biological half-life are gamithromycin, tildipirosin, tilmicosin and tulathromycin (macrolides).

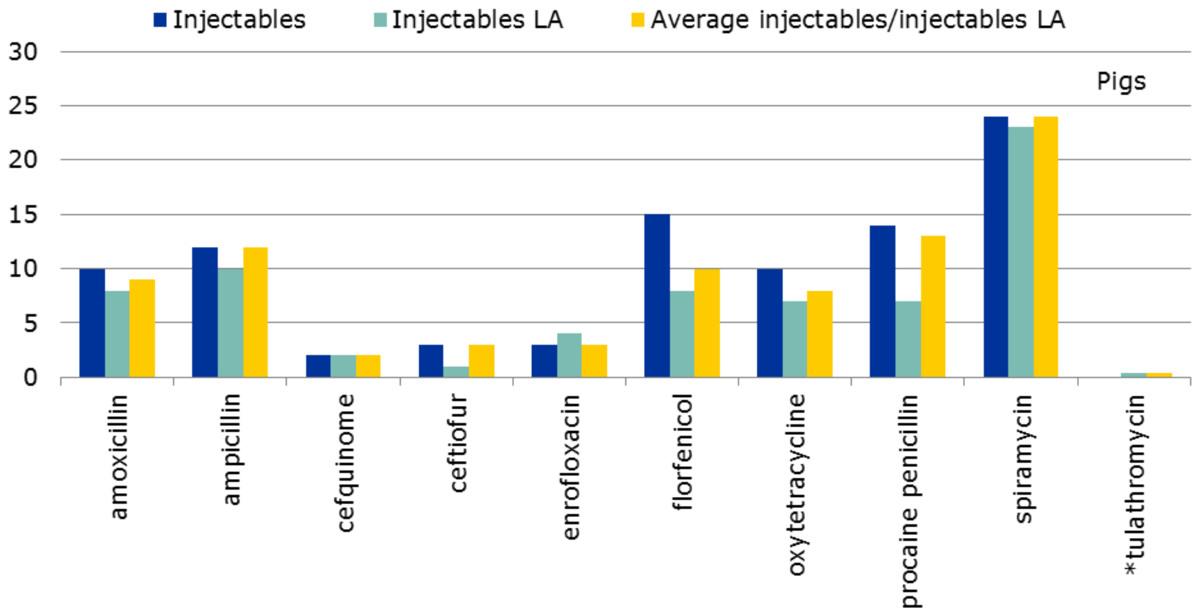
The data sets provided by the nine MSs consisted of 15 substances for which the single substance injectable VMPs were given as long-acting; 13 for cattle and 10 for pigs (Figure 15, Figure 16). Note that tildipirosin is also included in the data sets but identification of number of days for duration of effect is pending so therefore it is not included in Figure 15 and Figure 16.

Figure 15. Preliminary DDDvet (mg/kg) for injectables and long-acting injectables and the average DDDvet of these for cattle



* Long-acting only

Figure 16. Preliminary DDDvet (mg/kg) for injectables, long-acting injectables and average DDDvet of these for pigs



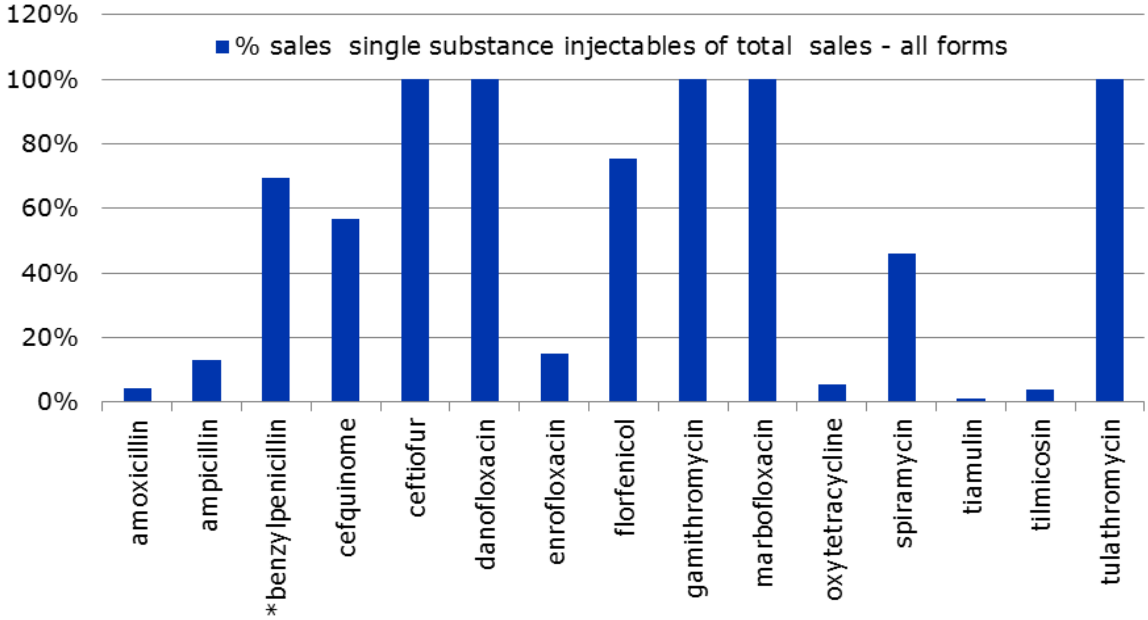
* Long-acting only

The ESVAC sales data are not stratified into injectables and long-acting injectables. As it would be very time-consuming to stratify sales into injectables and long-acting injectables by use of the “raw” sales data provided at product level for the 26 EU/EEA countries, similar impact analyses as for oral forms have not been completed.

The sales of injectable VMPs in the 26 EU/EEA countries in 2012 were 600 tonnes of which the most-selling substances were benzylpenicillin (131 tonnes) mainly as procaine benzylpenicillin, oxytetracycline (68 tonnes), amoxicillin (54 tonnes), florfenicol (38 tonnes) and enrofloxacin (18 tonnes) (ESVAC 2012 report, unpublished data).

Figure 17 shows the percentage sales as injectables of total sales for those antimicrobials that are specified as long-acting injectables in the data sets provided by the nine MSs.

Figure 17. Percentage sales (in tonnes active substance) of injectables and long-acting injectables single substance VMPs of total sales (all forms), for those substances that were specified as long-acting in the data sets from the nine MSs



*Major part sold as procaine benzylpenicillin

For the most-selling injectable substances – amoxicillin and oxytetracycline - minor differences are observed between the preliminary DDDvet (mg/kg) for injectables and long-acting injectables. This is also the case for the CIAs with highest priority for human medicine. For pigs exceptions are for ceftiofur and enrofloxacin, which show moderate differences; however, of the observations on dosing for ceftiofur injections for pigs in the data sets from the nine MSs, 80 were for injectables and only one was for long-acting injectables. For enrofloxacin 80 observations were for injectables and two were for long-acting injectables.

For cattle and pigs notable differences are seen between the preliminary DDDvet for injectables and long-acting injectables for florfenicol. The number of observations for long-acting florfenicol injectables for cattle was 45 of 58, while for pigs these figures were 35 of 51, indicating that long-acting injections dominate for florfenicol. Moreover, sales of florfenicol as injectable VMP accounts for close to 75% of all sales of this substance in the 26 EU/EEA countries in 2012. Separate DDDvet will be assigned for injectable and long-acting injectables of florfenicol.

Also for ampicillin, benzylpenicillin (procaine benzylpenicillin) and spiramycin for cattle notable differences were observed between preliminary DDDvet for injectables and long-acting injectables. For ampicillin the proportion sold as injectable in general is low; furthermore, the number of observations for long-acting injectables is low for both ampicillin and spiramycin. Therefore, assigning the same DDDvet for injectables and long-acting injectables for ampicillin and spiramycin is suggested to have a minor impact on the output. For benzylpenicillin (procaine benzylpenicillin) the number of observations for long-acting injectables is 2 of 48 for cattle and 4 of 49 for pigs, indicating that the numbers of long-acting injectables marketed are very small.

The DDDvet by substances and species in injectable and long-acting injectable VMPs will be assigned as the average of all observations of these. Exceptions will be identified in the lists of DDDvet and DCDvet.

The preliminary DDDvet for benzylpenicillin and procaine benzylpenicillin for cattle are 15 mg/kg and 14mg/kg; for pigs these are 16 mg/kg and 14mg/kg, respectively. The differences are minor but in order to identify consumption of prodrugs and because huge differences are observed for the DCDvet for benzylpenicillin and procaine benzylpenicillin prodrugs will be assigned separate DDDvet (see Chapter (4.2.2.).

Prodrugs and its active substance will be assigned separate DDDvet.

4.2. DDDvet – combination products

4.2.1. Oral forms

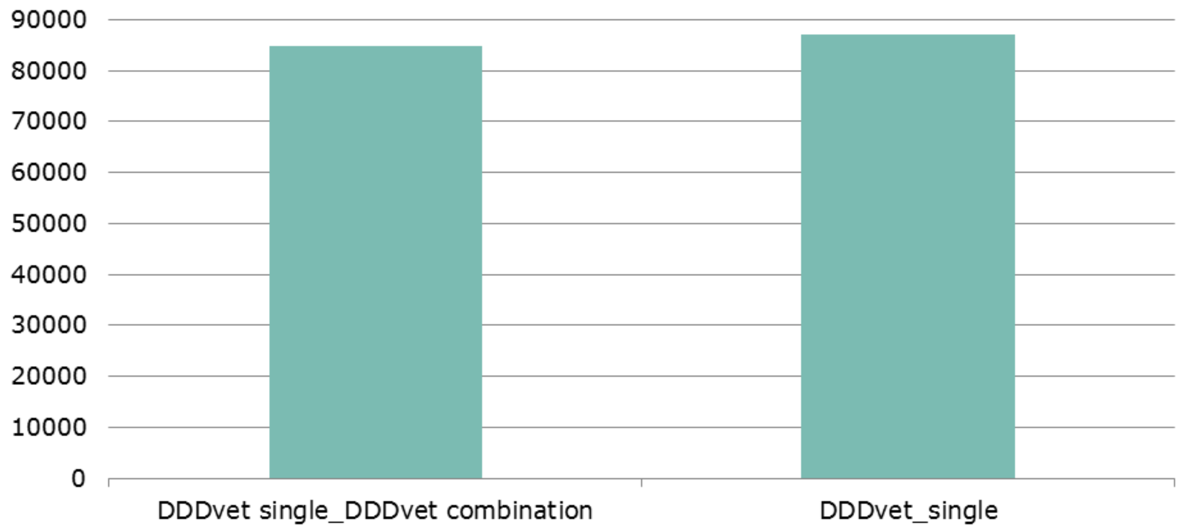
The preliminary DDDvet values show that these may vary between single VMPs and combination VMPs (VMPs containing more than one antimicrobial). The impact on the total output of applying DDDvet for single substance VMPs for reporting consumption for the same substance in combination VMPs were assessed by use of the preliminary DDDvet for amoxicillin and oxytetracycline.

4.2.1.1. Amoxicillin

Preliminary DDDvet for pigs for amoxicillin for single and combination VMPs were applied for the impact analyses - i.e. 17 mg/kg and 28 mg/kg. It should be noted that for most substances the DDDvet for a substance in a combination VMP is typically lower than the DDDvet for single substance VMP.

Sales of amoxicillin oral powder, oral solution and premix in 26 EU/EEA countries in 2012 as single substance VMPs were 1,385 tonnes and for combination VMPs was 96 tonnes. In the analysis it was assumed that all oral powder, oral solution and premix sold in the 26 EU/EEA countries were given to pigs.

Figure 18. Estimated numbers of DDDvet sold (millions) of amoxicillin oral powder, oral solution and premix as single and combination VMP calculated by application of DDDvet single and DDDvet combination respectively, and by application of DDDvet single for the sales of both single and combination substance VMPs these forms assuming that the complete amount sold was used in pigs



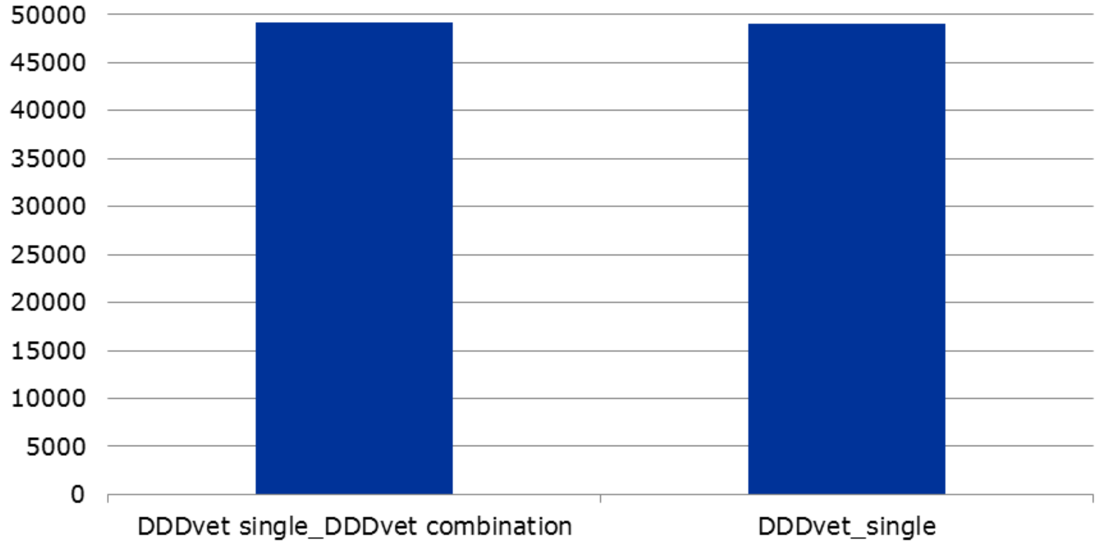
The difference between the estimated outputs for amoxicillin is 3% (higher) compared to when applying DDDvet single for sales of amoxicillin both for single and combination VMPs (Figure 18).

4.2.1.2. Oxytetracycline

Preliminary DDDvet for pigs for oxytetracycline for single and combination VMPs oral forms were applied for the impact analyses - i.e. 26 mg/kg and 24 mg/kg.

Sales of oxytetracycline in 26 EU/EEA countries in 2012 of oral powder, oral solution and premix in single substance VMPs were 1,253 tonnes and for combination VMPs it was 24 tonnes. In the analysis it was assumed that all oral powder, oral solution and premix sold in the 26 EU/EEA countries were given to pigs.

Figure 19. Estimated numbers of DDDvet sold (millions) of oxytetracycline oral powder, oral solution and premix as single and combination VMP calculated by application of DDDvet single and DDDvet combination, respectively, and by application of DDDvet single for the sales of both single and combination substance VMPs these forms assuming that all sales were used in pigs



The output when applying DDDvet single for oxytetracycline calculating both sales as single and combination VMP was only 0.2% lower compared to analysis by use of separate DDDvet (Figure 19).

The results indicates that application of the same DDDvet for amoxicillin and oxytetracycline for analysing sales of these as combination VMPs and single substance VMP has almost no impact on the output in calculated numbers of DDDvet. The explanation for this is that amount sold as combination VMP is minor and the outputs were therefore not impacted by the difference between the DDDvet single and DDDvet combination.

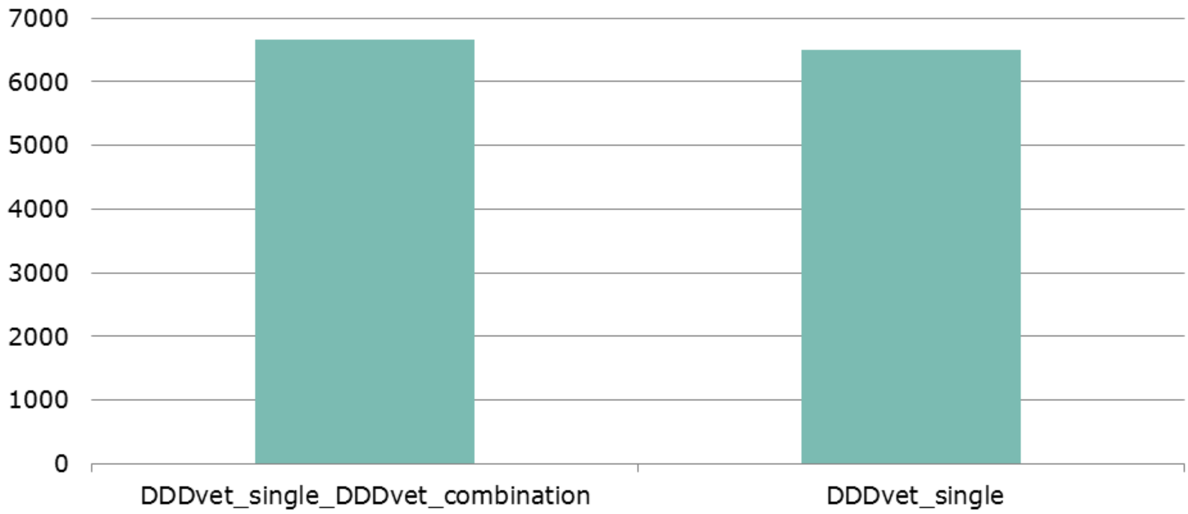
The single substance DDDvet for an oral form and species will be assigned for the same substance in a combination VMP. Exceptions are described in chapter 4.2.3.

4.2.2. Injectables

Of the most-selling single injectable antimicrobials in the 26 EU/EEA countries in 2012 the sales of the same substances in combination injectable VMPs were minor except for benzylpenicillin (ESVAC 2012, unpublished data). Therefore, an impact assessment has only been completed for benzylpenicillin.

Benzylpenicillin is mainly sold as the prodrug procaine benzylpenicillin; 78 tonnes as single and 13 tonnes as combination injectable VMPs (ESVAC sales 2012, unpublished data). These data and the preliminary DDDvet for the prodrug procaine benzylpenicillin as single and combination injectable VMPs (14mg/kg and 12mg/kg, respectively) were used for the impact analysis assuming that the complete sales were for pigs.

Figure 20. Estimated numbers of DDDvet sold (millions) of procaine benzylpenicillin injectable VMPs as single and combination VMP calculated either with separate DDDvet for single and combination VMPS, respectively or with DDDvet single substance products for all sales assuming that the complete amount was administered to pigs



If the single DDDvet for procaine benzylpenicillin was used to calculate sales of both single and combinations VMPs, the number of DDDvet would be 2% lower for pigs compared to when calculated by specific single and combination DDDvet (Figure 20).

Since sales of substances in combination injectable VMPs of the most-selling single injectable VMPs in the 26 EU/EEA countries in 2012 generally were very low the impact of applying single substance DDDvet for injectables for the overall output is thought to be relatively low.

The DDDvet given for single substance oral products will be assigned for the same substance and species in a combination oral VMP. Exceptions are described in chapter 4.2.3.

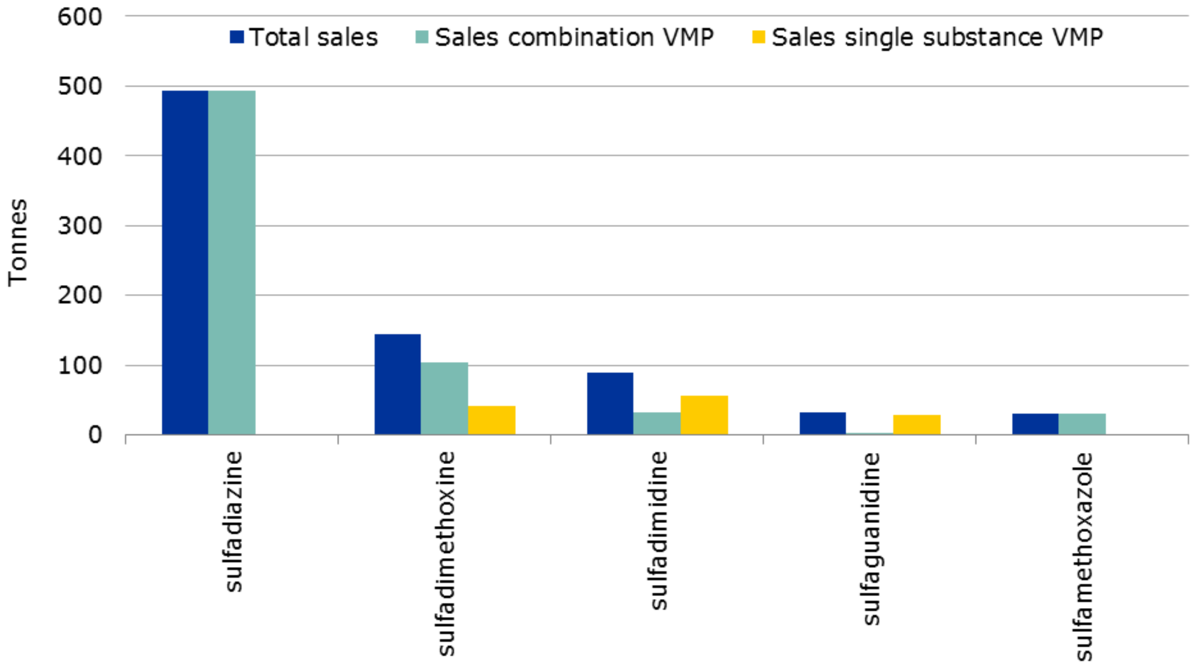
4.2.3. Synergistic combinations – oral forms and injectables

For fixed combinations the therapeutic effect can be improved due to a synergistic effect if one substance is influenced and enhanced by another substance (true therapeutic advantage) – i.e. sulfonamides combined with trimethoprim and amoxicillin potentiated with clavulanic acid. Fixed combinations may also be used to broaden the activity spectrum by combining more than one active substance. In such cases the benefit is that it can simplify administration of the medicinal products in cases where two different antimicrobials are regarded as needed in order to obtain satisfactory therapeutic effect and may facilitate owners' compliance.

For combinations such as sulfonamide-trimethoprim the dose of the sulfonamide component is typically substantially lower compared to the dose for the same sulfonamide in single substance VMPs, due to the synergistic effect of this combination (White et al., 1981).

The major proportion of sales of sulfonamides in 26 EU/EEA countries in 2012 was for combination products, of which in particular sulfadiazine but also sulfadimethoxine accounted for the major part (Figure 21); these sulfonamides were almost exclusively combined with trimethoprim (ESVAC sales data 2012, unpublished data).

Figure 21. Sales of the most-selling sulfonamides as single substance and in combination VMPs in 26 EU/EEA countries in 2012 (ESVAC 2012, unpublished data)



Preliminary DDDvet for sulfadiazine and sulfadimethoxine show that the DDDvet are substantially lower for combination VMPs (Table 16). No sulfadiazine dosing for single substance VMPs was reported by any of the nine MSs.

Table 16. Preliminary DDDvet for sulfadiazine and sulfadimethoxine. Note that there are no data for oral powder single substance VMPs for these substances in the data sets for the nine countries

	Species	Inj.-single	Inj.-combi.	Oral powder – combi.	Oral solution - single	Oral solution combi.	Premix-single	Premix-combi.
Sulfadiazine	Cattle		13	21		42		25
Sulfadiazine	Pigs		14	23		25		22
Sulfadimethoxine	Cattle	30		17	38	17		26
Sulfadimethoxine	Pigs	30	19	17	47	26	50	26

Separate DDDvet will be assigned for single substance sulfonamide VMP and the same sulfonamide in combination with trimethoprim.

In human medicine the DDDs for an antimicrobial in combination with enzyme inhibitors are identical to the active substance, except for amoxicillin and amoxicillin combined with enzyme inhibitor that are set to 3 g and 1 g, respectively (Table 17).

Table 17. DDD for antimicrobials as single substance human medicinal products (HMPs) and in combination with an enzyme inhibitor (O=oral; P=parenteral) (http://www.whocc.no/atc_ddd_index/)

	DDD	Administration route	Substances	DDD	Adm.R	Note
Ampicillin	2 g	P	Ampicillin and enzyme inhibitor	2 g	P	Refers to ampicillin
	2 g	O				
Amoxicillin	1 g	P	Amoxicillin and enzyme inhibitor	3 g	P	Refers to amoxicillin
	1 g	O		1 g	O	Refers to amoxicillin
Piperacillin	14 g	P	Piperacillin and enzyme inhibitor	14 g	P	Refers to piperacillin
Ticarcillin	15 g	P	Ticarcillin and enzyme inhibitor	15 g	P	Refers to ticarcillin

The difference between the preliminary DDDvet for amoxicillin and amoxicillin combined with clavulanic acid is minor for injectable products in cattle and moderate for injectable products in pigs (Table 18) and this is also the case for oral products. For pigs the number of observations for amoxicillin combined with clavulanic acid is minor which is likely to reflect the low number of such products marketed for pigs (Table 18).

Amoxicillin and amoxicillin combined with clavulanic acid and similar combinations will be assigned the same DDDvet – i.e. the average of the observations of amoxicillin (single substance VMP) and amoxicillin in combination with an enzyme inhibitor.

Table 18. Preliminary DDDvet for amoxicillin, amoxicillin + clavulanic acid and the average of these for injectable products for pigs and cattle

Species	Substance	ATCvet code	Numbers of observations	Average dose (DDDvet)
Cattle	Amoxicillin	QJ01CA04	33	9
	Amoxicillin + clavulanic acid	QJ01CR02	12	8
		QJ01CA04 + QJ01CR02	**45**	**9**
Pigs	Amoxicillin	QJ01CA04	55	10
	Amoxicillin + clavulanic acid	QJ01CR02	4	7
		QJ01CA04 + QJ01CR02	**59**	**10**

4.3. DCDvet – single substance products

4.3.1. Oral forms

The number of treatment days is typically higher for premix compared to oral powder and oral solution and in particular for pigs; this is reflected in the preliminary DCDvet as shown in Table 19, Table 20 and Table 21. The substances presented in these tables were the most selling oral single substance VMPs in 26 EU/EEA countries in 2012 (Figure 10). One approach could be to assign separate DCDvet for premix and for all other oral forms.

Table 19. Preliminary DCDvet (mg/kg) for single substance products for broilers for oral powder, oral solution and premix, average DCDvet all oral forms and average DCDvet all oral forms when premix is excluded

	Oral powder	Oral solution	Premix	Average all oral forms	Average orals – premix excluded
Amoxicillin	77	71	150	78	74
Chlortetracycline	223	162	188	196	206
Colistin	32	20	68	25	22
Doxycycline	62	66	52	64	65
Enrofloxacin		41		41	41
Lincomycin	50	30	378	69	45
Neomycin	139	137	30	114	138
Oxytetracycline	303	282	300	299	299
Tetracycline	100	481		405	405
Tiamulin	108	72	106	89	83

Table 20. Preliminary DCDvet (mg/kg) for single substance products for cattle for oral powder, oral solution and premix, average DCDvet all oral forms and average DCDvet all oral forms when premix is excluded

	Oral powder	Oral solution	Premix	Average all oral forms	Average orals – premix excluded
Amoxicillin	97			65[1]	65[1]
Chlortetracycline	110	126	194	133	113
Colistin	29	20		24	24
Doxycycline	42	43		42	42
Enrofloxacin	25	22		22	22
Neomycin	92	201	30	122	152
Oxytetracycline	112	77	145	123	104
Tetracycline	120	75	80	92	98
Tylosin	534	368		414	414

[1]Lower than oral powder because includes other oral forms as well

Table 21. Preliminary DCDvet (mg/kg) for single substance products for pigs for oral powder, oral solution and premix, average DCDvet all oral forms and average DCDvet all oral forms when premix is excluded

	Oral powder	Oral solution	Premix	Average all oral forms	Average orals – premix excluded
Amoxicillin	80	70	179	107	75
Chlortetracycline	193	96	230	207	183
Colistin	29	23	46	29	25
Doxycycline	47	51	83	57	50
Enrofloxacin		10		10	10
Lincomycin	54	92	134	89	67
Neomycin	107	156	131	133	134
Oxytetracycline	107	80	282	174	92
Tetracycline	210	207	340	220	208
Tiamulin	75	62	81	72	67
Tylosin	114	140	98	119	129

An impact analysis was performed in order to compare numbers of DCDvet when oral powder, oral solution and premix are analysed separately by use of specific DCDvet, when the average DCDvet for all orals were used and when premixes were analysed separately by its specific DCDvet.

Explanation of the axis shown in Figure 22 and Figure 23:

- DCDvet by oral form = (tonnes oral powder sold substance X/DCDvet oral powder) + (tonnes oral solution sold substance X/DCDvet oral solution) + (tonnes premix sold substance X/DCDvet premix)
- DCDvet average all oral forms = (tonnes oral powder + oral solution + premix sold of substance X)/(average DCDvet of all oral forms)
- DCDvet average oral forms (premix excluded)/DCDvet premix = (tonnes oral powder + oral solution sold of substance X)/(average DCDvet of all oral forms-premix excluded) + (tonnes premix sold of substance X/DCDvet premix)

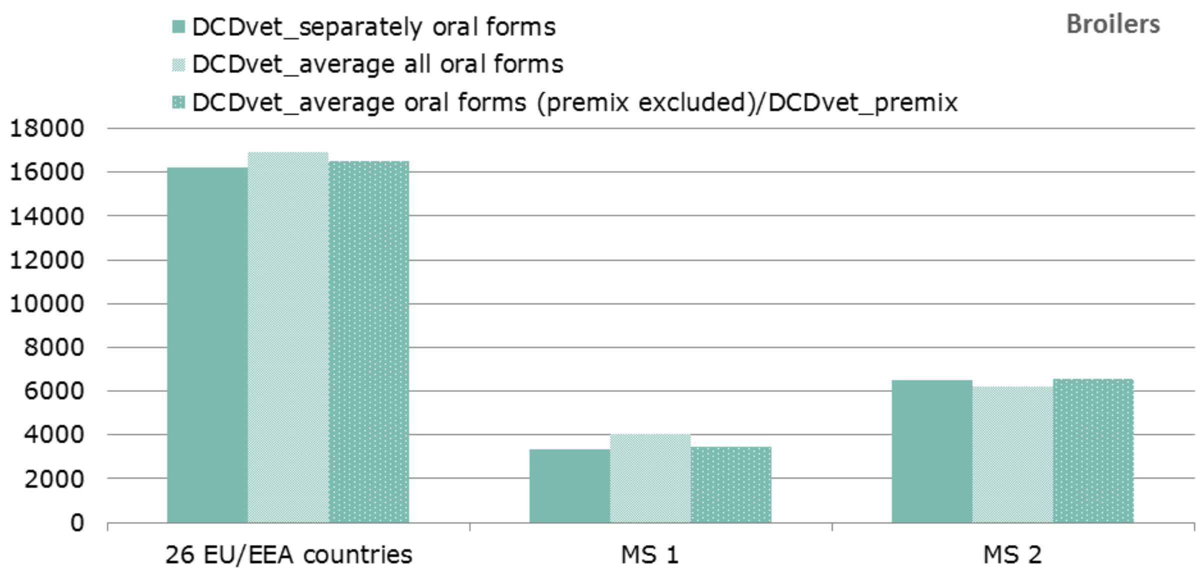
4.3.1.1. Amoxicillin

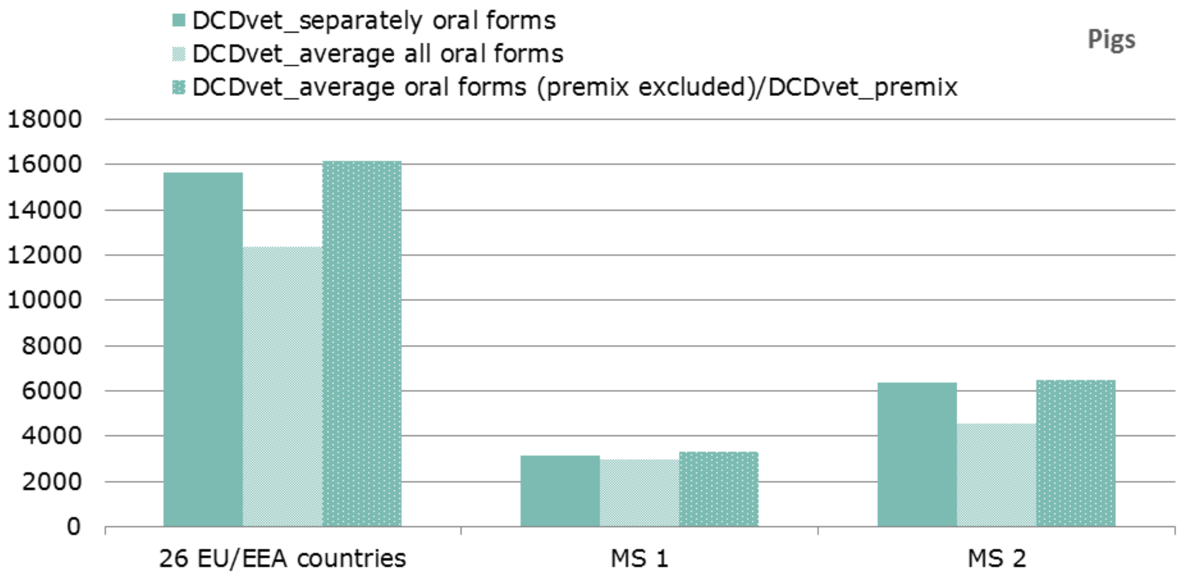
Preliminary DCDvet for amoxicillin used for the impact analyses are shown in Table 19 and Table 21. The tonnes sold of oral powder, oral solution and premix of amoxicillin and oxytetracycline in 26 EU/EEA countries in 2012 as well as in two MSs as provided to ESVAC 2012 were used for the impact analyses (Table 22). The complete amount was considered as sold for use either for broilers and pigs, respectively.

Table 22. Sales (tonnes) of amoxicillin in single substance VMPs oral solution, oral powder and premix in 2012 in 26 EU/EEA countries and two different MSs

	Oral powder	Oral solution	Premix
Sales 26 EU/EEA countries	863	265	194
Sales MS 1	198	<0.5	120
Sales MS 2	333	153	<0.5

Figure 22. Numbers of DCDvet (millions) of single amoxicillin VMPs calculated by use of 1) separate DDDvet oral powder, oral solution and premix, 2) average DCDvet orals and 3) average DCDvet orals (premix excluded) for oral powder add oral solution and DCDvet premix for premix. Sales data for 26 EU/EEA countries and two specific MSs in 2012 were applied for the calculation and it was assumed that the complete amounts sold were used in either broilers or pigs





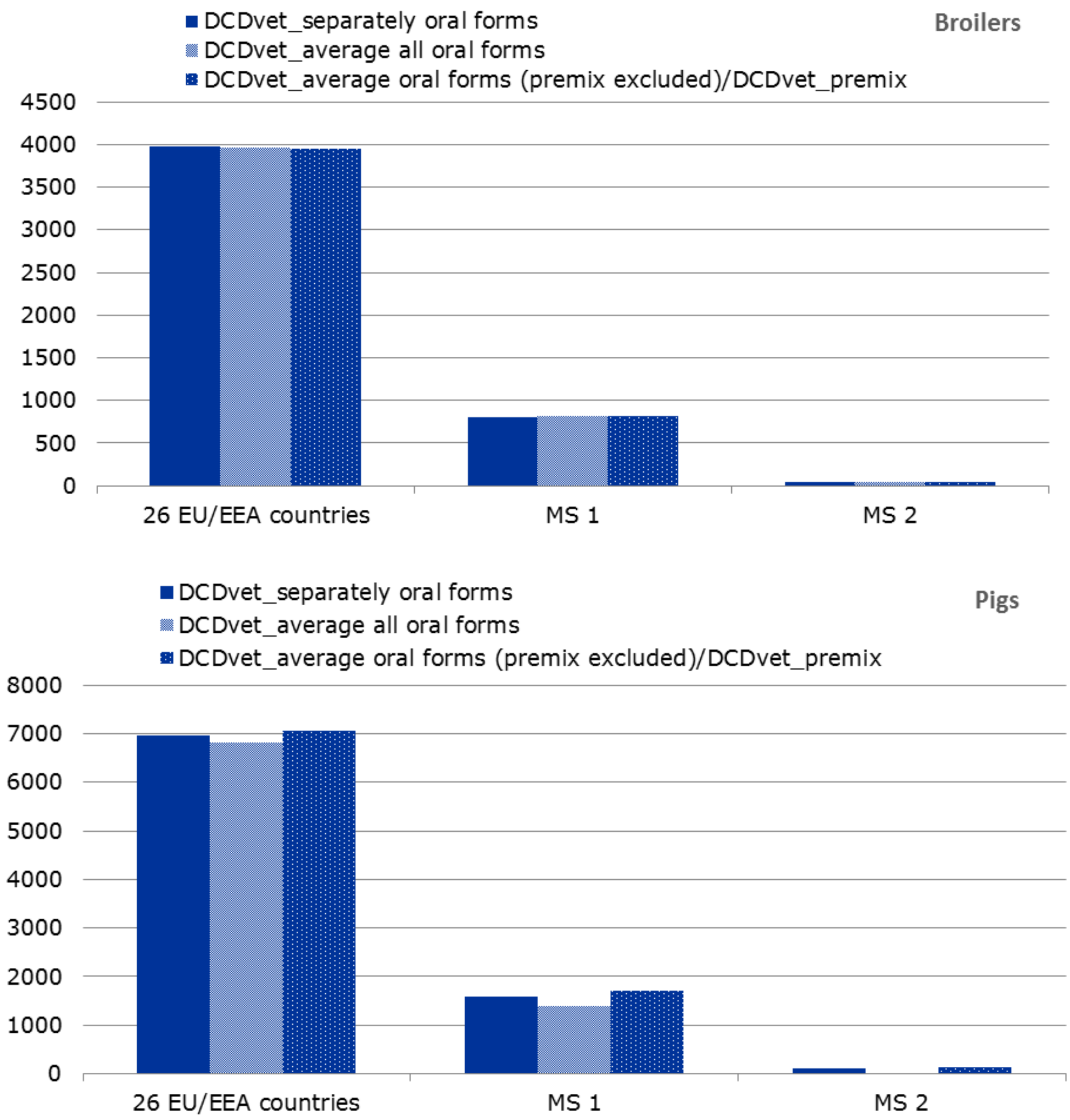
4.3.1.2. Oxytetracycline

Preliminary DCDvet for oxytetracycline applied for the impact analyses shown in Table 19 and Table 21, and the sales data for amoxicillin oral powder, oral solution and premix shown in Table 23 were used for the impact analyses assuming that the complete amounts were used either for broilers or pigs.

Table 23. Sales (tonnes) of oxytetracycline in single substance VMPs oral solution, oral powder and premix in 2012 in 26 EU/EEA countries and two different MSs

	Oral powder	Oral solution	Premix
Sales 26 EU/EEA countries	227	161	797
Sales MS 1	97	19	127
Sales MS 2	11	0	0

Figure 23. Numbers of DCDvet (millions) of single oxytetracycline VMPs calculated by use of 1) separate DDDvet oral powder, oral solution and premix; 2) average DCDvet orals and 3) average DCDvet orals (premix excluded) for oral powder and oral solution and DCDvet premix for premix. Sales data for 26 EU/EEA countries and two different MSs in 2012 were applied for the calculation and it was assumed that the total amounts sold were used for either broilers or pigs



Broilers

For broilers the difference in output for amoxicillin when using separate DCDvet for premix and for all other oral VMPs for the analysis compared to when the average DCDvet of all observations of oral forms was used to analyse data from 26 MSs and two specific MSs, was 2%, 15% and 5%, respectively. For oxytetracycline it was 0%, 0.1% and 0.2%, respectively (Figure 22, Figure 23).

Pigs

For pigs the change in output when using separate DCDvet for premix and for all other oral VMPs for the analysis compared to when the DCDvet average of all observation of oral forms was used for amoxicillin is 31% for the 26 EU/EEA countries, for MS 1 it is 11% and for MS 2 43%. For oxytetracycline the corresponding figures were 3%, 22% and 89% (Figure 22, Figure 23).

The results of the analyses show that the impact on the output when using separate DCDvet for premix and DCDvet for all other oral VMPs versus the DCDvet average of all observations of oral forms is influenced by the distribution of sales as oral powder, oral solution and premix - overall and by MS.

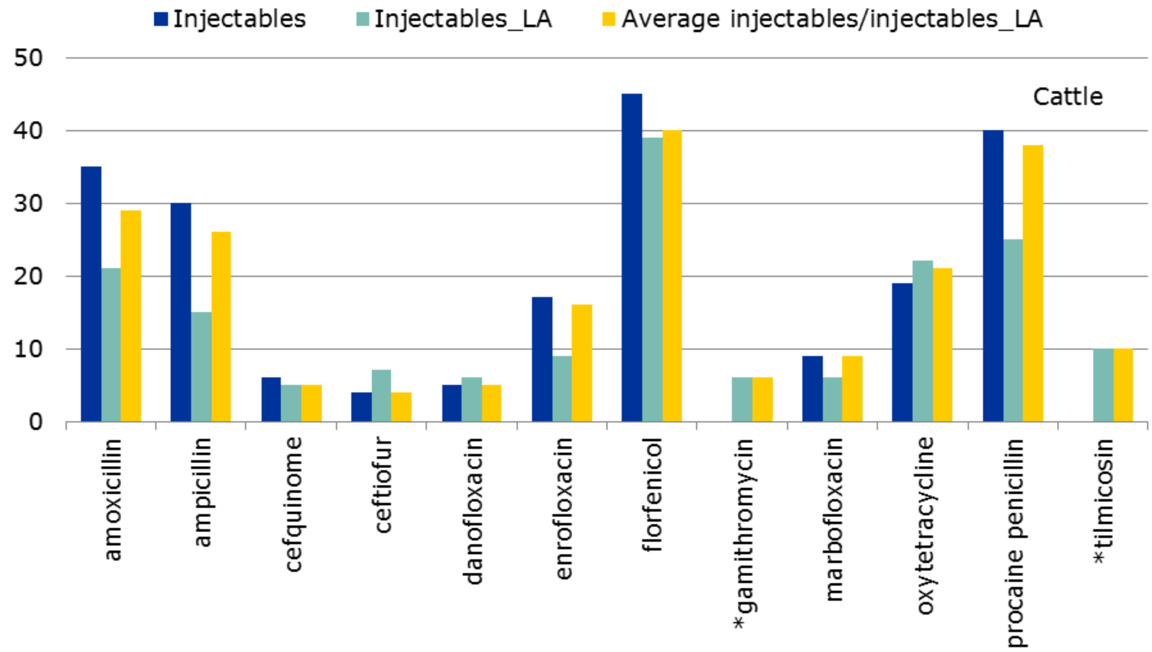
The preliminary DCDvet show that the DCDvet for premix is not consistently higher than for other oral forms, except for pigs. It is generally acknowledged that the main area for implementing management measures for the containment of AMR is at national/local level and thus valid measures for changes across years within a country/locally are important. Recognizing DCDvet is a technical unit of measurement and that the same value (DCDvet) will be used across years, it will allow for identification of changes at country/local level. To assign the same DCDvet for all oral forms would make the list of DCDvet easier to manage in terms of analysing and reporting of the data and also for maintaining the list.

The same DCDvet will be assigned for all oral forms for each combination of antimicrobial substance and species. Exceptions will be explained in the list of DCDvet.

4.3.2. Injectables

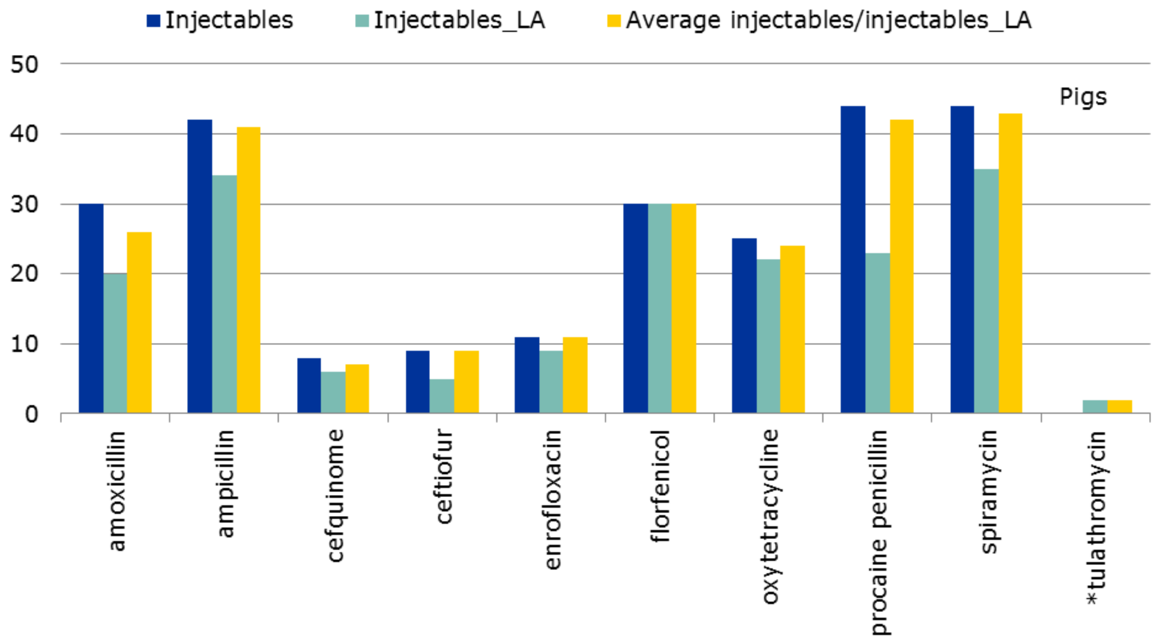
In the data sets on dosing provided by the nine MSs a total of 13 single substance injectables were given as long-acting injectables for cattle and 10 VMPs for pigs by the MSs (Figure 24, Figure 25).

Figure 24. Preliminary DCDvet (mg/kg) for injectables and long-acting injectables and the average of these for cattle – single substance products



* Long-acting only

Figure 25. Preliminary DCDvet (mg/kg) for injectables and long-acting injectables and the average of these for pigs - single substance products



* Long-acting only

The discussion and conclusions on DDDvet for injectables and long-acting injectables (Chapter 4.1.2) also applies for assignment of DCDvet. One exception is florfenicol for which the difference between DCDvet for injectables and long-acting injectables is minimal and thus the DCDvet will be assigned as the average of the observations for injectables and long-acting injectables.

The same DCDvet will be assigned for single substance injectables and long-acting injectables for each substance and species and will be assigned as the average of these by substance and species. Separate DCDvet will be assigned for prodrugs and its active substance.

4.4. DCDvet – combination products

4.4.1. Oral forms

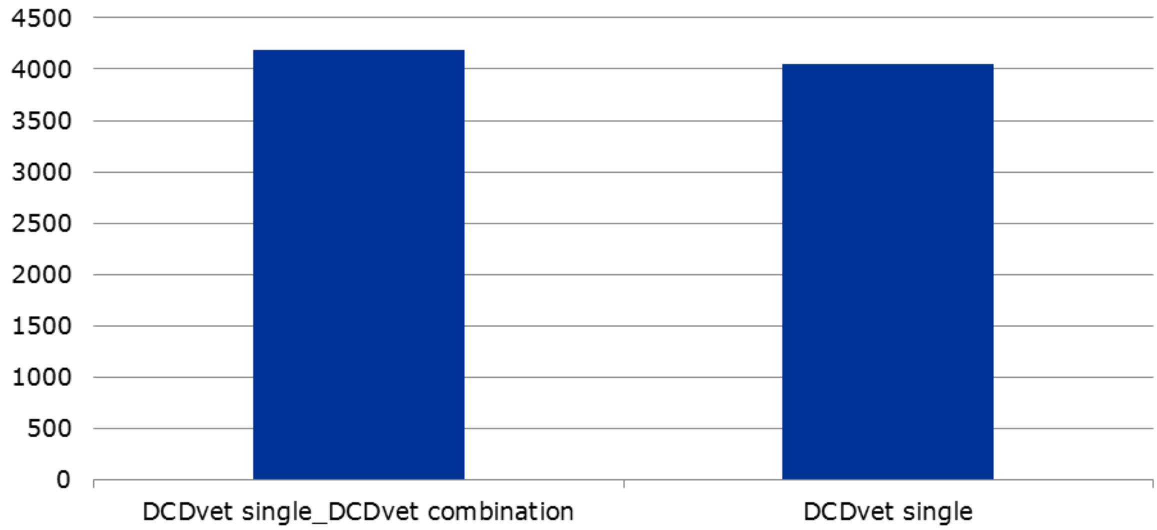
The preliminary DCDvet values show that these may vary between single VMPs and combination VMPs for oral forms. The impact on the total output by applying DCDvet for single substance oral VMPs for reporting consumption for the same substance in combination VMPs was assessed by use of sales data of oxytetracycline and the preliminary DCDvet. Note that for pigs premix was analysed separately (Figure 26 and Figure 27).

Sales of oxytetracycline as oral powder, oral solution and premix in 26 EU/EEA countries in 2012 as single substance VMPs were 1,185 tonnes and 24 tonnes for combinations.

4.4.1.1. Oxytetracycline - broilers

The preliminary DCDvet for oxytetracycline in single and combination VMPs for oral administration to broilers were 299 mg/kg and 108 mg/kg, respectively.

Figure 26. Estimated numbers of DCDvet sold (millions) of oxytetracycline oral powder, oral solution and premix as single and combination VMP calculated by application of DCDvet single and DCDvet combination respectively, and by application of DCDvet single for the sales of both single and combination substance VMPs these forms in 26 EU/EEA countries in 2012 assuming that the complete amount sold was used in broilers



The difference between the two outputs was 3.4%.

4.4.1.2. Oxytetracycline - pigs

Sales of oxytetracycline in 26 EU/EEA countries in 2012 of oral powder, oral solution and premix in single substance VMPs were 1,185 tonnes and for combination VMPs it was 24 tonnes. In the analysis it was assumed that all oral powder, oral solution and premix sold in the 26 EU/EEA countries were given to pigs.

Explanation of the axis shown in Figure 27:

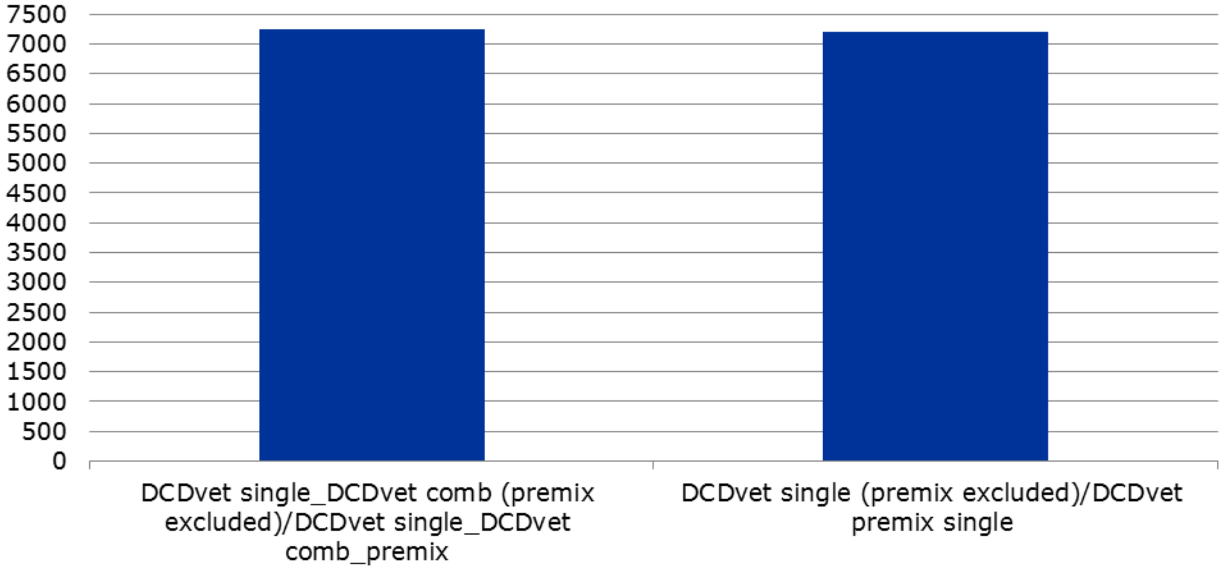
- DCDvet single - DCDvet comb (premix excluded)/DCDvet single – DCDvet comb premix = (tonnes oral powder + oral solution single sold substance X /DCDvet oral single - premix excluded) + (tonnes oral powder + oral solution combination sold substance X /DCDvet oral combination - premix excluded) + (tonnes single premix sold substance X/DCDvet premix single) + (tonnes combination premix sold substance X/DCDvet premix combination substance)
- DCDvet single (premix excluded)/DCDvet premix single = (tonnes powder + oral solution sold as single and combination VMP substance X)/DCDvet oral single – premix excluded) + (tones premix sold as single and combination VMP substance X/DCDvet premix single)

Preliminary DCDvet for oxytetracycline aggregated by oral forms (weighted mean) were used for the impact analyses (Table 24).

Table 24. Preliminary DCDvet for oxytetracycline for pigs used in the analysis

	DCDvet single premix	DCDvet single average orals forms (premix excluded)	DCDvet combination premix	DCDvet combinations average orals forms (premix excluded)
Pigs	282	92	150	94

Figure 27. Estimated numbers of DCDvet sold (millions) of oxytetracycline oral powder, oral solution and premix as single or combination VMP calculated by using 1) DCDvet single premix, DCDvet single average oral forms excluding premix, DCDvet combination premix, DCDvet combination average oral forms excluding premix respectively, and by application of 2) DCDvet single premix and DCDvet single average oral forms excluding premix single for the total sales of these forms assuming that all sales were used for pigs



The difference between the two outputs was 0.5% (Figure 27).

The results (Figure 26,Figure 27) indicate that using the single DCDvet for reporting sales of VMP has almost no impact on the total output on calculated numbers of DCDvet. The explanation for this is that the amount sold as combination VMP is minor and the outputs were therefore not impacted by the difference between DCDvet single and DCDvet combination.

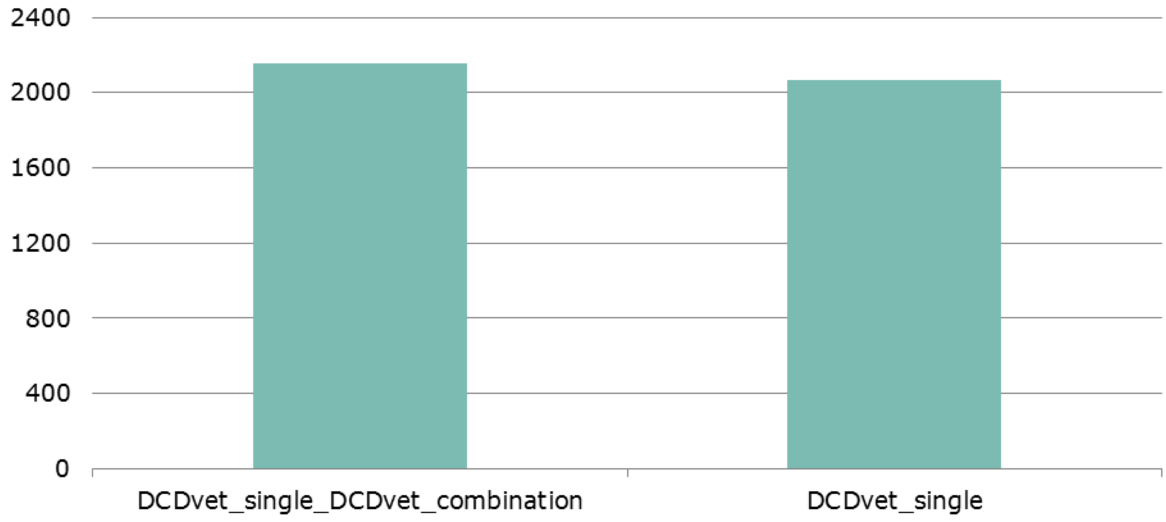
As a general rule the single substance DCDvet will be assigned for the same substance and species in a combination oral VMP. Exceptions are described in chapter 4.2.3.

4.4.2. Injectables

The sales as combination VMPs of the most-selling single antimicrobial injectables in the 26 EU/EEA countries were very low except for amoxicillin and benzylpenicillin (mainly sold as the prodrug procaine benzylpenicillin). For amoxicillin, when compared to total sales, the proportion of injectable amoxicillin was negligible. For combination injectables only two substances are given as long-acting in the same VMP - procaine benzylpenicillin and benzathine benzylpenicillin. The sale of this combination in the 26 EU/EEA countries was negligible (ESVAC, unpublished data). The impact of using single substance DCDvet for injectables and long-acting injectables, respectively, for the same substance and species for the substances in combination injectable, is therefore thought to be low. An exception is for the prodrug procaine benzylpenicillin.

The preliminary DCDvet for the prodrug procaine benzylpenicillin as single and combination VMPs are 44 mg/kg and 34 mg/kg, respectively, for pigs. Benzylpenicillin is mainly sold as the prodrug procaine benzylpenicillin; 78 tonnes as single and 13 tonnes as combination injectable VMPs (ESVAC sales 2012, unpublished data). These data and the preliminary DDDvet for the prodrug procaine benzylpenicillin as single and combination injectable VMPs were used for the impact analysis assuming that the complete sales were for pigs.

Figure 28. Estimated numbers of DCDvet sold (millions) of procaine benzylpenicillin injectable VMPs as single and combination VMP calculated either by using specific DCDvet for single and combination products or by using DCDvet for single products for all sales assuming that all procaine benzylpenicillin injectables was administered to pigs



If the single DDDvet for procaine benzylpenicillin was applied to calculate sales of both single and combinations VMPs the numbers of DCDvet would be 4% lower compared to when calculated by single and combination DCDvet (Figure 28). The impact of assigning the single substance DCDvet for the same substance and species in a combination injectable VMP on the overall output will be low.

The single substance DCDvet will be assigned for the same substance and species in a combination injectable VMP.

4.4.3. Synergistic combinations – oral forms and injectables

See considerations, including exceptions, outlined in chapter 4.2.3.

Separate DCDvet will be assigned for single substance sulfonamide product and the DCDvet for the same sulfonamide in combination with trimethoprim.

5. Intramammary LC products and intrauterine products

For intramammary LC products 92 observations were included in the final data sets from the seven MSs that delivered data. For 50 observations the daily dose was 1 intramammary (IM)/teat per day and for 42 it was 2 IM/teat per day; thus the mode DDDvet is 1 IM/teat. For 45 observations the number of treatment days was 3; thus the mode DCDvet is 3 IM/teat. For pirlimycin (N=6) the number of treatment days was 8 for all observations (central authorised product).

The DDDvet and DCDvet for intramammary LC products will usually be assigned as 1 IM/teat and 3 IM/teat, respectively. Pirlimycin will be assigned a separate DCDvet.

For 26 of the 44 observations on dosing for intrauterine products (IUP) the daily dose was 1 IUP/ per animal and day; for 23 observations the treatment dose was 2 IUP/ per animal.

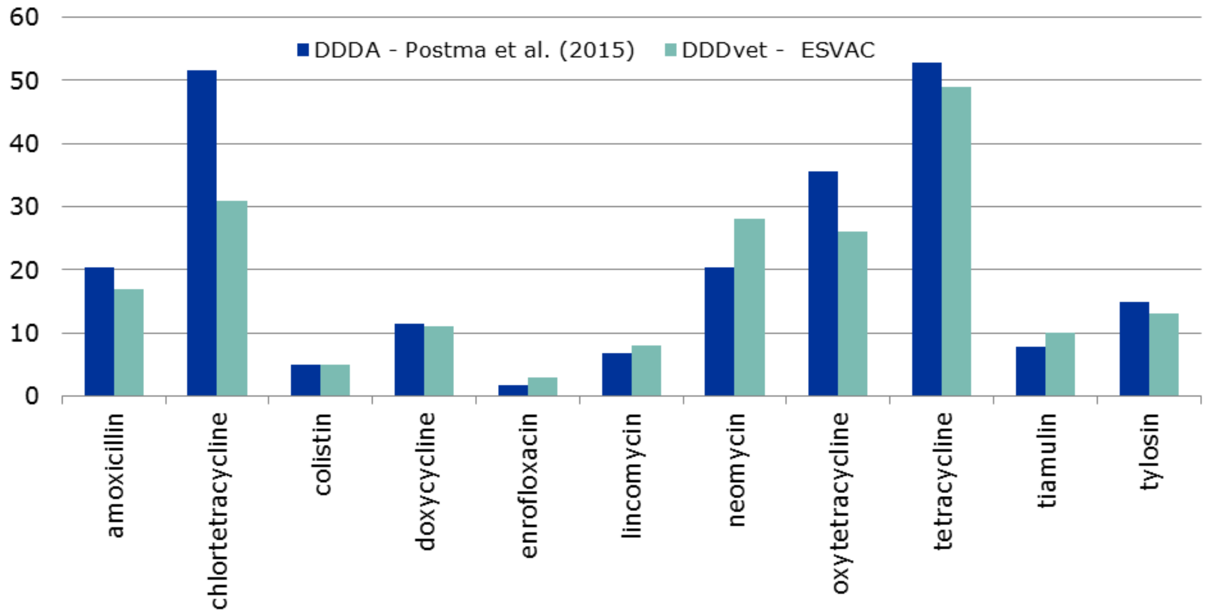
The DDDvet and DCDvet for intrauterine products will usually be assigned as 1 IUP/animal and 2 IUP/animal, respectively. Exceptions will be given in the lists of DDDvet and DCDvet.

6. Discussion on preliminary DDDvet – ESVAC

In a recent paper defined daily doses animal (DDDAs) for pigs - based on data from four European countries (Belgium, France, Germany and Sweden) - were published (Postma, Sjolund et al., 2015). A comparison between the defined daily dose animals (DDDA) published in that paper and the preliminary ESVAC DDDvet for pigs was performed for the most-selling single substances in oral VMPs shown in Figure 29 and for injectables in Figure 30.

In the study by Postma, Sjolund et al. (2015) the DDDAs were assigned separately for pharmaceutical forms for administration through water/feed and other oral forms, while for ESVAC it is suggested to assign the same DDDvet for all oral forms for each substance and species. To facilitate the comparison, the DDDA for administration through feed/water by Postma, Sjolund et al. (2015) and the oral DDDvet of ESVAC were used for the analysis.

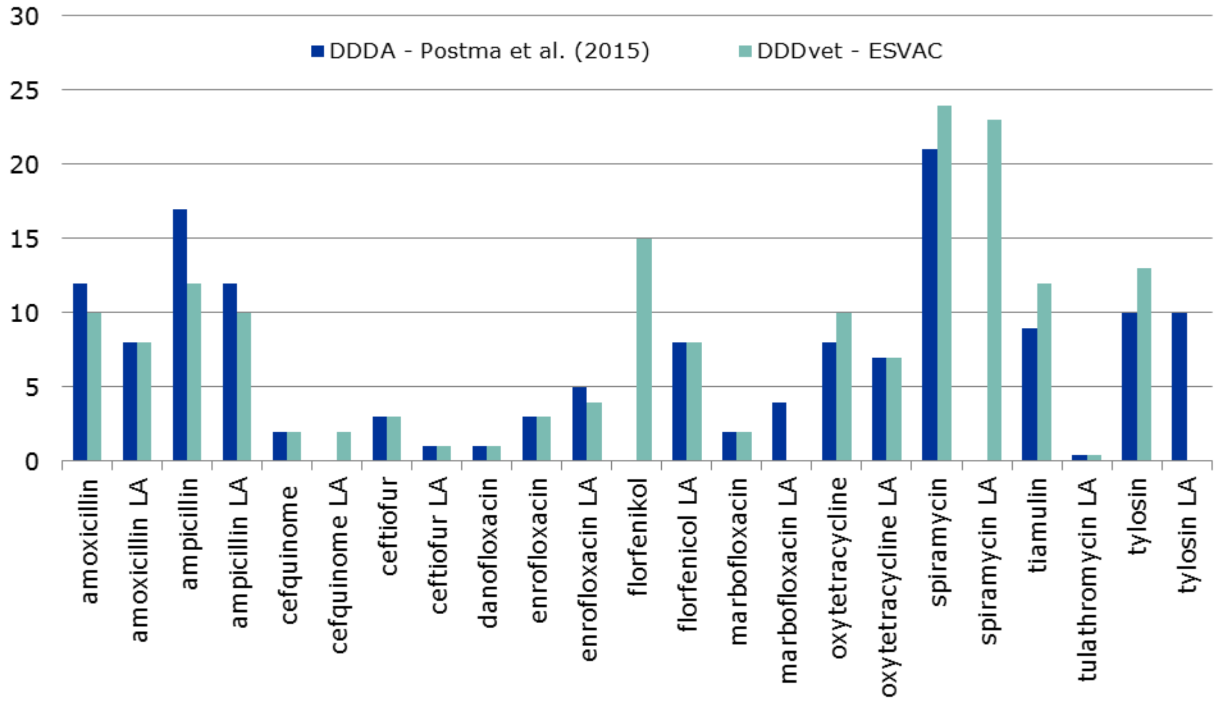
Figure 29. Comparison of DDDA assigned by Postma, Sjolund et al. (2015) for pharmaceutical forms to be administered through feed or water and ESVAC preliminary DDDvet for all oral forms for pigs. DDDA/DDDvet is given in mg/kg.



The defined daily dose differed for all substances except for colistin but for most the differences were minor. The largest deviation between the values is seen for chlortetracycline (Figure 29). The deviations might be explained by the differences in number of countries involved (and thus number of VMPs) - Postma, Sjolund et al. (2015) obtained data from four countries while ESVAC obtained data from nine countries.

The ESVAC DDDvet tended to be lower than those of Postma, Sjolund et al. (2015) and this could be partly explained by the exclusion by ESVAC of outliers prior to assignment of the preliminary DDDvet. The ESVAC preliminary DDDvet are based on data from five more countries compared to the DDDAs published by Postma, Sjolund et al. (2015) and thus countries with higher daily doses (ESVAC) will have less impact on the average values; this could also explain the variations.

Figure 30. Comparison of DDDA assigned by Postma, Sjolund et al. (2015) for parenteral pharmaceutical forms and ESVAC preliminary DDDvet for injectables and long-acting (LA) injectables for pigs. DDDA/DDDvet is given in mg/kg. The DDDAs for long-acting injectables by Postma, Sjolund et al. (2015) have been divided by the long-acting factor given for each substance



Of the 18 injectables/long-acting injectables for which both Postma, Sjolund et al. (2015) and ESVAC have assigned DDDA/DDDvet for pigs, 10 were identical and of these 5 were for long-acting injectables. For the other 8 the difference varied between 14% and 33% (Figure 30). The differences observed can probably be explained by the differences in number of countries involved. Difference between Postma, Sjolund et al. (2015) DDDAs and ESVAC DDDvet occurs more frequent for the non-long-acting than for the long-acting injectables.

7. Reporting consumption of antimicrobials in animals

The aim of this document is to provide a transparent methodology for the assignment of DDDvet and DCDvet; but it is important to also reflect on which indicators can be used for the reporting of data. Suggestions and examples for reporting are given below. Further discussions are needed on this subject prior to reporting of data collected by species.

7.1. Aim of reporting

The indicator used should aim to fit the purpose of the reporting. In human medicine DDDs were established for the purpose of drug consumption studies and mainly in order to follow therapeutic trends. The additional and main purpose of establishing DDDvet and DCDvet for veterinary antimicrobial VMPs is to address antimicrobial resistance, which has been described in Chapter 6.

It is suggested to apply indicators which enable to:

1. Identify changes in antimicrobial consumption/consumption patterns by species/production type, antimicrobial class and weight group within a country;
2. Identify differences in antimicrobial consumption/consumption patterns by species/production type, antimicrobial class and weight group across countries;
3. Compare antimicrobial consumption between the human and animal sector.

Of these, points 1 and 2 are addressed in the following paragraphs.

Human medicine

In human medicine the DDDs are assigned for an adult of 70 kg (WHO, 2015b). One of the main indicators applied to report consumption of antimicrobials in the EU/EEA area is numbers of DDD/1,000 inhabitants/day; the consumption is usually reported on ATC level 3 (ECDC, 2015).

Veterinary medicine

In veterinary medicine, DDDvet and DCDvet will be assigned per kg animal for oral and injectable products. Based on this, DDDvet and DCDvet can be calculated by weight group – e.g. for oxytetracycline the DDDvet oral is 26 mg/kg giving 1.3 g for finishers (ESVAC standardised weight for finisher: 50 kg, see **Table 25**). Slaughter pigs are usually slaughtered when 5-6 months old and for a part of those slaughtered in the beginning of a calendar year, part of their lifespan was during the previous calendar year. Broilers are usually slaughtered when they are approximately 40 days old. In contrast to humans, slaughter pigs and broilers are not at risk of being treated during a whole year. The suggested indicators for the ESVAC data for reporting on consumption of veterinary antimicrobial agents are therefore numbers of DDDvet or DCDvet consumed/1,000 animals produced or livestock for each weight group/production type by country and year (EMA/ESVAC, 2013b).

7.1.1. Measuring changes within and across countries

For the following analyses consumption figures of oxytetracycline for pigs have been applied. Data on tonnes used and on numbers of pigs are invented numbers.

To identify the consumption and consumption patterns of antimicrobials for the various production stages of pigs it is suggested to collect data for the weight groups and to apply the standard weight for calculation of DDDvet as shown in Table 25.

Table 25. Animal species and weight groups/production type for which data on consumption for pigs will be collected in ESVAC. Average weight for reporting of data (adapted from reflection paper (EMA/ESVAC, 2013b))

Weight group/ production type	Age period	Average weight at treatment
Sows/boars	Pig meant for production of piglets	220 kg
Suckling piglets	Birth to start of weaning	4 kg
Weaners	Weaning period	12 kg
Finishers	End of weaning period to slaughter	50 kg

7.1.1.1. Reporting by weight group

In order to explain how to measure changes in consumption within a specific weight group some examples are given in Table 26 and Table 27. These are examples of calculating numbers of DDDvet/1000 animals/year for oxytetracycline consumption in finishers (50 kg) that will identify changes across years and differences between countries, respectively. The preliminary DDDvet for oral oxytetracycline has been applied for the calculation - 1.3 g for 50 kg finishers.

Table 26. Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDvet(finisher)/1,000 finishers/year, for one country for the years 2011-2013

	Numbers finishers	OTC - tonnes used	DDDvet (g/50kg) finishers – oral	No. DDDvet/1000 finishers / year
2011	10,000,000	8.5	1.3	654
2012	10,400,000	8.0	1.3	592
2013	11,000,000	7.2	1.3	503

The results (Table 26) imply that, for example, with the amount of OTC used in 2011, 654 out of 1000 finishers with a standardized weight could be treated one day during that year.

Table 27. Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDvet(finishers)/1,000 finishers/year, for one year for countries A, B and C

	Numbers finishers	OTC - tonnes used	DDDvet (g/50 kg) finishers– oral	No. DDDvet/1000 finishers / year
Country A	25,000,000	76	1.3	2,338
Country B	14,000,000	16	1.3	879
Country C	10,000,000	8	1.3	615

The type of analysis shown above can be applied for all weight groups and will provide detailed information on the changes within a country.

7.1.1.2. Reporting overall consumption by species

Data can also be reported as overall consumption in pigs by country and year by use of data on overall consumption independently from collection by weight group. The indicator could be number DDDvet(kg)/1000 pigs produced/year - i.e. how many kg's pig of 1,000 pigs produced could have been treated with the amount of antimicrobial used. The preliminary DDDvet per kg pig for oral antimicrobials applied for the analysis is 26 mg/kg. An example of the output is shown in **Table 28**.

Table 28. Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDvet(kg)/1,000 pigs/year, for one country for the years 2011-2013. Note that the DDDvet and DCDvet are given in mg/kg

	Numbers pigs produced	OTC - tonnes used	DDDvet(pigs) – oral	No. DDDvet/1000 pigs produced/year
2011	10,000,000	9.9	26	38,077
2012	10,400,000	9.1	26	33,654
2013	11,000,000	8.0	26	27,972

This implies that with the amount of OTC used in 2011, a total of 38,077 DDDvet (mg/kg) were used per 1000 produced pigs during that year.

7.1.2. Reporting consumption at farm level

Consumption data can also be reported at farm level, using the same units of measurement. In Table 29 an example is given of three treatments with oxytetracycline on a farm producing 4,000 slaughter pigs per year - numbers of pigs are invented

Table 29. Consumption of oxytetracycline (OTC) at farm level, reported by use of various units of measurement. It is assumed that the farm produces 4,000 slaughter pigs per year. Note that DDDvet and DCDvet are given in mg/kg unless indicated otherwise

Treatment	DDDvet	DCDvet	Kg used active substance	No. DDDvet	No. DDDvet by weight group	No. DCDvet	No. DCDvet per weight group
A: 50 sows; injection; two doses: 10 mg/kg	9	25	0.22	24,444	111	8,800	40
B: 1,000 weaners; oral powder; dose: 25 mg/kg; 7 days	26	174	2.1	80,769	6,731	12,069	1,006
C: 50 weaners; injection; dose: 10 mg/kg; two doses	9	25	0.012	1,333	111	480	40
Total on the farm			*2.332*	*106,546*	*6,953*	*21,349*	*1,086*
Total per 1000 slaughter pigs			**0.583**	**26637**	**1,738**	**5,337**	**272**

Appendix 2

This appendix describes the instructions provided to the 9 MSs filling the ESVAC template for collecting SPC data.

1. General instructions for the filling of the template

- Data for centrally authorized products should also be filled in;
- Data need only to be filled in for one pack size per VMP;
    - Lines with other pack sizes may be deleted if preferred.
- If preferred, lines with VMPs authorized for other species than the target species of the worksheet may be deleted;
- Long-acting products:
    - For the purpose of the data collection, a VMP is considered to be long-acting if it maintains therapeutic levels for at least 24 hours;
    - Please indicate for long-acting products "YES" in the field for 'Dosing interval > 1 day (yes/no)', and give the duration of effect in days in the field 'Duration of effect (days) if it is given in the SPC; else record "999";
    - The number of treatment days should be given for the whole period during which the animals are exposed to the VMP (i.e., when a long-acting VMP should be administered twice and a treatment interval of two days is given in the SPC, the number of treatment days should be recorded as four);
    - When a long-acting product is intended to be administered once, the 'Duration of effect (days)' should be given as "NA" (Not Applicable), and the 'Dosing interval >1 day' should be answered with "YES";
    - Please give 'Duration of effect' in number of days if it is given in the SPC; else record "999".
- Intramammary products:
    - Abbreviations in worksheet 'Examples Intramammary': LC - lactating cows, DC – dry cow;
    - For dry cow treatment (INTRAMAM-DC): treatment is once and for four teats;
    - For lactating cows (INTRAMAM): dose per teat per day.
- Using the 'Comments' field:
    - Use the field sparsely: only fill in particular cases, e.g. when dose or length of treatment information is unspecified, or when different doses for different indications are given (see examples in the following chapters).
- Please give intervals in number of days;
- Please make sure to use a '.' (period) as the decimal sign.

SPCs sometimes give unclear information on daily dose and treatment duration, including different dosing for various age classes. Below, examples on how to deal with these issues when filling in the SPC information are shown. When information is missing, the code '999' can be used to indicate a missing value. Examples of the use of '999' are shown below.

2. Detailed instructions

If the main indication is clear, dosing should always be entered for this.

2.1. Main indication unclear

Example of SPC information	How to fill in template
Marbofloxacin 100 mg/ml (injection): Dose: respiratory disease one injection of 8 mg/kg or mastitis 2 mg/kg for 3 days	Enter the lowest and highest dose given, regardless of the indication (i.e. 2 mg/kg and 8 mg/kg). Add a comment in the comment section (i.e. represents range of the two indications). Treatment duration should also be entered as minimum and maximum number of days (i.e. 1 and 3 days).

2.2. Therapeutic or preventive use

Indicated for both therapeutic and preventive use

Example of SPC information	How to fill in template
Colistin (oral powder): Therapeutic dose: 4-8 mg/kg Disease prevention dose: 2-4 mg/kg	Give lowest and highest dose in the template (i.e. 2 and 8 mg/kg), and add a comment in the comments field (i.e. represents therapeutic and prevention use).
Tiamulin (premix): *One indication 8 mg/kg for 10 days, other indication 1.6 mg/kg for 42 days*	Give lowest and highest dose in the template (i.e. 1.6 and 8 mg/kg) and minimum and maximum number of days for treatment duration (i.e. 10 and 42 days), and add a comment in the comments field (i.e. represents therapeutic and prevention use).

2.3. Daily dose

Both daily dose and one long-acting dose given for the same VMP

Example of SPC information	How to fill in template
Oxytetracycline (injection): Daily dose 5-10 mg/kg; long-acting dose 20 mg/kg	Enter product twice[1] in template (i.e. in two lines): one line with information about daily dose etc. and one line with information about long-acting dose. Give the reason/explanation in the comment section (i.e. long-acting).

[1]Or as many times as necessary according to the information given in the SPC.

Different daily doses for young and adult animals

Examples of SPC information	How to fill in template
Spiramycin (injection): Dose: for veal calf 75000 UI/kg, for cattle 30000 UI/kg	Give lowest and highest daily dose in the template (i.e. 30,000 and 75,000 UI/kg).
Cefquinome (injection): Dose for veal calf 2 mg/kg for 3 days, for cattle 1 mg/kg for 3-5 days	Give lowest and highest daily dose in the template (i.e. 1 and 2 mg/kg) and minimum and maximum number of days for treatment duration (i.e. 3 and 5 days).

Two different doses for the same product presentation and indication

Examples of SPC information	How to fill in template
Florfenicol (injection): Dose: two injections of 20 mg/kg or one injection of 40 mg/kg	Give lowest and highest daily dose in the template (i.e. 20 and 40 mg/kg) and minimum and maximum number of treatments (i.e. 1 and 2), and add in the comments field: two injections of 20 mg/kg or one injection of 40 mg/kg.

Dose is given in ppm

Example of SPC information	How to fill in template
Tylosin (premix): Dose: 40-100 g/1,000 kg feed	Leave the daily dose variable fields empty, and give the information in the comment section (i.e. dose: 40-100 g/1,000 kg feed).

Based on standardised feed and water intake per animal species/weight group (where applicable) ESVAC will calculate ppm into mg/kg**.**

Dose is given per animal and not in mg/kg

Example of SPC information	How to fill in template
Dihydrostreptomycin (injection): Dose: 5 g of dihydrostreptomycin per animal (one injection)	Leave the daily dose variable fields empty, and give the information in the comment section (i.e. daily dose: 5 g/animal).

ESVAC will calculate dose into mg/kg by use of standardised average weight per animal species

2.4. Treatment duration

Unclear upper limit of treatment duration

Examples of SPC information	How to fill in template
Benzylpenicillin (injection): Dosing: 20 mg/kg; for at least 3 days	Lower limit: 3; upper limit: 999 Give description in comments.
Trimethoprim and sulfadiazine (injection): Dosing: 12-24 mg/kg; till 2 days after symptoms disappear	Lower limit: 3; upper limit: 999 Give description in comments.

Unclear lower and upper limit of treatment duration

Examples of SPC information	How to fill in template
Trimethoprim and sulfadoxine (injection): Dosing: 12-24 mg/kg; until symptomless 2 days	Lower limit: 999; upper limit: 999 Give description in comments.
Oxytetracycline (oral powder): Dosing: 40 mg/kg; length not given	Lower limit: 999; upper limit: 999 Give description in comments.

Unclear treatment duration

Example of SPC information	How to fill in template
Enrofloxacin (injection): Dosing: in some cases two injections are necessary	Give 999 for number of days and in the comment field: in some cases two injections are necessary

2.5. Other issues

Unclear dosing interval of long-acting antimicrobial VMPs

Example of SPC information	How to fill in template
Danofloxacin (injection): Dosing: 6 mg/kg; interval 36-48 hrs "if needed"	Give the interval (i.e. 1.5 – 2 days), comment field: interval 36-48hrs "if needed".

Appendix 3

1. References

ECDC. 2015. European Surveillance of Antimicrobial Consumption Network (ESAC-Net). In European Centre for Disease Prevention and Control, http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx.

EMA/ESVAC. 2011. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Trends in the sales of veterinary antimicrobial agents in nine European countries. Reporting period: 2005-2009. First ESVAC report. In http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf. 1-77.

EMA/ESVAC. 2012. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 19 EU/EEA countries in 2010. Second ESVAC report. In http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/10/WC500133532.pdf. 1-72.

EMA/ESVAC. 2013a. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011 (EMA/236501/2013). Third ESVAC report. In http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf. 99.

EMA/ESVAC. 2013b. 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 In http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf.

EMA/ESVAC. 2014. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012 (EMA/333921/2014). Fourth ESVAC report. In http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf.

Postma, M., M. Sjolund, L. Collineau, S. Losken, K.D. Stark, J. Dewulf, M. Andreasen, A. Backhans, C. Belloc, and U. Emanuelson. 2015. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *Journal of Antimicrobial Chemotherapy* 70:294-302.

White, G., D. Piercy, and H. Gibbs. 1981. Use of a calf salmonellosis model to evaluate the therapeutic properties of trimethoprim and sulphadiazine and their mutual potentiation *in vivo*. *Research in veterinary science* 31:27-31.

WHO. 2015a. ATCvet Index 2014. In WHO Collaborating Centre for Drug Statistics Methodology; Norwegian Institute of Public Health, http://www.whocc.no/atcvet/atcvet_index/.

WHO. 2015b. Guidelines for ATC classification and DDD assignment 2015. In WHO Collaboration Centre for Drug Statistics Methodology, Oslo.

2. Links to SPCs for the MSs that provided data to assign DDDvet and DCDvet

Country	Links to where SPCs can be found
Czech Republic	http://www.uskvbl.cz/en/authorisation-a-approval/marketing-authorisation-of-vmps/list-of-vmps/authorised-by-national-and-mrdc-procedures
Denmark	http://www.produktresume.dk/docushare/dsweb/View/Collection-10
Finland	http://www.fimea.fi/laaketieto/valmisteyhteenvedot
France	http://www.ircp.anmv.anses.fr/
Germany	https://portal.dimdi.de/websearch/servlet/FlowController/AcceptFZK#__DEFANCHOR__
Netherlands	http://www.diergeneesmiddeleninformatiebank.nl/ords/f?p=111:1:0::::P0_DOMAIN,P0_LANG:V,NL
Spain	https://sinaem4.aemps.es/consavetPub/fichasTecnicas.do?metodo=detalleForm
Sweden	http://www.lakemedelsverket.se/LMF/Lakemedel/Veterinara/?letter=A
United Kingdom	http://www.vmd.defra.gov.uk/ProductInformationDatabase/

Appendix 4

1. Water and feed intake

Water and feed intake calculations are required to provide an estimate of antimicrobial consumption per mg/kg body weight when the dose is only provided as a portion of the feed or water intake.

An online search was performed to identify daily feed and water intake by the three species (pig, broiler and cattle). The data sources are listed per species in the reference list at the end of this appendix.

The proposed standardised feed and water intake for the three species (Table 1) was calculated by first calculating the average intake given by each data source, and then calculating arithmetic mean of all data per species. Only sources enabling calculation of intake per kilogram animal were used; i.e. sources providing data per animal were excluded if no weight indication was given. Feed intake for cattle is based on dry matter intake.

Sound data on feed/water intake per kg animal was sparse, especially for cattle and broilers and that the data in Table 1 may be revised following the consultation period.

Table 1. Standard feed and water intake for broilers, cattle and pigs applied for the calculation of dose in mg/kg animal

Species	Feed intake (kg/kg animal)	Water intake (l/kg animal)
Broiler	0.13	0.23
Cattle	0.02	0.10
Pig	0.04	0.10

The feed and water intake will vary for many reasons including amongst others age, production type and health status amongst others. The data on water and feed intakes is therefore a compromise aiming at standardization.

2. References for water and feed intake

Broilers

Gardiner and Hunt. Water consumption of meat-type chickens. Can. J. Anim. Sci. (1984); 64: 1059-1061

Hubbard Management Guide Broiler (2014) (http://www.hubbardbreeders.com/media/hubbard_broiler_management_guide__078897700_0945_07012015.pdf)

Ontario Ministry of Agriculture, Food and Rural Affairs. Water requirements of livestock in Ontario. (2007) (http://www.omafra.gov.on.ca/english/engineer/facts/07-023.htm)

Pesti et al. Water consumption of broiler chickens under commercial conditions. Poultry Science (1985); 64: 803-808

Vencobb Broiler Management Guide (2014) (http://www.venkys.com/vh-breeds/vencobb-broiler-broiler-breeder/vencobb-100-broiler/)

Cattle

British Columbia Ministry of Agriculture and Lands. Livestock watering requirements – Quantity and Quality. (2006) (http://www.agf.gov.bc.ca/resmgmt/publist/500Series/590301-1.pdf)

Merck Manuals Feeding guidelines for large-breed dairy cattle (2014) (http://www.merckmanuals.com/vet/management_and_nutrition/nutrition_cattle/nutritional_requirements_of_dairy_cattle.html#v4638295)

Report to European Commission (ERM, 1999) in report Nitrogen output of livestock excreta (July 2007; ADAS report to DEFRA)

Pigs

Extracted from: Carr. Garth Pig Stockmanship Standards. (1998) (http://www.thepigsite.com/stockstds/18/daily-feed-intake)

Hendersons. Growing Pig Daily Feed & Water intake.(http://www.hendersons.co.uk/pigequip/Pig_growth_rate.html)

Horney. University of California. Project Pig Production Planner – Average weights, daily gain, and feed intakes for growing swine by age in weeks. (https://extension.usu.edu/cache/files/uploads/Project_Pig_Planner.pdf)

Lammers, Stender and Honeyman. Niche Pork production, Iowa State University. Feed and Growth. IPIC NPP340. (2007) (http://www.ipic.iastate.edu/publications/IPICNPP.pdf)

May. Michigan State University Extension. Estimating water usage on Michigan Swine Farms. (http://msue.anr.msu.edu/uploads/236/43605/lyndon/Water_Use_for_Swine_Farms.doc)

Merck Manuals. Nutritional Requirements of Pigs (2011) (http://www.merckmanuals.com/vet/management_and_nutrition/nutrition_pigs/nutritional_requirements_of_pigs.html)

Ontario Ministry of Agriculture, Food and Rural Affairs. Water requirements of livestock in Ontario. (2007) (http://www.omafra.gov.on.ca/english/engineer/facts/07-023.htm)

Swine handbook nutrition and feeds (http://mysrf.org/pdf/pdf_swine/s1.pdf)

Zimmerman et al. Diseases of Swine. (2012). (https://books.google.co.uk/books?id=jVaemau17J4C&pg=PA10&lpg=PA10&dq=veterinary+practice+section+table+1.3+recommended+water+requirements&source=bl&ots=MZ1nepeps0&sig=5M4kRtU3ZgPUFtFHPAcyWs0u-f0&hl=en&sa=X&ei=9uaXVKTmMYv4UtnygKAL&ved=0CCEQ6AEwAA#v=onepage&q=veterinary%20practice%20section%20table%201.3%20recommended%20water%20requirements&f=false)