Principles on assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA)
Draft

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Comments should be provided using this template. The completed comments form should be sent to ESVAC@ema.europa.eu
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1. Summary

These draft principles describe the approach suggested for the assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA) for antimicrobial veterinary medicinal products (VMP) and the principles themselves. The principles aim to guide EMA on the assignment of DDDAs and DCDAs. A summary of the suggested principles is included in Chapter 2.

These principles may be subjected to exceptions that will be clearly identified when publishing the DDDA and DCDA values.

The definitions and units suggested to be applied are described in Chapter 8 and the general principles in Chapter 9. These principles are based on the aim of assignment of DDDAs and DCDAs (Chapter 6). Impact analyses as well as other assessments and considerations are outlined in Appendix 1, including some examples for reporting of data by use of DDDA and DCDA.

The development of the draft 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 suggested principles for assigning DDDAs for veterinary medicinal products have, to the extent possible, been harmonised with principles for human medicinal products in order to facilitate comparability of antimicrobial consumption in animals with consumption in humans.

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 and recommendations 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 DDDAs and DCDAs 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 products and intrauterine devices.

The data obtained on dosing were validated in terms of quality and harmonization across the nine countries and preliminary DDDAs and DCDAs were assigned following exclusion of outliers. The final data sets on oral and injectables consisted of 2,199 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 688 unique records for each substance in a combination VMP.
Preliminary DDDAs and DCDAs 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 draft principles.

DDDAs and DCDAs will be assigned per kg animal for oral and injectable products providing a basis for calculation and reporting DDDAs and DCDAs by weight group.

It is suggested to assign separate DDDAs for injectables, intramammary products, intra-uterine devices and oral products for each substance and species.

The impact analyses (see Appendix 1) have shown that similar approaches and principles can be applied to derive DDDA and DCDA 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 DDDAs and DCDAs 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 to 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 DDDA and DCDA a degree of pragmatism is therefore required to reach the right balance between having a highly complex but accurate system in which a DDDA/DCDA is defined for every possible ‘use case’ and having a more simple system in which similar ‘use cases’ are combined requiring fewer DDDAs/DCDAs 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 DDDA or DCDA. Taking into account that DDDA and DCDA 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 DDDA and DCDA refers to the value assigned per kg animal unless otherwise indicated.

**It should be noted that DDDA and DCDA 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 DDDA and DCDA values will nearly always be a compromise. Established DDDAs or DCDAs are not applicable for commercial use such as pricing and analyses of drug costs.**
2. Summary – recommendations principles

Table 1 summarize the general principles recommended for the assignment of DDDAs and DCDA. The general principles (chapter 9) and Appendix 1 suggest exceptions from these rules for example for synergistic combinations and assignment of separate DCDA for premix for pigs. Exception to the principles will be explained in the lists of DDDAs and DCDA.

Table 1. Summary of the calculation of DDDAs and DCDA and the suggested general principles for assignment of DDDAs and DCDA for each combination of substance, species and form. Single equals to VMPs with one active substance; Combinations equals to VMPs with two (or more) active substances

<table>
<thead>
<tr>
<th>Unit of measurement</th>
<th>Calculation</th>
<th>Oral single</th>
<th>Oral combinations</th>
<th>Injectable single</th>
<th>Injectable combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DDDA</td>
<td>• Calculated as average of all observations on daily dose by species, substance and form.</td>
<td>• Assign the same DDDA for all oral forms.</td>
<td>• Assign the same DDDA as for oral single forms.</td>
<td>• Assign the same DDDA for injectables and long-acting injectables. • Prodrugs will be assigned separate DDDA.</td>
<td>• Assign the same DDDA as for single injectables, long-acting injectables and prodrugs.</td>
</tr>
<tr>
<td>• DCDA</td>
<td>• Calculated as average of all observations – daily dose multiplied by number treatment days – by species, substance and form.</td>
<td>• Assign the same DCDA for all oral forms.</td>
<td>• Assign the same DCDA as for oral single forms.</td>
<td>• Assign the same DCDA for injectables and long-acting injectables. • Prodrugs will be assigned separate DCDA.</td>
<td>• Assign the same DCDA as for single injectables, long-acting injectables and prodrugs.</td>
</tr>
</tbody>
</table>
3. Acknowledgements

The members of the ESVAC ad hoc working group on technical units Inge van Geijlswijk, Christina Greko, Erik Jacobsen, Irene Litleskare, Gérard Moulin (chair) and Cedric Müntener are thankfully acknowledged for assisting the development of this project as well providing scientific advice and valuable comments during the development of these principles.

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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
- **DCDA** = defined course dose animal
- **DDD** = defined daily dose (human)
- **DDDA** = defined daily dose animal
- **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
- **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 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 only 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 and as a first step a pilot collecting data on consumption in pigs in volunteering EU/EEA countries is planned to be rolled out mid-2015.

Following the suggestion of the reflection paper, ESVAC will as a first step collect data on consumption for the following species: broiler, cattle and pigs and consequently assignment of DDDAs and DCDAs for these species-production categories is prioritized.

The reflection paper further suggests applying DDDA and DCDA 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 DDDA and DCDA 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, thus ensuring transparency.

This document suggests principles for the assignment of DDDA and DCDA for veterinary antimicrobial agents. The impact analyses, other assessments and considerations supporting the suggested principles are described in Appendix 1.

These principles are in general thought to be applicable if in the future DDDAs and DCDAs 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 DDDAs and DCDAs will be used to analyse and report data on consumption by species collated by ESVAC.

Reporting consumption of antimicrobials in animals using DDDA or DCDA represents a substantial improvement over reporting consumption by weight (mass) of active substance. DDDA and DCDA 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 DDDA and DCDA 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 medicine.

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

In order to facilitate comparison of the consumption of antimicrobials by humans and animals, the principles for assignment of DDDAs (and DCDAs) 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 and not defined course doses.
7. Antimicrobial agents and animal species for which DDDAs and DCDAs will be assigned

DDDA and DCDA will be assigned for antimicrobial agents belonging to the ATCvet groups shown in Table 2 for oral, injectable, intramammary injectors and intrauterine devices.

DDDAs and DCDAs 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%–0.49% of total sales in 2012 (EMA/ESVAC, 2014).

DDDAs and DCDAs are intended to be assigned for broilers, cattle and pigs.

Table 2. Veterinary antimicrobial agents for which DDDA and DCDA will be assigned according to ATCvet codes) (WHO, 2015a)

<table>
<thead>
<tr>
<th>Groups of antimicrobial agents</th>
<th>ATCvet codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial agents for intestinal use</td>
<td>QA07AA; QA07AB</td>
</tr>
<tr>
<td>Antimicrobial agents for intrauterine use</td>
<td>QG01AA; QG01AE; QG01BA; QG01BE QG51AA; QG51AG</td>
</tr>
<tr>
<td>Antimicrobial agents for systemic use</td>
<td>QJ01</td>
</tr>
<tr>
<td>Antimicrobial agents for intramammary use</td>
<td>QJ51</td>
</tr>
<tr>
<td>Antimicrobial agents used as antiparasitic agents</td>
<td>QP51AG</td>
</tr>
</tbody>
</table>
8. Definitions and units

8.1. Definitions DDDA and DCDA

The basic definitions of the units are:

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

8.2. Definitions of administration routes/forms for list of DDDAs and DCDA

- 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 devices (IUD).

8.3. DDDA and DCDA units

The units used for DDDAs and DCDAs will be

- 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 devices = Units (UD)/animal.
9. General principles

The DDDAs and DCDAs 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 DDDA and DCDA. Exceptions will be explained in the list of DDDAs and DCDAs.

DDDAs will usually be assigned by species and kg animal. Exceptions are intramammary products and intrauterine devices.

The assignment of DDDAs and DCDAs 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.

\[
\text{Average} = \frac{(a_1+a_2 + a_3+...+ a_n)}{n}
\]

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.

Review of a DDDA or DCDA should be considered if the dosing changes substantially from the one identified, in e.g. the Summary of Product Characteristics (SPC) of a substance, pharmaceutical form and/or species. As changes of DDDAs or DCDAs 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 DDDAs or DCDAs and when existing DDDAs or DCDAs need to be revised.

9.1. Assignment of DDDAs

9.1.1. Single substance products – oral products and injectables

Oral and injectable products will be assigned separate DDDAs.

Oral products

For each combination of species and substance for oral VMPs containing a single substance, the DDDAs 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 DDDAs.

Injectables

Injectables and long-acting injectables will usually be given the same DDDA 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 DDDAs.

Separate DDDAs will be assigned for injectable prodrugs and their active substance - e.g. for procaine benzylpenicillin and benzylpenicillin.
9.1.2. Combinations - oral and injectable products

Substances in combination products (2nd and 3rd ingredient) will be assigned the same DDDA 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 DDDAs (e.g. synergistic combinations).

9.1.3. Intramammary products

9.1.3.1. Intramammary – lactating cow

The DDDA for VMPs used to treat lactating cows will be assigned as the number of intramammary injectors per teat per day.

9.1.3.2. Intramammary – dry cow

For VMPs used in the dry cow period no DDDAs will be assigned (see 9.2.3.2.).

9.1.4. Intrauterine devices

The DDDA will be assigned as the number of intrauterine devices per animal per day.

9.2. Assignment of DCDA

9.2.1. Single substance products - oral products and injectables

Oral products

For each combination of species and substance for oral products containing a single substance, the DCDA 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 DCDA (e.g. premixes for pigs).

Injectables

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

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

9.2.2. Combinations – oral products and injectables

Oral products

Substances in oral combination products will usually be assigned the same DCDA as the one assigned for the single substance product. Exceptions will be explained in the list of DCDA (e.g. synergistic combinations).

Injectables

Substances in injectable combination products will be assigned the same DCDA as the substance in single substance products. This principle will also apply for injectable prodrugs. Exceptions will be explained in the list of DCDA (e.g. synergistic combinations).
9.2.3. Intramammary products

9.2.3.1. Intramammary – lactating cow

The DCDA for lactating cows will be assigned as the number of intramammary injectors (UD) per teat per treatment course.

9.2.3.2. Intramammary – dry cow

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

9.2.4. Intrauterine devices

DCDA will be assigned as numbers of units (UD) per animal per treatment course.
Appendix 1

This appendix provides general considerations and impact analyses supporting the suggested principles for assignment of DDDAs and DCDAs. First, the data that produce the basis for the impact analyses and considerations are described.

1. Assignment of preliminary DDDAs and DCDAs

1.1. Collection and analysis of data on dosing

With the aim to assist the development of the general principles for the assignment of DDDA and DCDA 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.

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 DDDAs and DCDAs 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 was used as a basis for the development of the SPC template. The final SPC template included the following administration routes/forms: bolus/tablets, injection, injection long-acting, intramammary products, intrauterine devices, 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-malarials 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.

The national ESVAC sales register was used to prepare country specific SPC templates. 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

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 by use of R (R open source software version 3.1.0; R foundation for Statistical Computing, Vienna, Austria). Outliers (extreme values) were defined as values greater/smaller than the average dose (or duration) ±2 Standard Deviation (SD). For observations identified as outliers, the SPC information for the particular VMP was used to revise the data; if values were correct, the outliers were excluded from the data (93 observations were outlier for dose; 89 observations were outlier for treatment duration; 18 observations were outlier for both).

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

Following the quality check, validation of the data and exclusion of outliers the data sets from the nine countries consisted of a total of 2,887 observations: for single substance VMPs the data sets from the volunteer MSs consisted of 2,199 observations for antimicrobial, species and administration route/forms for which the data were collected and for combination VMPs of 688 observations for antimicrobials (almost solely 2nd ingredient), species and administration route/form (Table 3, Table 4). These data were applied to assign the preliminary DDDAs and DCDAs.

Table 3. Number of observations per species per administration route/form for single substance products in the data sets from 9 MSs

<table>
<thead>
<tr>
<th>Species</th>
<th>Bolus/tablet</th>
<th>Injection</th>
<th>Injection long-acting</th>
<th>Oral paste</th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broilers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>18</td>
<td>329</td>
<td>83</td>
<td>1</td>
<td>54</td>
<td>95</td>
<td>15</td>
<td>595</td>
</tr>
<tr>
<td>Pigs</td>
<td>3</td>
<td>419</td>
<td>82</td>
<td>3</td>
<td>189</td>
<td>292</td>
<td>208</td>
<td>1,197</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21</strong></td>
<td><strong>748</strong></td>
<td><strong>165</strong></td>
<td><strong>4</strong></td>
<td><strong>345</strong></td>
<td><strong>644</strong></td>
<td><strong>272</strong></td>
<td><strong>2,199</strong></td>
</tr>
</tbody>
</table>

Table 4. Number of observations per species per administration route/form for combination products in the data sets from nine MSs

<table>
<thead>
<tr>
<th>Species</th>
<th>Bolus/tablet</th>
<th>Injection</th>
<th>Oral paste</th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broilers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>12</td>
<td>125</td>
<td>23</td>
<td>17</td>
<td>14</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Pigs</td>
<td>195</td>
<td>2</td>
<td>61</td>
<td>85</td>
<td>78</td>
<td>14</td>
<td>421</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>320</strong></td>
<td><strong>98</strong></td>
<td><strong>145</strong></td>
<td><strong>111</strong></td>
<td><strong>421</strong></td>
<td><strong>688</strong></td>
</tr>
</tbody>
</table>
1.4. Calculation of preliminary DDDA and DCDA

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 (antimicrobial, species and administration route) - 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

<table>
<thead>
<tr>
<th>Range daily dose given</th>
<th>Fixed daily dose given</th>
<th>Daily dose</th>
<th>Range number of treatment days given</th>
<th>Fixed number of treatment days given</th>
<th>Number of treatment days</th>
<th>Course dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose mg/kg min</td>
<td>Daily dose mg/kg max</td>
<td>Daily dose mg/kg</td>
<td>Treatment days min</td>
<td>Treatment days max</td>
<td>Treatment days</td>
<td>Treatment days</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>15*</td>
<td>5</td>
<td>5</td>
<td>4*</td>
<td>80*</td>
</tr>
</tbody>
</table>

*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 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 average of the daily doses given for the substance and administration route in question.

For the DDDA the average (arithmetic mean) of all observations for each unique combination of species, antimicrobial substance and administration route/form included in the data sets – e.g. pig/colistin/oral forms was calculated by use of the following formula:

\[ \text{Average} = \frac{a_1 + a_2 + a_3 + \ldots + a_n}{n} \]

The same approach was applied for the calculation of DCDAs (average of all observations on course dose).
2. Definition of DDDA and DCDA

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 DDDAs and DCDAs 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 group (e.g. finisher pigs) the DDDAs and DCDAs will be assigned by kg animal allowing for further calculations of numbers of DDDA and DCDA consumed by weight group.

DDDA and DCDA will generally be assigned by kg animals based on the following definitions:

- The DDDA is the assumed average dose per kg animal per species per day;
- The DCDA is the assumed average dose per kg animal per species 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.
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 products, intrauterine devices, oral paste, oral powder, oral solution and premix. If DDDAs and DCDAs 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 DDDAs and DCDAs for substances in combination VMPs would add to the number by 272 (Figure 3).

**Figure 2.** Numbers of DDDAs to be assigned for single substance products of antimicrobial agents for veterinary medicinal products (N =265), estimated from data provided by nine EU MSs. *Note that the numbers are preliminary.*
In total, more than 800 DDDAs and DCDAs 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, DDDAs and DCDAs for intramammary products and intrauterine devices would still add to that number.

In order to make the list of DDDAs and DCDAs manageable for analyses and reporting of data the impact of e.g. assigning the same DDDA and DCDA 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 DDDAs and DCDAs.

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 2014 (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.
Principles on assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA)

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 DDDAs for e.g. injectable amoxicillin and oxytetracycline are about 2 and 4 times higher than for the oral forms, respectively. Therefore, it is suggested to assign DDDAs and DCDAs 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 much higher than in human medicine and some substances have a much longer biological half-life than the sulfonamides previously mentioned. Therefore it should be assessed whether DDDA and DCDA 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). It is therefore suggested to assign separate DDDAs and DCDAs for injectable prodrugs.
3.1.3. Intramammary products and intrauterine devices

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 is suggested for intramammary VMPs and intrauterine devices.

The suggested 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);

The suggested indicator to report consumption of intramammary products is:

- Number of injectors of the VMP/1,000 dairy cows/year.

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 analyses 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 DDDAs 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 6 and Figure 7.

**Table 6.** Calculated numbers of DDDAs (thousands) and DCDAs (thousands) per kg pig of three different products consumed in pigs

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pack size</th>
<th>Strength</th>
<th>No. sold</th>
<th>DDDA (1000)</th>
<th>DCDA (1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prod 1 Oxytetracycline</td>
<td>1,000 g</td>
<td>70 mg/g</td>
<td>100</td>
<td>233</td>
<td>47</td>
</tr>
<tr>
<td>Prod 2 Colistin</td>
<td>1,000 g</td>
<td>20 mg/g</td>
<td>100</td>
<td>400</td>
<td>80</td>
</tr>
<tr>
<td>Prod 3 Colistin</td>
<td>1,000 g</td>
<td>12 mg/g</td>
<td>100</td>
<td>240</td>
<td>48</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>1,000 g</td>
<td>70 mg/g</td>
<td>100</td>
<td>233</td>
<td>47</td>
</tr>
</tbody>
</table>
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 DDDA and DCDA have been used for single and combination VMP in this analysis.

**It is suggested to assign and report DDDA and DCDA also for the 2nd (and 3rd) ingredient for combination VMPs.**

### 4. Impact analyses and other assessments

In order to make the list DDDAs and DCDAs manageable for the analyses 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, including:

1. Whether the same DDDA could be assigned for each antimicrobial and species for all oral forms and injectables, respectively;
2. Whether the DDDAs 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 DCDA could be assigned for each antimicrobial and species for all oral forms and injectables, respectively;
4. Whether the DCDAs 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. DDDAs - single substance products

4.1.1. Oral forms

In a study by Postma et al. (2015) on assigning DDDAs 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 DDDAs separately for oral solutions compared to applying the same DDDAs 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 "DDDA average oral powder and premix/DDDA 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**

- **DDDA by oral form** = \( \frac{\text{tonnes oral powder sold substance X/DDDA oral powder}}{\text{tonnes oral solution sold substance X/DDDA oral solution}} + \frac{\text{tonnes premix sold substance X/DDDA premix}}{\text{average DDDA of all oral forms}} \)
- **DDDA average oral powder and premix/DDDA oral solution** = \( \frac{\text{tonnes oral powder + premix of substance X}}{\text{average DDDA of oral powder + premix of substance X}} + \frac{\text{tonnes oral solution sold of substance X/DDDA oral solution}}{\text{average DDDA of all oral forms}} \)
- **DDDA average oral forms** = \( \frac{\text{tonnes oral powder + oral solution + premix sold of substance X}}{\text{average DDDA of all oral forms}} \)

4.1.1. Amoxicillin

Preliminary DDDAs for single substance VMPs of amoxicillin for pigs for oral solution, oral powder and premix shown in Table 7 were used for the various impact analyses.
**Table 7.** Preliminary DDDAs (mg/kg) for amoxicillin single substance VMPs for pigs for the major oral forms and DDDA average of oral powder and premix

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Average oral powder and premix</th>
<th>Average all oral forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>20</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>17</td>
</tr>
</tbody>
</table>

**Annual outputs**

The preliminary DDDAs and sales data shown in Table 7 and Table 8, respectively, were applied for the impact analyses on annual output.

**Table 8.** 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

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Sales 26 EU/EEA countries</td>
<td>863</td>
<td>265</td>
<td>194</td>
</tr>
<tr>
<td>B. Sales MS 1</td>
<td>198</td>
<td>&lt;0.5</td>
<td>120</td>
</tr>
<tr>
<td>C. Sales MS 2</td>
<td>333</td>
<td>153</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>
**Figure 11.** Calculated numbers of DDDAs (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 DDDAs amoxicillin calculated by application of DDDA for each oral form was 5%, 2% and 7% lower for A, B and C, respectively, compared to the output when oral solution was calculated separately (Figure 11).

The numbers of DDDAs calculated by application of DDDA for each oral form was 8%, 7% and 9% lower for A, B and C, respectively, compared to the output when average DDDAs were applied.

Changes across time

In order to assess the impact of applying DDDA as average of oral forms compared to applying DDDAs by the various oral forms on identifying changes in consumption across time, sales data for amoxicillin single substance VMPs from one MS for 2010 and 2012 were applied (Table 9).

**Table 9.** Sales (tonnes) of amoxicillin in single substance VMPs oral solution, oral powder and premix in 2010 and 2012 in one MS

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>207</td>
<td>&lt;0.5</td>
<td>135</td>
</tr>
<tr>
<td>2012</td>
<td>198</td>
<td>&lt;0.5</td>
<td>120</td>
</tr>
</tbody>
</table>

**Figure 12.** Calculated numbers of DDDAs (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 7.6% reduction in consumption from 2010 to 2012 was observed when DDDAs for the three oral forms were applied to analyse sales by these forms. When using average DDDAs for these forms the estimated decline was 7.3% (Figure 12).

Preliminary DDDAs for single substance VMPs of oxytetracycline for pigs for oral solution, oral powder and premix shown in Table 10 were used for the impact analyses.
Table 10. Preliminary DDDAs (mg/kg) for oxytetracycline for the major oral forms for pigs

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Average oral powder and premix</th>
<th>Average all oral forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>27</td>
<td>20</td>
<td>30</td>
<td>29</td>
<td>26</td>
</tr>
</tbody>
</table>

Annual output

The sales data shown in Table 11 were used for the impact analyses.

Table 11. Sales (tonnes) of oxytetracycline 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 for use in pigs

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Sales 26 EU/EEA countries</td>
<td>227</td>
<td>161</td>
<td>797</td>
</tr>
<tr>
<td>B. Sales MS 1</td>
<td>97</td>
<td>19</td>
<td>127</td>
</tr>
<tr>
<td>C. Sales MS 2</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
**Figure 13.** Calculated numbers of DDDAs (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 11)
The numbers of DDDAs oxytetracycline calculated by application of DDDA for each oral form was 2% and 0.4% lower for A and B, respectively, compared to the output when oral solution was calculated separately (Figure 13). The numbers of DDDAs calculated by using DDDA for each oral form was 6%, 7% and 4% lower for A, B and C, respectively, compared to the output when average DDDAs were applied.

**Changes across time**

In order to assess the impact of using DDDA as average for all oral forms compared to applying DDDAs 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 12).

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

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>158</td>
<td>33</td>
<td>198</td>
</tr>
<tr>
<td>2012</td>
<td>97</td>
<td>19</td>
<td>127</td>
</tr>
</tbody>
</table>

**Figure 14.** Calculated numbers of DDDAs (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 12.1% reduction in sales from 2010 to 2012 was observed when specific DDDAs for the three oral forms were applied to analyse sales; when the average DDDAs of these forms were applied the estimated reduction was 11.3% (Figure 14). The results indicate that applying the DDDA as average of all oral forms for pigs for amoxicillin and oxytetracycline, respectively, had a relatively minor impact on the output compared to when the form-specific DDDAs were used. This is also the case when oral solutions are analysed separately.

Applying the average DDDA oral forms for the estimation on changes across years had almost no impact compared to when the “form”-specific DDDAs were used to analyse sales of oral powder, oral solution and premix.

It is suggested to assign the single DDDA for the same substance in a combination VMP.
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 activity is above 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, 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; 12 for cattle and 10 for pigs (Figure 15, Figure 16).

Figure 15. Preliminary DDDAs (mg/kg) for injectables, long-acting injectables and average DDDA of these for cattle

* Long-acting only
Figure 16. Preliminary DDDAs (mg/kg) for injectables, long-acting injectables and average DDDA of these for pigs

The ESVAC sales data of injectables 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.
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.

For the most-selling injectable substances – amoxicillin and oxytetracycline - minor differences are observed between the preliminary DDDAs (mg/kg) for injectables and long-acting injectables. This is also the case for the CIAs with highest priority for human medicine. Notable differences are seen between the preliminary DDDAs for injectables and long-acting injectables for ampicillin, florfenicol and spiramycin. For ampicillin the proportion sold as injectable in general is low and thus assigning the same DDDA for injectables and long-acting injectables is suggested to have a minor impact on the output. It should be noted that for spiramycin, only one of five observations for the DDDA was for long-acting injectables.

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; it could therefore be considered to assign separate DDDAs for injectable and long-acting injectables of florfenicol.

It is suggested to assign the same DDDA for substances in injectable and long-acting injectable VMPs. Prodrugs and its active substance will be assigned separate DDDAs. Exceptions will be identified in the lists of DDDA and DCDA.

**4.2. DDDAs - combination products**

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). 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
4.2.1. Oral forms

The preliminary DDDAs show that these may vary between single VMPs and combination VMPs. The impact on the total output of applying DDDA for single VMPs for reporting consumption for the same substance in combination VMPs were assessed by use of the preliminary DDDAs for amoxicillin and oxytetracycline.

4.2.1.1. Amoxicillin

Preliminary DDDAs for pigs for amoxicillin for single and combination VMPs were applied for the impact analyses - i.e. 17 mg/kg and 25 mg/kg. It should be noted that for most substances the DDDA for a substance in combination VMP is typically lower than the DDDA 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 DDDA sold (millions) of amoxicillin oral powder, oral solution and premix as single and combination VMP calculated by application of DDDA single and DDDA combination respectively, and by application of DDDA 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 was 2% (higher) compared to when applying DDDA single for sales of amoxicillin both for single and combination VMPs (Figure 18).

4.2.1.2. Oxytetracycline

Preliminary DDDAs for pigs for oxytetracycline for single and combination VMPs 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 DDDA sold (millions) of oxytetracycline oral powder, oral solution and premix as single and combination VMP calculated by application of DDDA single and DDDA combination, respectively, and by application of DDDA 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 DDDA single for oxytetracycline calculating both sales as single and combination VMP was only 0.2% lower compared to analysis by use of separate DDDAs (Figure 19).

The results indicates that application of the same DDDA 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 DDDAs. 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 DDDA single and DDDA combination.

It is suggested as a general rule to assign the single substance DDDA for the same substance and species in a combination oral 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 DDDAs for the prodrug procaine benzylpenicillin as single and combination injectable VMPs (12 mg/kg and 9 mg/kg, respectively) were used for the impact analysis assuming that the complete sales were for pigs.
Figure 20. Estimated numbers of DDDA sold (millions) of procaine benzylpenicillin injectable VMPs as single and combination VMP calculated either with separate DDDA for single and combination VMPS, respectively or with DDDA single substance products for all sales assuming that the complete amount was administered to pigs.

If the single DDDA for procaine benzylpenicillin was used to calculate sales of both single and combinations VMPs, the number of DDDAs would be 5% lower for pigs compared to when calculated by specific single and combination DDDAs (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 DDDAs for injectables for the overall output is thought to be relatively low.

It is suggested to assign the single substance DDDA oral the same substance and species in a combination injectable VMP. Exceptions are described in chapter 4.2.3.

4.2.3. Synergistic combinations

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 substances 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 DDDAs for sulfadiazine and sulfadimethoxine show that that the DDDAs are substantially lower for combination VMPs (Table 13). No sulfadiazine dosing for single substance VMPs was reported by any of the nine MSs.

Table 13. Preliminary DDDAs 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadiazine</td>
<td>Cattle</td>
<td>15</td>
<td>21</td>
<td>42</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Pigs</td>
<td>15</td>
<td>23</td>
<td>25</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>Cattle</td>
<td>30</td>
<td>17</td>
<td>43</td>
<td>17</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>Pigs</td>
<td>30</td>
<td>19</td>
<td>47</td>
<td>26</td>
<td>50</td>
<td>26</td>
</tr>
</tbody>
</table>

It is suggested to assign separate DDDAs for single substance sulfonamide VMP and the same sulfonamide in combination with trimethoprim. Exceptions will be identified in the lists of DDDA and DCDA.
4.3. DCDAs – 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 DCDAs as shown in Table 14, Table 15 and Table 16. 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 DCDAs for premix and for all other oral forms.

Table 14. Preliminary DCDAs (mg/kg) for single substance products for broilers for oral powder, oral solution and premix, average DCDA all oral forms and average DCDA all oral forms when premix is excluded

<table>
<thead>
<tr>
<th>Substance</th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Average all oral forms</th>
<th>Average orals – premix excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>78</td>
<td>71</td>
<td>150</td>
<td>78</td>
<td>73</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>223</td>
<td>162</td>
<td>188</td>
<td>196</td>
<td>206</td>
</tr>
<tr>
<td>Colistin</td>
<td>32</td>
<td>21</td>
<td>68</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>62</td>
<td>66</td>
<td>52</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>41</td>
<td></td>
<td>41</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Lincomycin</td>
<td>45</td>
<td>30</td>
<td>378</td>
<td>66</td>
<td>42</td>
</tr>
<tr>
<td>Neomycin</td>
<td>145</td>
<td>141</td>
<td>30</td>
<td>118</td>
<td>143</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>306</td>
<td>298</td>
<td>300</td>
<td>303</td>
<td>304</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>238</td>
<td>481</td>
<td>400</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Tiamulin</td>
<td>101</td>
<td>75</td>
<td>106</td>
<td>88</td>
<td>83</td>
</tr>
</tbody>
</table>

*Lower than oral powder because includes other oral forms as well
Table 16. Preliminary DCDAs (mg/kg) for single substance products for pigs for oral powder, oral solution and premix, average DCDA all oral forms and average DCDA all oral forms when premix is excluded

<table>
<thead>
<tr>
<th>Substance</th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
<th>Average all oral forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>83</td>
<td>70</td>
<td>171</td>
<td>105</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>200</td>
<td>96</td>
<td>230</td>
<td>210</td>
</tr>
<tr>
<td>Colistin</td>
<td>29</td>
<td>23</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>47</td>
<td>51</td>
<td>83</td>
<td>57</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincomycin</td>
<td>52</td>
<td>92</td>
<td>134</td>
<td>87</td>
</tr>
<tr>
<td>Neomycin</td>
<td>64</td>
<td>83</td>
<td>131</td>
<td>92</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>112</td>
<td>80</td>
<td>266</td>
<td>173</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>214</td>
<td>207</td>
<td>340</td>
<td>221</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>74</td>
<td>57</td>
<td>83</td>
<td>70</td>
</tr>
<tr>
<td>Tylosin</td>
<td>155</td>
<td>140</td>
<td>98</td>
<td>131</td>
</tr>
</tbody>
</table>

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

4.3.1.1. Amoxicillin

Preliminary DCDAs for amoxicillin used for the impact analyses are shown in Table 14 and Table 16. 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 17). The complete amount was considered as sold for use either for broilers and pigs, respectively.

Table 17. 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

<table>
<thead>
<tr>
<th>Sales 26 EU/EEA countries</th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales MS 1</td>
<td>198</td>
<td>&lt;0.5</td>
<td>120</td>
</tr>
<tr>
<td>Sales MS 2</td>
<td>333</td>
<td>153</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>
Figure 22. Numbers of DCDAs (millions) of single amoxicillin VMPs calculated by use of 1) separate DDDAs oral powder, oral solution and premix, 2) average DDDA orals and 3) average DCDA orals (premix excluded) for oral powder add oral solution and DCDA 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 DCDAs for oxytetracycline applied for the impact analyses shown in Table 14 and Table 16, and the sales data for amoxicillin oral powder, oral solution and premix shown in Table 18 were used for the impact analyses assuming that the complete amounts were used either for broilers or pigs.
Table 18. 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

<table>
<thead>
<tr>
<th></th>
<th>Oral powder</th>
<th>Oral solution</th>
<th>Premix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales 26 EU/EEA countries</td>
<td>227</td>
<td>161</td>
<td>797</td>
</tr>
<tr>
<td>Sales MS 1</td>
<td>97</td>
<td>19</td>
<td>127</td>
</tr>
<tr>
<td>Sales MS 2</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 23. Numbers of DCDAs (millions) of single oxytetracycline VMPs calculated by use of 1) separate DDDAs oral powder, oral solution and premix, 2) average DDDA orals and 3) average DCDA orals (premix excluded) for oral powder and oral solution and DCDA 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 change in output when using separate DCDA for premix and for all other oral VMPs for the analysis compared to when the DCDA average of all observations of oral forms was used, was minor both for amoxicillin (4%–5%) and oxytetracycline (0.1%–1%) (Figure 22, Figure 23).

Pigs

For pigs the change in output when using separate DCDA for premix and for all other oral VMPs for the analysis compared to when the DCDA average of all observation of oral forms was used for amoxicillin is 27% for the 26 EU/EEA countries, 38% for MS 2 and for MS 1 it is 9%. For oxytetracycline the corresponding figures were 4%, 22% and 84% (Figure 22, Figure 23).

The results of the analyses show that the impact on the output when using separate DCDA for premix and DCDA for all other oral VMPs versus the DCDA 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 DCDAs show that the DCDA for premix is not consistently higher than for other oral forms, except for pigs. 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 for changes across years within a country/locally are important. Recognizing DCDA is a technical unit of measurement and that the same value (DCDA) will be used across years, it will allow for identification of changes at country/local level. To assign the same DCDAs for all oral forms would make the list of DCDAs easier to manage in terms of analysing and reporting of the data and also for maintaining the list.

It is suggested to assign the same DCDA for all oral forms for each combination of antimicrobial and species. Exceptions will be identified in the lists of DDDA and DCDA

4.3.2. Injectables

In the data sets on dosing provided by the nine MSs a total of 12 single substance injectables were given as long-acting injectables for cattle and 10 VMPs for pigs by the MSs (Figure 24, Figure 25).
Principles on assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA)

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

* Long-acting only

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

* Long-acting only

For cattle and pigs the preliminary DCDAs were higher for all injectable substances compared to the same substance in long-acting injectables except for enrofloxacin; the difference was biggest for
ampicillin. For cattle the differences were higher than for pigs. This would have a substantial impact on the output. The difference between the average DCDA injectables and long-acting injectables compared to the DCDA ("ordinary") injectables is minor. This is due to a substantially higher number of observations for injectables compared to LA injectables which then affects the average. This is explained by the relatively low numbers of LA injectables in the data sets compared to "ordinary" injectables.

It is suggested to assign the same DCDAs for single substance injectables and long-acting injectables for each substance and species. Since different DDDAs are assigned for prodrugs and its active substance this is also suggested for DCDA.

4.4. DCDA – combination products

4.4.1. Oral forms

The preliminary DCDAs show that these may vary between single VMPs and combination VMPs for oral forms. The impact on the total output by applying DCDA for single substance oral VMPs for reporting consumption for the same substance in combination VMPs was assessed by use of sales data of amoxicillin and the preliminary DCDAs.

Sales of oral powder, oral solution and premix in 26 EU/EEA countries in 2012 as single substance VMPs were 1,321 tonnes and 96 tonnes for combinations.

4.4.1.1. Amoxicillin

The preliminary DCDAs for amoxicillin in single and combination VMPs for broilers were 105 mg/kg and 142 mg/kg, respectively.

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

The difference between the two outputs was 1.8%.
4.4.1.2. Oxytetracycline

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 graph 27 and 28**

  - **DCDA single - DCDA comb (premix excluded)/DCDA single – DCDA comb premix** =
    
    (tonnes oral powder + oral solution single sold substance X /DCDA oral single - premix excluded) +
    
    (tonnes oral powder + oral solution combination sold substance X /DCDA oral combination - premix excluded) + (tonnes single premix sold substance X/DCDA premix single) + (tonnes combination premix sold substance X/DCDA premix combination substance)

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

Preliminary DCDAs for oxytetracycline aggregated by oral forms (weighted mean) were used for the impact analyses (Table 19).

**Table 19.** Preliminary DDDAs for oxytetracycline for pigs used in the analysis (Figure 27)

<table>
<thead>
<tr>
<th>DCDA single premix</th>
<th>DCDA single average orals forms (premix excluded)</th>
<th>DCDA combination premix</th>
<th>DCDA combinations average orals forms (premix excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>266</td>
<td>94</td>
<td>150</td>
</tr>
</tbody>
</table>
Figure 27. Estimated numbers of DCDA sold (millions) of oxytetracycline oral powder, oral solution and premix as single or combination VMP calculated by using 1) DCDA single premix, DCDA single average oral forms excluding premix, DCDA combination premix, DCDA combination average oral forms excluding premix respectively, and by application of 2) DCDA single premix and DCDA 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 DCDA for reporting sales of VMP has almost no impact on the total output on calculated numbers of DCDAs. 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 DCDA single and DCDA combination. It is suggested as a general rule to assign the single substance DCDA 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 DCDA 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 DCDA for the prodrug procaine benzylpenicillin as single and combination VMPs are 42 mg/kg and 26 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 DDDAs 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 DCDA sold (millions) of procaine benzylpenicillin injectable VMPs as single and combination VMP calculated either by using specific DCDAs for single and combination products or by using DCDA for single products for all sales assuming that all procaine benzylpenicillin injectables was administered to pigs.

If the single DDDA for procaine benzylpenicillin was applied to calculate sales of both single and combinations VMPs the numbers of DDDAs would be 8% lower compared to when calculated by single and combination DDDAs (Figure 28). The impact of assigning the single substance DCDA for the same substance and species in a combination injectable VMP on the overall output will be low.

It is suggested as a general rule to assign the single substance DCDA for the same substance in a combination injectable VMP.

### 4.4.3. Synergistic combinations

See considerations outlined in chapter 4.2.3.

It is suggested to assign separate DCDAs for single substance sulfonamide VMP and the same DCDA for sulfonamide in combination with trimethoprim.

### 5. Discussion on preliminary DDDAs - ESVAC

In a recent paper DDDAs for pigs with data from four European countries – Belgium, France, Germany and Sweden - were published (Postma et al., 2015). A comparison between the DDDAs published in that paper and the preliminary ESVAC DDDAs 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 et al. (2015) the DDDAs were assigned separately for pharmaceutical forms for administration through water/feed and other oral forms, while for ESVAC it’s suggested to assign the same DDDA by all oral forms for each substance and species. To facilitate the comparison, the DDDAs...
Principles on assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA)

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 DDDAs for all oral forms for pigs. DDDAs is given in mg/kg

The DDDAs differed for all substances except for colistin but for most of the DDDAs the differences were minor. The largest deviation between the DDDAs is seen for chlortetracycline (Figure 29). The deviations between the DDDAs 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 DDDAs tended to be lower for ESVAC and this could partly be explained by the exclusion by ESVAC of outliers prior to assignment of the preliminary DDDAs. The ESVAC preliminary DDDAs are based on data from five more countries compared to Postma, Sjolund et al. 2015 and thus countries with higher daily doses (ESVAC) will have less impact on the average DDDAs; this could also explain the variations.
Figure 30. Comparison of DDDAs assigned by Postma, Sjolund et al. 2015 for parenteral pharmaceutical forms and ESVAC preliminary DDDAs for injectables and long-acting (LA) injectables for pigs. DDDAs are given in mg/kg. The DDDAs for long-acting injectables by Postma, Sjolund et al. 2015 have been subdivided by the long-acting factor given for each substance.

For three of the 18 DDDAs - cepquinome, ceftiofur and marbofloxacin (none long-acting) - the DDDAs are identical (Figure 30); for seven other substances the difference was ≥ 20%. The difference tends to be bigger for some of the none long-acting (e.g. florfenicol and spiramycin) compared to the long-acting. These differences might be explained by the differences in number of countries involved. For ampicillin the difference is of the same magnitude for injectables and long-acting injectables. Differences between the DDDAs for the long-acting injectables could be due to different definition of the treatment duration (long-acting factor) between Postma, Sjolund et al. 2015 and ESVAC.

Note that Postma, Sjolund et al. 2015 include DDDAs for long-acting marbofloxacin and tylosin and ESVAC DDDAs include gamithromycin and tilmicosin as LA injectables (data not shown in Figure 30).

6. Reporting consumption of antimicrobials in animals

The aim of this document is to provide principles for the assignment of DDDA and DCDA; but it is important to also reflect on which indicators to be used for the reporting of data. Suggestions and examples for reporting are given below. Further discussions are, however, needed on this subject prior to reporting of data collected by species.

6.1. Aim of reporting

The indicator used should aim to fit the purpose of the reporting. In human medicine DDD was established for the purpose of drug consumption studies and mainly in order to follow therapeutic trends. The additional and main purpose of establishing DDDA and DCDA for veterinary antimicrobial VMPs is to address antimicrobial resistance, which has been described in Chapter 6.
It is suggested to apply indicators enabling 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, 1 and 2 are addressed below.

**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 per year; the consumption is usually reported on ATC level 3 (ECDC, 2015). The indicator applied to report consumption is numbers of DDD/1000 inhabitants/year.

**Veterinary medicine**

In veterinary medicine, DDDAs and DCDAs will be assigned per kg animal for oral and injectable products. Based on this, DDDAs and DCDAs can be calculated by weight group – e.g. for oxytetracycline the DDDA is 27 mg/kg giving 1,350 mg for finishers (ESVAC standardised weight for finisher: 50 kg, see Table 20). 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 less than 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 DDDA or DCDA consumed/1,000 animals produced or livestock for each weight group/production type by country and year (EMA/ESVAC, 2013b).

### 6.1.1. 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 DDDAs as shown in Table 20.

**Table 20.** 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))

<table>
<thead>
<tr>
<th>Weight group/production type</th>
<th>Age period</th>
<th>Average weight at treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sows/boars</td>
<td>Any pig meant for production of piglets</td>
<td>220 kg</td>
</tr>
<tr>
<td>Suckling piglets</td>
<td>Birth to start of weaning</td>
<td>4 kg</td>
</tr>
<tr>
<td>Weaners</td>
<td>Weaning period</td>
<td>12 kg</td>
</tr>
<tr>
<td>Finishers</td>
<td>End of weaning period to slaughter</td>
<td>50 kg</td>
</tr>
</tbody>
</table>
6.1.1.1. Reporting by weight group

In order to measure changes in consumption within a specific weight group the approach shown in a Table 21 and Table 22 is suggested. These are examples of calculating numbers of DDDA/1000 animals/year for oxytetracycline consumption in finishers (50 kg) that will identify changes across years and differences between countries, respectively. The preliminary DDDA for oxytetracycline has been applied for the calculation - 1.3 g for 50 kg finishers.

**Table 21.** Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDA/1,000 finishers/year, for one country for the years 2011-2013

<table>
<thead>
<tr>
<th>Numbers finishers</th>
<th>OTC - tonnes used</th>
<th>DDDA finishers (g) - oral</th>
<th>DDDA/1000 finishers / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>10,000,000</td>
<td>8.5</td>
<td>1.3</td>
</tr>
<tr>
<td>2012</td>
<td>10,400,000</td>
<td>8.0</td>
<td>1.3</td>
</tr>
<tr>
<td>2013</td>
<td>11,000,000</td>
<td>7.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Table 22.** Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDA/1,000 finishers/year, for one year for countries A, B and C

<table>
<thead>
<tr>
<th>Numbers finishers</th>
<th>OTC - tonnes used</th>
<th>DDDA finishers (g) - oral</th>
<th>DDDA/1000 finishers / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country A</td>
<td>25,000,000</td>
<td>76</td>
<td>1.3</td>
</tr>
<tr>
<td>Country B</td>
<td>14,000,000</td>
<td>16</td>
<td>1.3</td>
</tr>
<tr>
<td>Country C</td>
<td>10,000,000</td>
<td>8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

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

6.1.1.2. 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 DDDA(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 DDDA per kg pig for oral antimicrobials applied for the analysis is 26 mg/kg. An example of the output is shown in Table 23.

**Table 23.** Consumption of oxytetracycline (OTC) oral powder, oral solution and premix, in numbers of DDDA(kg)/1,000 pigs/year, for one country for the years 2011-2013

<table>
<thead>
<tr>
<th>Numbers pigs produced</th>
<th>OTC - tonnes used</th>
<th>DDDA(kg) pigs - (mg) - oral</th>
<th>DDDA(kg)/1000 pigs produced/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>10,000,000</td>
<td>9.9</td>
<td>26</td>
</tr>
<tr>
<td>2012</td>
<td>10,400,000</td>
<td>9.1</td>
<td>26</td>
</tr>
<tr>
<td>2013</td>
<td>11,000,000</td>
<td>8.0</td>
<td>26</td>
</tr>
</tbody>
</table>
6.1.2. Reporting consumption at farm level

Consumption data can also be reported at farm level, using the same units of measurement. In Table 24 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 24.** 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.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DDDA (mg/kg)</th>
<th>DCDA (mg/kg)</th>
<th>Kg used active substance</th>
<th>No. DDDA&lt;sub&gt;kg&lt;/sub&gt;</th>
<th>No. DDDA</th>
<th>No. DCDA&lt;sub&gt;kg&lt;/sub&gt;</th>
<th>No. DCDA per weight group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - 50 sows; injection; two doses: 10 mg/kg</td>
<td>10</td>
<td>23</td>
<td>0.22</td>
<td>22,000</td>
<td>100</td>
<td>9,565</td>
<td>43.5</td>
</tr>
<tr>
<td>B - 1,000 weaners; oral powder; dose: 25 mg/kg; 7 days</td>
<td>26</td>
<td>173</td>
<td>2.1</td>
<td>80,769</td>
<td>6,731</td>
<td>12,139</td>
<td>1,012</td>
</tr>
<tr>
<td>C - 50 weaners; injection; dose: 10 mg/kg; two doses</td>
<td>10</td>
<td>23</td>
<td>0.012</td>
<td>1,200</td>
<td>100</td>
<td>522</td>
<td>43.5</td>
</tr>
<tr>
<td>Total on the farm</td>
<td></td>
<td></td>
<td>2.332</td>
<td>103,969</td>
<td>6,931</td>
<td>22,226</td>
<td>1,099</td>
</tr>
<tr>
<td>Total per 1000 slaughter pigs</td>
<td></td>
<td></td>
<td>0.583</td>
<td>25,992</td>
<td>1,783</td>
<td>5,557</td>
<td>275</td>
</tr>
</tbody>
</table>
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 chapters 3-7).
- 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

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Marbofloxacin 100 mg/ml (injection):</em> Dose: respiratory disease one injection of 8 mg/kg or mastitis 2 mg/kg for 3 days</td>
<td>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).</td>
</tr>
</tbody>
</table>

2.2. Therapeutic or preventive use

Indicated for both therapeutic and preventive use

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Colistin (oral powder):</em> Therapeutic dose: 4-8 mg/kg Disease prevention dose: 2-4 mg/kg</td>
<td>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).</td>
</tr>
<tr>
<td><em>Tiamulin (premix):</em> One indication 8 mg/kg for 10 days, other indication 1.6 mg/kg for 42 days</td>
<td>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).</td>
</tr>
</tbody>
</table>

2.3. Daily dose

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

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Oxytetracycline (injection):</em> Daily dose 5-10 mg/kg; long-acting dose 20 mg/kg</td>
<td>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).</td>
</tr>
</tbody>
</table>

\(^1\)Or as many times as necessary according to the information given in the SPC.
### Different daily doses for young and adult animals

<table>
<thead>
<tr>
<th>Examples of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spiramycin (injection):</strong></td>
<td>Give lowest and highest daily dose in the template (i.e. 30,000 and 75,000 UI/kg).</td>
</tr>
<tr>
<td>Dose: for veal calf 75000 UI/kg, for cattle 30000 UI/kg</td>
<td></td>
</tr>
<tr>
<td><strong>Cefquinome (injection):</strong></td>
<td>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).</td>
</tr>
<tr>
<td>Dose for veal calf 2 mg/kg for 3 days, for cattle 1 mg/kg for 3-5 days</td>
<td></td>
</tr>
</tbody>
</table>

### Two different doses for the same product presentation and indication

<table>
<thead>
<tr>
<th>Examples of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Florfenicol (injection):</strong></td>
<td>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.</td>
</tr>
<tr>
<td>Dose: two injections of 20 mg/kg or one injection of 40 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

### Dose is given in ppm

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tylosin (premix):</strong></td>
<td>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).</td>
</tr>
<tr>
<td>Dose: 40-100 g/1,000 kg feed</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

#### Unclear lower and upper limit of treatment duration

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

#### Unclear treatment duration

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrofloxacin (injection):</td>
<td>Give 999 for number of days and in the comment field: in some cases two injections are necessary</td>
</tr>
<tr>
<td>Dosing: in some cases two injections are necessary</td>
<td></td>
</tr>
</tbody>
</table>

### 2.5. Other issues

#### Unclear dosing interval of long-acting antimicrobial VMPs

<table>
<thead>
<tr>
<th>Example of SPC information</th>
<th>How to fill in template</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danofloxacin (injection):</td>
<td>Give the interval (i.e. 1.5 – 2 days), comment field: interval 36-48hrs &quot;if needed&quot;.</td>
</tr>
<tr>
<td>Dosing: 6 mg/kg; interval 36-48 hrs &quot;if needed&quot;</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3

1. References


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.

It should be noted that 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

<table>
<thead>
<tr>
<th>Species</th>
<th>Feed intake (kg/kg animal)</th>
<th>Water intake (l/kg animal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broiler</td>
<td>0.13</td>
<td>0.23</td>
</tr>
<tr>
<td>Cattle</td>
<td>0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Pig</td>
<td>0.04</td>
<td>0.10</td>
</tr>
</tbody>
</table>

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


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

Cattle


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

Pigs


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


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=5M4kRtU3ZgpUFTHPAcyw50u-f0&hl=en&sa=X&ei=9uaXVKTMYv4UtnqyKAL&ved=0CCEQ6AEwAA#v=onepage&q=veterinary%20practice%20section%20table%201.3%20recommended%20water%20requirements&f=false)