ANNEX: CONTENT CONVERSION OF ANTIMICROBIAL ACTIVE INGREDIENTS IN VETERINARY MEDICINES INTO KILOGRAMS

ANIMUSE – 9TH Round

World Organisation for Animal Health
Founded as OIE
I
f you need to convert quantities of raw material, the most used one.

Section 1

Transformation of bulk quantities, e.g. from import of active ingredients into the required format.

Section 2

Data on veterinary medicinal products, including conversion from International Units (IU) to kg.

Section 3

Recommendations for further optional conversions, aimed at achieving refined reporting of active entities, the ultimately desired format.

If such calculations are made, they should be reported to WOAH.

The following abbreviations and symbols will be used:

<table>
<thead>
<tr>
<th>Symbol/abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength % w/v</td>
<td>amount of antimicrobial agent per unit of veterinary product per cent weight per volume</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>t</td>
<td>ton (metric)</td>
</tr>
<tr>
<td>ml</td>
<td>millilitre</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
</tbody>
</table>
1. For data on bulk quantities

Such information is usually sourced from customs, import or other bulk trading. It will likely come as a weight in a number of possible units (e.g. metric tons) of chemical compound and needs to be converted to kg. When conversion into kg is necessary, follow the steps below. If additional conversion factors are needed, please contact WOAH at antimicrobialuse@woah.org.

**Step 1:** Multiply the amount of antimicrobial agent, i.e. the chemical compound as declared on the product label with the appropriate conversion factor from the table 1 below.

\[
\text{Antimicrobial agent (kg)} = \text{antimicrobial agent (unit Z) x conversion factor}
\]

When data are on bulk quantities.
The weight of raw materials to manufacture veterinary products

<table>
<thead>
<tr>
<th>Unit reported (unit Z)</th>
<th>Conversion factor to kg (for multiplication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metric ton</td>
<td>1000</td>
</tr>
<tr>
<td>Imperial ton (long)</td>
<td>1016</td>
</tr>
<tr>
<td>Imperial ton (short)</td>
<td>907.18</td>
</tr>
<tr>
<td>Stone (Imperial)</td>
<td>6.35</td>
</tr>
<tr>
<td>Imperial Pound</td>
<td>0.4536</td>
</tr>
<tr>
<td>Ounce</td>
<td>0.0283</td>
</tr>
</tbody>
</table>

2. For data on veterinary medicinal products

For veterinary medicinal products containing antimicrobial agents, data on quantities sold is likely to be available as numbers of packages of product sold or imported, with each package containing a specified quantity of medicinal product with a specified amount of antimicrobial agent.

In such cases, the amount of antimicrobial agent (chemical compound as declared on the product label) per package needs to be calculated first, and subsequently the result needs to be multiplied with the number of packages of the presentation sold to obtain the overall amount of antimicrobial agent, which should be reported in kg.

The most common ways to indicate the content of the antimicrobial agent(s) of a veterinary medicinal product are:

(i) Strength in mg or g of the active ingredient per volume or weight or other unit, (for example: ml, kg, tablet or piece),

(ii) Strength in International Units (IU) per weight, volume or other unit,

(iii) Strength in per cent (%), weight per weight (w/w) or weight per volume (w/v).

Each situation requires a different kind of mathematical conversion.
2. (i) – Content of antimicrobial active ingredient (antimicrobial agent) stated in milligram per volume or weight or other unit (for example millilitre, litre, kilogram, tablet) of content

**Step 1: Calculation of the content of antimicrobial agent per package**

Multiply the amount of antimicrobial agent (chemical compound as declared on the product label) per unit of content, that is, the strength of the product, with the total number of units contained in the package.

**Content of antimicrobial agent per package**

\[ \text{Content of antimicrobial agent per package} = \text{Strength (amount antimicrobial agent per unit)} \times \text{number of units per package} \]

**Example A:**
Tiamulin 100 g/kg premix for medicated feeding stuff; package sizes: (a) 1 kg, (b) 5 kg and (c) 20 kg

Calculation of content of antimicrobial agent, tiamulin, per package:

(a) Pack content = 100 g/kg x 1 kg = 100 g
(b) Pack content = 100 g/kg x 5 kg = 500 g
(c) Pack content = 100 g/kg x 20 kg = 2000 g

**Example B:**
Tetracycline intrauterine tablet containing 2000 mg tetracycline hydrochloride per tablet; package sizes: (a) carton with 1 blister of 5 intrauterine tablets, (b) carton with 4 blisters of 5 intrauterine tablets each (20 tablets), (c) carton with 20 blisters of 5 intrauterine tablets each (100 tablets).

Calculation of content of antimicrobial agent, tetracycline, per package:

(a) Pack content = 2000 mg x 5 = 2 g x 5 = 10 g
(b) Pack content = 2000 mg x 20 = 2 g x 20 = 40 g
(c) Pack content = 2000 mg x 100 = 2 g x 100 = 200 g

**Example C:**
Tilmicosin 300 mg/ml solution for injection for cattle; package sizes: containers of 100 ml and 250 ml packs of (a) 6, (b) 10 and (c) 12 units of 100 ml and 250 ml.

Calculation of content of antimicrobial agent, tilmicosin, per package:

(a) Container content = 300 mg/ml x 100 ml = 30000 mg = 30 g
   Pack content: (a) 6 x 30 g = 180 g,
   (b) 10 x 30 g = 300 g
   (c) 12 x 30 g = 360 g
(b) Container content = 300 mg/ml x 250 ml = 75000 mg = 75 g
   Pack content: (a) 6 x 75 g = 450 g,
   (b) 10 x 75 g = 750 g
   (c) 12 x 75 g = 900 g

**Step 2: Sum up** the antimicrobial agent contained in all presentations and packages sold or imported.

**Convert all contents** of antimicrobial agent calculated under step 1 to the same weight unit and add up the total.
Step 3: If necessary, convert the total sum of antimicrobial agent contained in all packages of all presentations sold to kg.

Multiply the result from step 2 with an appropriate conversion factor to achieve the result in kg.

2. (ii) content of antimicrobial agent (chemical compound as declared on the product label) in International Units (IU) per weight, volume or other unit (for example millilitre, litre, kilogram, tablet) of content

Where the strength of the antimicrobial agent in the veterinary medicinal product is stated International Units (IU) per unit of finished product, an additional conversion step is necessary to obtain results in mg, g, or kg. Table 2 is used to convert content of antimicrobial agents declared in IU on the product label into mg for reporting to WOAH; either divide the total number of IUs of an antimicrobial agent by the value in the column "International Units (IU) per mg" for this agent in Table 2, or, if multiplication is preferred, multiply the total number of IUs with the conversion factor listed for the agent. To convert mg values into kg, please multiply the result of the conversion with $1 \times 10^{-6}$ equalling 0.000001.

For some antimicrobial agents in veterinary medicinal products, the IU content or strength may be stated in respect to the active entity rather than to the chemical compound actually included; for example: a product may contain penethamate hydroiodide, or procaine benzylpenicillin, but the stated strength in IU refers to benzylpenicillin (product X containing penethamate hydroiodide, equivalent to xx IU benzylpenicillin, or, product Y containing procaine benzylpenicillin, equivalent to yy IU benzylpenicillin). For such cases, use the conversion factor for the relevant active entity listed in table 2 (in the examples used: benzylpenicillin). To convert mg values into kg, please multiply the result of the conversion with $1 \times 10^{-6}$ equalling 0.000001.

If additional conversion factors are needed or have been used, please contact WOAH at antimicrobialuse@woah.org.

Step 1: Calculating the content of antimicrobial agent per package in IU

Multiply the amount of IU antimicrobial agent per unit of content with the total number of units contained in the package.

\[
\text{Content of antimicrobial agent per package in IU} = \text{Strength (amount IU antimicrobial agent per unit)} \times \text{number of units per package}
\]

Step 2: Converting the content of antimicrobial agent per package in IU into mg

\[
\text{Content of antimicrobial agent per package in mg} = \text{Content of antimicrobial agent in IU} \times \text{conversion factor}
\]

Steps 3-4: Follow steps 2-3 described for (i)
Table 2: Conversion of International Units (IU) of certain antimicrobial agents into mg and relevant active entities, based on the ESVAC conversion factors¹

<table>
<thead>
<tr>
<th>Antimicrobial agent in the veterinary medicine</th>
<th>Antimicrobial active entity for reporting to WOAH</th>
<th>International Units per mg</th>
<th>Conversion factor for multiplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apramycin</td>
<td>Apramycin</td>
<td>552</td>
<td>0.00181</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Bacitracin</td>
<td>74</td>
<td>0.013514</td>
</tr>
<tr>
<td>Benzylpenicillin (penicillin G)</td>
<td>Benzylpenicillin</td>
<td>1670</td>
<td>0.0006</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>Chlorotetracycline</td>
<td>1000</td>
<td>0.001</td>
</tr>
<tr>
<td>Colistin methane sulfonate sodium (colistimethate sodium INN)</td>
<td>Colistin</td>
<td>12700</td>
<td>0.000079</td>
</tr>
<tr>
<td>Colistin sulfate</td>
<td>Colistin</td>
<td>20500</td>
<td>0.000049</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>Dihydrostreptomycin</td>
<td>777</td>
<td>0.00129</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin</td>
<td>920</td>
<td>0.001087</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Gentamicin</td>
<td>620</td>
<td>0.001613</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Kanamycin</td>
<td>796</td>
<td>0.001256</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Neomycin</td>
<td>762</td>
<td>0.00131</td>
</tr>
<tr>
<td>Neomycin B (Framycetin)</td>
<td>Neomycin B (Framycetin)</td>
<td>706</td>
<td>0.00142</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Oxytetracycline</td>
<td>880</td>
<td>0.00114</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Paromomycin</td>
<td>750</td>
<td>0.00133</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Polymyxin B</td>
<td>8403</td>
<td>0.000119</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>Rifamycin</td>
<td>887</td>
<td>0.001127</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>Spiramycin</td>
<td>3200</td>
<td>0.000313</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Streptomycin</td>
<td>760</td>
<td>0.00132</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Tetracycline</td>
<td>982</td>
<td>0.00102</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Tobramycin</td>
<td>875</td>
<td>0.001143</td>
</tr>
<tr>
<td>Tylosin</td>
<td>Tylosin</td>
<td>1000</td>
<td>0.001</td>
</tr>
</tbody>
</table>

2. (iii) – content of antimicrobial agent (chemical compound as declared on the product label) in per cent (% weight per weight (w/w) or weight per volume (w/v) of content

The amount of antimicrobial agent contained in a veterinary medicine concerned may be stated in per cent weight per weight (% w/w) (example 1: product X contains tylosin 100% w/w, or example 2, product Y contains amoxicillin 22.2% w/w) or in per cent weight per volume (% w/v) (example: product Z contains procaine benzylpenicillin 30% w/v). Such figures first need to be converted into mg/g, g/g, or mg/ml, followed by the calculations described under (i).

Converting % w/w: Conversion calculations are performed by relating the content of antimicrobial agent to 1g of the finished product. Divide the percentage value by 100 to obtain the amount of antimicrobial agent in g per g finished product.

\[
\text{value antimicrobial agent in g per gram finished product} = \frac{\text{value} (\%)}{100} \times \frac{1 \text{ g} (\text{finished product})}{1 \text{ g}}
\]

Example 1: Product X containing 100% w/w tylosin will contain 100/100 x g = 1 g tylosin per g finished product.

Example 2: Product Y containing 22.2% w/w amoxicillin will contain 22.2/100 = 0.222 g amoxicillin per g finished product.

Continue with Steps 1-3 of (i)

² Applies to all derivatives/compounds of benzylpenicillin
Converting % w/v: Conversion is based on the assumption that 1 ml of the products weighs 1000 mg. Multiply the percentage value with 10 to obtain the content in mg/ml.

\[
\text{value antimicrobial agent in g per ml finished product} = \frac{\text{value (\%)x 10 x mg}}{\text{1 ml (finished product)}}
\]

Example: Product Z containing 30% w/v benzylpenicillin will contain \((30 \times 10 \text{ mg})/\text{1 ml}\), equal to 300 mg/ml benzylpenicillin.

Continue with Steps 1-3 of (i)

3. Additional recommendations for further conversions of quantities of antimicrobial agents

For pragmatic reasons WOAH accepts the reporting of antimicrobial agents in amounts of chemical compound as declared on the product label of the veterinary medicinal product. However, WOAH Members may wish to carry out further calculations to report amounts of active entity. If such further calculations are carried out, please describe them in the WOAH template.

Calculating the total amount expressed in weight of chemical compound as declared on the product label of a veterinary medicinal product into antimicrobial active entity (e.g. salt, ester or prodrug into base)

This step may be carried out once the steps described in section 1 or section 2. (i) have been completed.

As an example, for the antimicrobial agent tiamulin that is often available in the form of tiamulin hydrogen fumarate (the chemical compound as declared on the product label), the conversion formula to tiamulin (the active entity) would be:

- Salt (including base): Tiamulin hydrogen fumarate MW 609.8
- Base: Tiamulin MW 493.7
- Conversion factor = MW base/MW salt (including base) = 0.81

Multiply the final result in kg obtained by following steps 1 to 3 with the appropriate conversion factor

\[
\text{Content of active entity (kg)} = \frac{\text{Content of chemical compound as listed on the label (kg)}}{\text{conversion factor}}
\]

Taking the conversion factors of certain derivates or compounds used by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) program managed by the European Medicines Agency, as a starting point, table 3 lists the suggested conversion factors for relevant derivates or compounds in order to obtain the corresponding amount of the active entity.

If additional conversion factors are needed or have been used, please contact WOAH at antimicrobialuse@woah.org.
Table 3: Conversion of content stated in mg, g or kg of derivate/compounds of antimicrobial agents in the veterinary product into corresponding mg, g or kg antimicrobial active entity for reporting to WOA\textsubscript{H}, based on the ESVAC conversion factors\textsuperscript{3}

<table>
<thead>
<tr>
<th>Derivate or compound</th>
<th>Active entity</th>
<th>Conversion factor for multiplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benethamine benzylpenicillin\textsuperscript{4}</td>
<td>Benzylpenicillin</td>
<td>0.61</td>
</tr>
<tr>
<td>Benzathine benzylpenicillin\textsuperscript{5}</td>
<td>Benzylpenicillin</td>
<td>0.68</td>
</tr>
<tr>
<td>Cefapirin benzathine\textsuperscript{6}</td>
<td>Cefapirin</td>
<td>0.78</td>
</tr>
<tr>
<td>Cefalexin benzathine\textsuperscript{7}</td>
<td>Cefalexin</td>
<td>0.74</td>
</tr>
<tr>
<td>Cloxacillin benzathine\textsuperscript{8}</td>
<td>Cloxacillin</td>
<td>0.78</td>
</tr>
<tr>
<td>Oxacillin benzathine\textsuperscript{9}</td>
<td>Oxacillin</td>
<td>0.77</td>
</tr>
<tr>
<td>Penethamatehydriodide\textsuperscript{10}</td>
<td>Benzylpenicillin</td>
<td>0.60</td>
</tr>
<tr>
<td>Procaine benzylpenicillin\textsuperscript{11}</td>
<td>Benzylpenicillin</td>
<td>0.57</td>
</tr>
</tbody>
</table>

**Step 1-3:** As described in section 2. (i)

**Step 4:** Multiply the final result in kg obtained by following steps 1 to 3 with the appropriate conversion factor listed in table 3

\[
\text{Antimicrobial agent (active entity)(kg)} = \text{antimicrobial agent (chemical compound as declared on the product label)(kg)} \times \text{derivate or compound conversion factor}
\]

\textsuperscript{3} \url{https://www.ema.europa.eu/en/medicines/human/medicine/product.jsp?webContentId=WC500489269}

\textsuperscript{4} Conversion factor for benethamine benzylpenicillin is updated from 0.65 to 0.61

\textsuperscript{5} Conversion factor for benzathine benzylpenicillin is updated from 0.74 to 0.68

\textsuperscript{6} Conversion factor for cefapirin benzathine is updated from 0.41 to 0.78

\textsuperscript{7} Conversion factor for cefalexin benzathine is updated from 0.36 to 0.74

\textsuperscript{8} Conversion factor for cloxacillin benzathine is updated from 0.43 to 0.78

\textsuperscript{9} Conversion factor for oxacillin benzathine is updated from 0.69 to 0.77

\textsuperscript{10} Conversion factor for penethamatehydriodide is updated from 0.63 to 0.60

\textsuperscript{11} Conversion factor for procaine benzylpenicillin is updated from 0.61 to 0.57