EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2015
EMA/326801/2015
Veterinary Medicines Division

Overview of comments received on "Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet)"[1] (EMA/710019/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Veterinary Medicines Directorate, United Kingdom
2	Federation of Veterinarians of Europe
3	IFAH-Europe
4	Veterinary Epidemiology Unit, Faculty of Veterinary Medicine, Ghent University, Belgium • Jeroen Dewulf • Merel Postma Centre of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA) - Scientific Unit data-collection and –analysis, Belgium • Evelyne De Graef • Wannes Vanderhaeghen • Veerle Piessens • Bénédicte Callens

[1] Note that the terms DDDA and DCDA have been changed to DDDvet and DCDvet in the principles document, and in the outcome of this document, in order to avoid confusion with national DDDA and DCDA values.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**1. Overarching Comments** The UK supports the broad objectives of this work, to achieve a form of measurement of antimicrobial consumption that controls for differences in potency and dose rate (which can distort systems based on mg/kg measurements) and allows comparisons to be made between consumption in different groups of animals. The UK is keen to ensure that focus on the primary objective of responsible use of medicines is supported by methods of measurement and not undermined. It is important that the methods are designed as much as possible to avoid deliberate or unintentional distortions in the choice of antimicrobial medicines, either at producer or Member State (MS) level. The UK has concerns about a system that is so difficult to communicate and explain to policy-makers and a wider audience. It currently requires a high level of immersion in the subject to gain an understanding, which raises concerns about transparency. This could be addressed through some modification to both the technical method and the documentation of the method. The UK has made some suggestions in Section 3 to help in the communication of this very complex and technical subject.	Many thanks. The aim of the principles is to provide a methodology for the assignment of DDDvet and DCDvet to be applied by ESVAC for reporting of consumption data by species. This is addressed in the first paragraph of the summary. In the summary it reads: “It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDvet and DCDvet values will nearly always be a compromise. Established DDDvet or DCDvet are not applicable for commercial use such as pricing and analyses of drug costs.” Similar disclaimers are included in the WHO Guidelines for ATC classification and DDD assignment (2015). Assigning DDDvet and DCDvet at substance and not product level is currently considered by Denmark to avoid misuse of the system Also Postma et al (2015) have assigned the units at substance level Communication about the use of this system at national level, including use of the assigned DDDvet and DCDvet, is out of scope of the document.
1	**2. Averaging**	

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	The UK has concerns that the averaging method will create a level of inaccuracy, as will the restriction of the calculation to the average of SPC information from 9 MS only. This could drive perverse consequences, such as the industry in some MS switching to products which have a lower dose rate than the average used to calculate the DDDA and DCDA applied to national quantity data. This would not be in the interests of responsible use of medicines. Specific concerns are elaborated in the next two sections about: - averaging across products with the same active substance; - averaging across SPCs from 9 Member States.	In defining DDDvet and DCDvet a degree of pragmatism is required to reach the right balance between having a highly complex but accurate system in which a DDDvet/DCDvet is defined for every possible 'use case' and having a more simplistic system in which similar 'use cases' are combined requiring fewer DDDvet/DCDvet to be defined. The approach also provides a system that is manageable. The methodology put forward in the principles document is considered to represent the optimum balance between accuracy and practicability.
1	**3. Averaging across products with same active substance** It is currently proposed that the same DDDA and DCDA are derived for various salts of an active substance. Assigning DDDAs and DCDAs for products based on the different salts of a substance would improve the accuracy since different molecular formulations between products might have influenced variation in the recommended dosage in the SPC.	See previous comments.
	The assignment of the same DDDAs and DCDAs for in-feed and in-water administration is of concern, even with exceptions. Postma and others (2015) identified that there are some products for which the dosage differences between the feed and water SPCs are substantial. Their study suggested that assigning separate DDDAs and DCDAs to these products would increase the accuracy of the DDDA and DCDA, which is a conclusion we would support.	See previous comments. In Postma et al (2015) it reads: "*In future DDDA-establishing exercises, consideration should be given to recording the feed administration route separately from the water route."* This has been addressed in Appendix 1 (chapter 4.1.1.) of the principles document.
	For instance, the two examples below show differences in the doses listed in the SPCs for a selection of products authorised in the UK. The dose rate shown is taken from the SPC of one UK authorised	In the summary of the principles it reads: It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug

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	product containing the active substance listed (there may of course be differences in the dose listed in the SPC of different products containing the same active substance and formulation). It is not possible for the UK to check whether these different formulations for these active substances have been treated as exceptions or not, so it would aid our understanding of the principles to see the completed calculations made on our SPCs. ***Example 1*** *Chlortetracycline authorised for use in chickens: the in-feed formulation (premix) dose is 20-30 mg/kg; whilst the in-water formulation (powder for oral solution) is 20-50 mg/kg.* ***Example 2*** *Tilmicosin authorised for use in pigs: the in-feed formulation (premix) dose is 8-16 mg/kg; whilst the in-water formulation (oral solution) is 15-20 mg/kg.* There are wide differences in treatment time periods for premix, oral powder and powder for oral solution (in-water). It appears that premix and oral powders tend to have very similar length of treatment time whereas powder for oral solution (in-water) tends to have a shorter treatment time in comparison. The examples below are for products authorised for use in pigs in the UK. ***Example 1*** *Lincomycin treatment days: powder for oral solution – 10 days; premix – 21 days.* ***Example 2*** *Tiamulin treatment days: powder for oral solution – 3-5 days; oral powder – 7-10 days; premix – 7-28 days.*	consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDvet and DCDvet values will nearly always be a compromise. Note that it is suggested to assign the DCDvet separately for premix for pigs; this will take into account differences in number of treatment days compared to other oral forms.

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1	**4. Averaging across SPCs from 9 Member States** The proposal would derive DDDA and DCDA for an active substance based on an average of dose rates listed in the SPCs of products authorised for use in only 9 MSs. This is problematic due to the lack of harmonisation of SPCs across the EU. The resulting DDDA and DCDA measures will not reflect all of the antimicrobial products authorised for use in Europe and therefore may not be representative of the countries excluded from the calculation, or even those included. An inevitable issue with this methodology is that the number of authorised products in a MS could impact on the calculated DDDAs/DCDAs. For example, a MS with a large number of authorised products will have a greater impact on the DDDAs and DCDAs calculated for each active substance than a country with fewer authorised antimicrobial medicines.	See previous comments. See previous comments.
1	**5. Review process** Consideration needs to be given to how DDDAs and DCDAs assigned to antimicrobial products are to be reviewed and updated, and how changes in the DDDA and DCDA for a product over time will be accounted for in trend data. For example, SPCs may change or new products might come onto the market changing the average. In human medicine the DDD is typically reviewed after 3 years. For this exercise the 9 MS provided lists of SPC information from 2012. Already this is out of date, with new products being added to the UK authorised product list on an ongoing basis. The VMD product list is updated daily and ideally the DDDA and DCDA information would need to be added as soon as new products come onto the market.	The aim of the principles is to provide a methodology for the assignment of DDDvet and DCDvet to be applied for reporting of consumption data obtained through ESVAC or nationally (public) monitoring. It is out of scope of the document to address future revision of DDDvet and DCDvet and its potential impact. Note that the Agency will, together with their experts on technical units of measurement, discuss strategies/approaches on amendments when required and also on revision of DDDvet and DCDvet.

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1	**6. Suggested approach** In practical terms it is proposed by the UK that the system should align with the ESVAC approach that asks MS to submit antimicrobial sales data at the level of each unique authorised product and formulation. This product-level approach is also now being suggested for MS collation and submission of the antimicrobial usage data to which the DDDA and DCDA measures will be applied. It is therefore suggested that the most practical and workable approach would be to assign DDDA and DCDA at the level of each individual authorised product at the time the product is authorised. ESVAC could issue guidance to MS authorities responsible for medicine authorisation and the derivation and assignment of DDDA and DCDA could in future become part of the authorisation process and development of the SPC. This approach could help to overcome the issues raised above. There would be a one-off exercise required to calculate and assign DDDA and DCDA for all existing authorised antimicrobial medicines. Following that the assignment of DDDA could be built into the existing medicine authorisation process and the burden would be minimal. It would then be the responsibility of all authorising authorities to update the DDDA and DCDA information whenever there was a change to the SPC.	See previous comments. The data collected by ESVAC contains more than 5,000 product presentations, and most of them are authorised for more than one animal species. Even if many of those products have more than one presentation and some of them are the same product with the same dosing, establishing DDDvet and DCDvet for each product, for the different major authorised species, for all EU antimicrobials would not be feasible. The main use of DDDvet and DCDvet is suggested to be for reporting surveillance data of veterinary antimicrobials across years and countries both by ESVAC. ESVAC recommend these to be used to report data obtained at national level for the reason of standardisation/harmonisation but that is up to each country to decide. Depending on the purpose of data collection and analysis at national level or during the course of specific studies, other measures might be more appropriate, such as

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		used daily dose or prescribed daily dose obtained through scientific studies as these values are thought to be closer to the practice.
	This may seem on the surface to be more arduous, as calculations would be needed for every authorised antimicrobial product. However the UK considers this approach to be more accurate, less confusing and more streamlined than one based on averaging. The UK is concerned that the current approach will in the long-run prove more costly to administer.	Note also that the human DDDs are not assigned at product level but at substance level.
	Essential to this suggested approach is an assumption that the products are administered at the correct dose rates as stated in the SPCs. There is still the potential that producers may choose to administer the products at a lower dose, to reduce the overall quantity and therefore number of DDDA and DCDA. However, this is not likely to be an issue unless the Member State is using the measure for enforcement purposes at farm or sector level. Major discrepancies could also be detected if another indicator based on total weight of active substance per 1000 animals were to be used alongside the indicator of number of DDDA or DCDA per 1000 animals, as suggested in section 5.9 (page 25) of the 2013 ESVAC Reflection paper.	See previous comments.
	In principle, if harmonisation of SPCs could be achieved and maintained across the EU then a product-by-product approach to deriving and applying DDDA and DCDA should be workable. This would prevent product-level DDDA/DCDA introducing competition at farm level and influencing prescribing choices. Given that harmonisation of all EU SPCs is still aspirational, the UK accepts that	See previous comments.

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	it is preferable to start somewhere, even if it is a compromise, as long as plans are built in to develop and improve the method in the years to come.	
2	FVE recognises the need for a harmonized system that allows for the easy collection of measurable data and for the transparent analysis of it. In that respect welcomes the use of DDDA and DCDA as technical units in the relevant studies FVE supports a Europe wide system o for monitoring of consumption of antimicrobials rather than sales of antimicrobials o that is simple and practical o that provides clear and accurate interpretation o FVE welcomes that the suggested principles for assigning DDDAs for veterinary medicinal products are being harmonised with the principles for human medicinal products in order to facilitate comparability of antimicrobial consumption in animals with consumption in humans. Additionally FVE agrees with the following principles - The establishment of DDDA and DCDA based on the SPCs. Further to this, we suggest that at a later stage (following this pilot exercise) the establishment of additional values is linked to the harmonization of SPCs that is foreseen in the proposal for the regulation of veterinary medicines. Harmonization of SPCs could facilitate the work for the establishment of DDDA and DCDA. - The analysis of data by species. Specific considerations should be also taken into account,	Thank you for the support. In the principles it is indicated that the same approach will be applied for the further amendment of the lists of DDDvet and DCDvet. This implies that the information on dosing will be available in the SPCs at the time of data collection.

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	e.g. different species of poultry (domestic chickens, turkeys, geese, ducks…) may be kept under very different forms of husbandry with different antimicrobial needs and uses, different species of fish, etc. - Use the assignment of values according to the ATCvet groups and the proposed units for each administration route/form. - The assignment of the same values for all oral forms. - The assignment of separate values for long-acting products and prodrugs. - The consideration of certain indicators for the analysis of data. However additional indicators should also apply to identify changes in the use of antibiotics, for example: specific indicators for combination products, authorization and use of ZnO in certain countries, etc. Additional points for consideration: ➔ At the moment we have examples where two systems for collection of data (state and private) are used, e.g. Germany. There should be a provision for collective collection of all data in each country. ➔ In countries where a collection system for consumption of antimicrobials in animals exists, national DDDA and DCDA values already apply. ESVAC should encourage Member States to use the ESVAC values. That will facilitate collection and analysis of data at European Union level. ➔ Consider collection of data for the use of specific products, e.g. ZnO in piglets, etc., as an indicator to identify changes in the use of antimicrobials	Note that the DDDvet and DCDvet will be assigned by cattle, pigs and broilers. The aim of the principles is to provide a methodology for the assignment of DDDvet and DCDvet. In Chapter 6 of the principles it reads among others: "…it is important to also reflect on which indicators to be used for the reporting of data. Further discussions are needed on this subject…" This is intended for further discussion by ESVAC in collaboration with the ESVAC ad hoc species expert group (EG) and the ad hoc working group (WG) on technical units of measurement. It is out of scope for this document to discuss how data on consumption is collected at national level. We agree that countries should be encouraged to use the ESVAC DDDvet and DCDvet for reporting data at national level within the EU/EEA, but the decision is on the hands of the countries. This is out of scope for the principles as the aim is to

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		provide a methodology for the assignment of DDDvet and DCDvet.
3	IFAH-Europe welcomes the paper on the principles of assignment of defined daily doses for animals (DDDA) and defined course doses for animals (DCDA). We applaud the intent to provide a meaningful picture of antimicrobial consumption and understand the work constraints involved. Generally, it is important to consider the advantages and the limitations of DDDA and DCDA. The great advantage of such measurement for antimicrobial consumption is of course the comparability between different antimicrobials, thus avoiding the difficulties tied to the use of weights (mg/kg BW) and the differences of potency among antimicrobials. Also, most importantly, comparability is allowed on time series. However, the use of DDDs brings its own limitations. DDDs do not reflect any true exposure but allow comparison on time series (evolution of exposure) or exposure to the different classes. These limitations and advantages were well understood when the human DDDs were conceptualized. Hence our remarks on the lines 289 to 298. Consequently, we take exception to the view that DDDA can be used for comparison with human data. We struggle to see the scientific value of comparing these data – given the fact that they do not reflect true exposure. It is important also to mention that ESAC data still remains incomplete as it does not include hospital use in some countries. We think that the value of the ESVAC data is to analyse the evolution of resistance in relationship with the evolution of consumption and exposure to different classes and that other approaches are not	Many thanks. We agree, but the methods put forward in the principles document are considered to represent the optimum balance between accuracy and practicability. The comment on comparison with human medicine has been deleted in the revised principles. See previous comments.

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	rooted in science. The comparison of DDD as in animals and DDDs in humans has in our view neither scientific merit nor scientific purpose. Regarding combinations, we concur that each active principle in synergistic combinations should not be counted twice. However, we think that limiting synergistic combinations to TMP-sulfa type of medicines is too restrictive. Care should be taken that assignment of DDDAs and DCDAs does not unduly influence the prescribing of antimicrobial products in a negative and artificial manner as practitioners choose products based on their DDDAs to limit the impact on farm/practice scores rather than the therapeutic need. This has the potential to negatively impact the reduction of antimicrobial resistance. Care should also be taken not to inadvertently stifle innovation, such as updating posology on older products, by making updated products appear less favourable than those which have not been updated.	Note that DDDvet and DCDvet will be assigned by substance/form and species and not at product level, the limitation of the combinations is done for pragmatic purposes. See comments above. The aim of the document is to provide a methodology for ESVAC for the assignment of DDDvet and DCDvet. These will to be applied by ESVAC for reporting of consumption data obtained through surveillance. Discussing updating of posology of older products is out of scope of the document.
4	• We welcome the idea of guidelines on the development of a comment European DDDA and DCDA list very much. Such a common list would be a very helpful tool in the quantification of antimicrobial use in animals and the comparison between countries. • Apart from the desire to harmonise the principles with human medicine, the document is currently quite vague on the (scientific) rationale behind the principles. It would therefore be interesting if the document would include more information on and a discussion of the current facts, issues and problems regarding the establishment of (principles for assigning) DDDA/DCDA values; for example, why is it currently the best solution to base the principles on the information provided in	Many thanks. The principles are based on recomendations given in the «Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals» (hereafter referred to as Reflection paper) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf.)

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	SPC's in the different MSs? On which (scientific) grounds are or should LA-factors be assigned?	The Reflection paper recommends to apply information from SPCs as it is easily available and provides a transparent system as most SPCs are published online and therefore publicly available. Therefore, the methodology is transparent, can be "verified" and can be repeated. Furthermore, before a veterinary medicinal product is given a marketing authorization by EU Member States or by EMA through the centralised procedure, a scientific assessment is conducted. This includes the scientific basis for the dosing recommended in the SPC. Regarding the dosing, the assessments take into account among others the pharmacokinetic properties of the substance. If a substance has a long biological half-life this is reflected in the dosing scheme/the SPC.
	• For an adequate assessment of the merits of the document, it is imperative that the actual DDDA and DCDA list is made available beforehand. This would allow checking the specific effect of certain proposed principles.	The methods put forward in the principles document are considered to represent the optimum balance between accuracy and practicability. The document further contains impact analysis that has been performed, which provide insight into the effects the proposed principles have on the output and explain the reasoning for the proposed principles. The DDDvet and DCDvet will be assigned once the revised principles are published (i.e. the agreed method).

3. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Introduction to the document	1	**Comment**: The UK considers that the document could benefit from having a statement early on in the text about the method by which the DDDA and DCDA have been derived, i.e. the averaging of main indication dose rates from SPCs of all authorised products across a number of MS, for each active substance, by species and administrative route/form. It would also be helpful if the text was clearer at the outset that the DDDA and DCDA have been, and intend to be, derived from the SPCs of products authorised in only 9 Member States and that they will then be applied to *all* authorised antimicrobial products used in any and all MS of the EU. **Proposed change**: Our suggestion would be something along these lines: *ESVAC has proposed to derive DDDAs and DCDAs for each active antimicrobial substance by species and administrative route/form. These DDDA and DCDA will be derived from the average across member states (MSs) of the dose rates of the main indications listed in the Summaries of Product Characteristics (SPCs) of products authorised for use in these countries.* *For the purposes of developing the principles, DDDA and DCDA have been derived from the SPCs of 9 MS,*	Note that the methodology for the calculation is described in Chapter 1.4 of Appendix 1 and in the summary of the principles. The text has been revised as appropriate.

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		who had volunteered to participate in the development of the draft principles approach. These 9 MS cover approximately 65 per cent of the food producing animals of the EU. *The DDDA and DCDA measures derived from the 9 MS will be applied [assigned] to the quantity of any authorised product used in the EU containing the same active substance, by species and administrative route. These units of measure will be applied to all antimicrobial products authorised in the EU as an indicator of antimicrobial use in all MS, whether or not their SPCs were used to derive the DDDA/DCDA*.	
Throughout the document	1	**Comment**: Need for clarity of the meaning of the terminology *assignment* and *assign* **Proposed change**: Throughout the document it would be helpful to make a clearer distinction between the method for *deriving* the DDDA and DCDA and the method for *applying* the DDDA and DCDA measurements. As drafted the document tends to use the word *assign* to mean both (1) the *derivation* of DDDA/DCDA for each combination of species, active substance and administration route/form and (2) the *application* of these DDDA /DCDA to authorised antimicrobial products across the EU. This dual meaning creates confusion for the reader. We suggest that the word *assign* in this context is more synonymous with *apply* – hence we *assign* a	WHO applies the term assignment: "Guidelines for ATC classification and DDD assignment 2015" (see list of reference of principles document). We have considered that the terms should be harmonized with the human guidelines as much as possible.

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		DDDA/DCDA to an authorised product based on active substance, for each species and route of administration/form.	
Throughout the document	1	**Comment**: Need for clarity of the term 'observation' **Proposed change**: We would also suggest that when the term 'observation' appears first in the main text (page 14) it should be defined in the text or should refer the reader to the list of terms and abbreviations. This will aid understanding by the reader.	Agreed and added in the revised principles.
Throughout the document	1	**Comment**: Need for clarity over the meaning and definition of the acronyms 'DDDA' and 'DCDA' **Proposed change**: The nomenclature used in the document around the acronyms 'DDDA' and 'DCDA' needs to be clearly explained and consistent. It should be clearly stated in the document whether or when the acronyms DDDA and DCDA are themselves the units and whether or when they are short-hand abbreviations with units assigned to them (e.g. kg or mg/kg). Sometimes we see DDDA or DCDA qualified with a subtext 'kg', sometimes a bracketed '(mg/kg)', and sometimes not, and these distinctions are not clearly explained or defined in the document. Our preference would be that the acronyms 'DDDA' and 'DCDA' are taken simply to be units, with one unit of DDDA being given to mean one average dose in mg/kg and one unit of DCDA being one treatment	This has been clarified in the revised principles.

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		course dose in mg/kg. The definition of DDDA (page 13, line 327) should be qualified with 'i.e. one DDDA will equal one average dose in mg/kg'. Similarly with DCDA (page 13, line 328), qualify with 'i.e. one DCDA will equal one average dose in mg/kg per treatment course'. Where the abbreviations 'DDDA' or 'DCDA' are being used to express the quantity or weight of active substance, then this should simply be denoted in kg, for instance, without the acronym. Where the nomenclature is being used to express a dose rate, then it would be preferable to stick with mg/kg and not to evoke 'DDDA' or 'DCDA'.	
At appropriate place in document	1	**Comment**: Need for clarity on how DDDA and DCDA are used to derive indicators **Proposed change**: We suggest including a few very simple worked examples and clear explanations to illustrate how the DDDA and DCDA will be used to derive indicators of antimicrobial usage. Making available an infographic to explain the calculation and an interactive tool for MS to test would also be very helpful. The following has been elaborated from page 56 of the consultation document, by way of illustration; *If 8 tonnes (8000 kg) of active substance X have been used in a population of 10,400,000 finishers, how many DDDA of X per 1000 pigs has been used?*	The main aim of the principles is to provide a transparent methodology for the assignment of DDDvet and DCDvet. The aim of this chapter is to present some examples of calculations/indicators. In depth discussion on which indicators to be used is out of scope for the principles.

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		In this case DDDA is defined as the dose per kg bodyweight when the active substance X is fed as a premix. This number (dose per kg) is then multiplied by a defined standard bodyweight for a finisher pig to give the DDDA for active substance X in finisher pigs i.e. the dose for one pig. In this case assume it is 1.3 grams (0.013 kg) *Number of DDDA for 10,400,000 finishers is therefore 8000/0.013 = 6153846.2* *Number of DDDA for 1000 finisher pigs is therefore 6153846.2/10400 = 592*	
100 -102	2	**Comment**: Agree	Noted.
105-106	2	**Comment**: Agree that monitoring of the use of antiparasitics should be further explored by ESVAC.	Note that the document addresses principles for assignment of DDDvet and DCDvet and not any possible future data collection by ESVAC on consumption of antiparasitics.
111-123	2	**Comment**: Agree. However at a later stage (following this pilot exercise) the establishment of additional values is better to be linked to the harmonization of SPCs that is foreseen in the proposal for the regulation of veterinary medicines. Harmonization of SPCs could facilitate the work for the establishment of DDDA and DCDA.	See previous comments.
170	2	**Comment**: Agree.	Noted.

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258	2	**Comment**: Agree. However, specific considerations should be also taken into account, e.g. different species of poultry (domestic chickens, turkeys, geese, ducks…) may be kept under very different forms of husbandry with different antimicrobial needs and uses, different species of fish, etc.	This is taken into account as the principles describe assignment of DDDvet and DCDvet for broilers, cattle and pigs. For pragmatic reasons DDDvet and DCDvet can only be established for the major species.
261	2	**Comment**: Agree with the assignment of the same values for similar products.	Note that DDDvet and DCDvet will be assigned by substance (generic), form and species not at product level.
273- 276	2	**Comment**: Agree.	Noted.
324-341	2	**Comment**: Agree.	Noted.
378-379	2	**Comment**: Agree.	Noted.
566-568	2	**Comment**: Agree.	Noted.
675-697	2	**Comment**: Agree.	Noted.
602-605	2	**Comment**: Agree.	Noted.
611-614	2	**Comment**: Agree.	Noted.
620-625	2	**Comment**: Agree.	Noted.
656 -657	2	**Comment**: Agree. However the consideration of specific indicators for the analysis of data should also apply to identify potential synergies and therefore	Noted.

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		changes in the use of antibiotics. **Proposed change**: It is suggested to assign and report DDDA and DCDA also for the 2nd (and 3rd) ingredient for combination VMPs-and use specific indicators that indicate synergies and allows for better analysis of data.	The principles suggest as a general rule to assign DDDvet and DCDvet for all ingredients in combinations of oral or injectable products, but allowing for exceptions as discussed in the principles document.
1154-1160	2	**Comment**: Agree.	Noted.
1269	2	**Comment**: Agree.	Noted.
290	3	**Comment:** The basis for risk profiling and risk assessment cannot be only antimicrobial consumption. **Proposed change:** As an aid for risk profiling and risk assessment regarding antibacterial drug resistance.	It refers to the terms of reference from the Commission. It indicates "as a basis for", which already takes into account your comment.
291	3	**Comment:** Surveillance of antibiotic consumption cannot be a basis for risk management. The basis for risk management is risk assessment. **Proposed change:** As a basis for setting risk management advices.	It refers to the terms of reference from the Commission.
297	3	**Comment:** Surveillance of antibiotic consumption cannot be a basis for assessing pollution of the environment as other elements (like the metabolism of the active principle, its degradation in nature and humans use of antibacterials) play a role in this	It refers to the terms of reference from the Commission.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: To contribute to the assessment of the spread and effect of antibacterial drug impact on the environment.	
348	3	**Comment:** It is unclear how multispecies presentations will be addressed, how will these be apportioned between the species given the differing animal weights and the species ratios vary across the member states.	The DDDvet and DCDvet will be assigned by species and form and are intended to be applied to analyse data on consumption by species obtained from surveillance.
355-357	3	**Comment:** It is also unclear on how DDDAs have been allocated to single dose long acting formulations when the duration of action is not specified on the SPC. Care should be taken that any duration of action put forward for calculating a DDDA is not used by practitioners to determine duration of action in the field. **Proposed Change:** A table and explanation of the specific approach used in addition to the graph provided would be helpful.	The calculations applied to obtain these values are described in Appendix 1, Chapter 1.4. Due to the huge number of observations the calculation as such is performed using an R-script developed based on what is described in Chapter 1.4 and in the principles; the output from running the R-script is the DDDvet and DCDvet values.
783	3	**Comment:** Whilst we understand the rationale of the proposal, we want to emphasize that any change in the mix of oral products (among powders, solutions and premix) will bring an apparent change in consumption that is not reflected in reality. The concept of having unique DDDs for all oral products is valid for time series comparison only if no change in the product mix occurs, which of course cannot be	In the summary of the principles it reads: It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDvet and DCDvet values will nearly always be a compromise.

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		guaranteed. Another argument is that, should these measures be adopted at farm level, this approach may create distortion on the choice of medicines at farm level independently of the normal benefit/risk balance which should guide the choice of the medicine. It is to be noted that the line 783 does not appear to be in full relation with the paragraph above. **Proposed change:** ~~It is suggested to assign the single DDDA for the same substance in a combination VMP~~. It is suggested to assign different DCDAs for oral powders, solubles and premixes for each combination of antimicrobial and species	Similar disclaimers are included in the WHO Guidelines for ATC classification and DDD assignment (2015). The principles and methods put forward in the principles document are considered to represent the optimum balance between accuracy and practicability. They allow for exceptions, such as assigning a separate DCD for premix in pigs.
791	3	**Comment:** 4.1.2 Tildipirosin should be added to this list of long biological half- life products. **Proposed change:** Add tildipirosin.	Agreed.
794	3	**Comment:** 4.1.2 The graph is not clear for some active ingredients. Nor is the specific calculation used clear, so it is currently impossible to comment on this section **Proposed change:** Add a table and provide details of the calculation used for each active ingredient.	See previous comments.
1002-1003	3	**Comment:** Whilst we understand the rationale of the proposal, we want to emphasize that any change in the mix of oral products (among powders, solubles and	See previous comments.

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		premix) will bring an apparent change in consumption that is not reflected in reality. The concept of having unique DCDs for all oral products is valid for time series comparison only if no change in the product mix occurs, which of course cannot be guaranteed. **Proposed change:** It is suggested to assign different DCDAs for oral powders, solubles and premixes for each combination of antimicrobial and species.	
1007	3	**Comment**: 4.3.2 The graph is not clear for some active ingredients. Nor is the specific calculation used clear, so it is difficult to comment on this section.	See previous comments.
1013	3	**Comment:** Figure 24 is actually figure 25 (pigs) not cattle. **Proposed change:** Please amend figure 24 with the correct data.	Corrected.
1159	3	**Comment:** We do not see the scientific merit of the comparison **Proposed change:** ~~Compare antimicrobial consumption between the human and animal sector.~~	The text has been deleted.
1172-1175	3	**Comment:** 6.1 It is not clear how this will work for multi-species formulations at a member state level. It should work at a farm level where the volume administered to different species will be known, but not at an aggregated level.	See previous comments.

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		Proposed change: Provide further explanation as to how this issue will be addressed.	
1186	3	**Comment:** 6.1.1.1 It is not clear how this will work for multi-species formulations at a member state level. It should work at a farm level where the volume administered to different species will be known, but not at an aggregated level. **Proposed change:** Provide further explanation as to how ESVAC are going to overcome this issue.	See previous comments.
1198	3	**Comment:** 6.1.1.2 It is not clear how this will work for multi-species formulations at a member state level. It should work at a farm level where the volume administered to different species will be known, but not at an aggregated level. **Proposed change:** Provide further explanation as to how ESVAC are going to overcome this issue.	See previous comments.
260-263	4	**Comment**: It would be interesting to include a list of the consulted websites with SPC-information in an appendix. **Proposed change**: provide websites in appendix	A list with links to databases with SPCs from the nine MSs that provided data to ESVAC has been included in the principles document. Note that the SPC information has been filled in and provided to ESVAC by ESVAC national contact points.
314-318	4	**Comment**: We agree that it is difficult to define DDDA for topical products; however, simply not defining	

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		DDDAs – without further comment – is probably the poorest solution. For those countries that would like to quantify the use of topical products, there could at least be a suggestion how to solve this problem. **Proposed change**: suggestions on how to assign DDDA for topical products for those countries that to want to include them. Some studies have been done on this and one way to approach this is by assuming a standardised duration of spray (e.g. 4 sec). Other solutions may exist.	In the Reflection paper it is recommended to not assign DDDvet for topical products or to collect sales or consumption data for these forms at EU-level. This is in line with the human DDD system. Furthermore, these forms are not included in the data on consumption of human antimicrobial agents in EU/EEA countries (ESAC-Net data).
343	4	**Comment**: It would be a good idea to provide some kind of 'mark' for the DDDA/DCDA values assigned by ESVAC, to be able to distinguish them from e.g. values used at national level. Since it is likely that the national values will remain to exist, at least in some countries, for some time **Proposed change**: e.g. $DDDA_{EC}$	For the reasons indicated in the comments of the respondent the Reflection paper suggested to apply the terms DDDvet and DCDvet because at that time these abbreviations were not used by any MSs to the best knowledge of ESVAC and its ad hoc WG. However, since then it has been identified that these abbreviations are used at national level or in targeted scientific studies. To avoid confusion in terms of which DDDvet/DCDvet values have been applied to report data, e.g. in national reports and scientific publications, the terms have been changed to DDDvet and DCDvet in the revised principles document. The terms DDDvet and DCDvet should preferably be reserved for the ESVAC units in order to avoid confusion whether it is national units or ESVAC units that have been used when others than ESVAC report data on consumption of antimicrobials.

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350-352	4	**Comment**: Given the frequent occurrence of differences between proposed dosing between main indications and other indications, it might be advisable to define the DDDA on the proposed dose for the main indication. We do understand that this information was not available in the current exercise but it could be requested in future exercises (when collecting data of all EU MS). **Proposed change**: define DDDA and DCDA as an average of the provided doses in the SPC for the main treatment indication.	As noted the main indication is not clearly given for many products, in particular not for many of the older products that are still used (often in considerable amounts). Therefore it cannot be claimed that DDDvet and DCDvet will be assigned for the main indication. It is also likely to differ across the EU because of differing disease panoramas and antimicrobial resistance situations. Note that it reads in Appendix 2, Chapter 2 on filling in the SPC information on dosing in the template: “When the main indication is clear dosing should always be entered”, implying that the main indication is taken into account for these products.
355-358	4	**Comment**: Including the LA-factor in the DDDA / DCDA may result in confusion and lack of transparency due to substantial disagreement with the used DDDA and the advised dosing. Therefore it would be more transparent if a separate column is used indicating the LA factor. This value can be set at 1 on default for all non-LA products and only has to be changed to the activity duration for the LA products. This would largely enhance transparency. It would not change anything for the calculations since in the final calculations to define the number of DDDA used the LA factor should be included to come up with the same result as in the current proposed system. Proposed change (if any): Ensure that LA-factors and DDDAs are at least separately presented in the list (a ‘unified’ DDDA can be included in parallel, but the separate values should be made available).	See previous comments on transparency. Note that the term "LA-factor" is not a term used in SPCs or by the WHO CC. Observations for which the duration of effect was not given by the MS due to lack of information in the SPCs, or for which this information could not be identified in textbooks, have been excluded from the data sets. Note that what the respondent refers to as the LA-factor – for non-long-acting injectables a factor of 1 is automatically applied to the method of calculation of DDDvet and DCDvet suggested by ESVAC (see Table 5). It is important that the lists of DDDvet and DCDvet are manageable for analysing the data obtained from surveillance of consumption of antimicrobials both for ESVAC and the EU/EEA countries. The format of the lists of DDDvet and DCDvet as well as publishing additional information in an annex such as the

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			factor for duration of effect for long-acting injectables will be addressed with the ad hoc WG technical units of measurement (hereafter referred to as ad hoc WG TU)
372; 383 (and elsewhere)	4	**Comment**: Throughout the text it is mentioned that exceptions to the rules will be given in the DDDA's list. Yet as the list is not provided, it is hard to evaluate what these exceptions would be? These exceptions may be the products or treatments that are often causing discussion in this field. **Proposed change**: provide full DDDA and DCDA list and clearly indicate the exceptions to the rules and provide justification for these exceptions.	Similar to the principles for human DDDs the principles are general and meant to guide the assignment of DDDvet and DCDvet. The exceptions, together with their justification, will be given in the lists of DDDvet and DCDvet when published following adoption of the principles. This will also apply for the amendment of the lists with new DDDvet and DCDvet when required. Please note that exceptions currently known have been mentioned in the principles document in the applicable sections.
381-384	4	**Comment**: From this statement it is not clear how combination products will be calculated in the total usage: will each ingredient be calculated separately (thus: doubling the treatment incidence)?; or will the 2nd ingredient DDDA be added to the first ingredient of the combination product? Or, is the DDDA for a combination product only based on the first ingredient? See also L645-657. **Proposed change**:clarify the way DDDA and DCDA will be determined for combined products	As indicated in the principles it is regarded that the most important aim for using DDDvet and DCDvet is in the context of AMR. The Reflection paper suggested using indicators other than treatment incidence for reporting consumption data. This is also in line with the WHO CC guidelines. Also for ESAC-Net indicators are used to report data. Resistance data are reported by indicator substance and not by combinations of substances. Similarly, the exposure (selection pressure) will be expressed by substance. Reporting consumption of combination products is important to identify changes in therapeutic trends across years at a national level in order to evaluate the effect of management measures. The DDDvet and DCDvet for combination products s can be calculated from the list of DDDvet and

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			DCDvet for single substance VMPs.
520-524	4	**Comment**: see previous comment on the use of main indication to define DDDA and DCDA **Proposed change**: use main indication in future definition of DDDA and DCDA list.	See the previous response.
Figure 2	4	**Comment**: The figure lacks data on intramammary products and intrauterine devices even though it is stated in L543-547 that these products are included. **Proposed change**: change figure or text	The number of observations on intramammary products and intrauterine products included in the data sets is now included in the text in the revised principles.
561-563	4	**Comment**: How many DDDA/DCDAs have finally been established in total? **Proposed change**: provide DDDA and DCDA list	The list will be developed when the principles (the methodology) have been published.
603 and 788-790	4	**Comment**: More scientific data should be provided concerning the biological half-life if this pharmacokinetic concept is proposed to play a role in the establishment of LA factors. Preferably a clear approach for the definition of the relevant duration of the LA effect should be provided to assure that the LA factors are defined in a standardised manner. **Proposed change**: Provide / propose an approach for the definition of the relevant duration of the LA effect	See previous comments on this subject.

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613-614	4	**Comment**: Concerning prodrugs, it is not so much important to have separate DDDA/DCDA values as it is to have a correspondence between the concentration and the DDDA/DCDA value; if the concentration is expressed as prodrug, so should be the DDDA/DCDA; if expressed as active substance, so should be the DDDA/DCDA. So, instead of defining separate DDDA/DCDA values, it can simply be requested to always use the concentration of active substance (which is normally indicated in the SPC).	To identify consumption of prodrugs it is important to assign separate DDDvet and DCDvet for these. Note that for such medicinal products the strength is declared for the prodrug and the data will be analysed based on the strength of the product.
Table 7, Table 10 a.o.	4	**Comment**: Will DDDA/DCDA values be rounded off to decimals? If yes, this will cause a considerable decrease in precision in many cases!! **Proposed change**: define the required number of digits behind the comma.	This has been defined in the revised principles.
683-783	4	**Comment**: The impact analysis is quite misleading! The outcome will depend on the consumption in the countries picked to perform the analysis. If you investigate the impact of averaging over all oral forms, it must be taken into account that there is a link between the quantity used of a form and the associated average DDDA: the more of a specific oral form that is used, the more its DDDA will impact the result! Furthermore, it is totally unclear how it was decided that the observed differences are 'relatively minor' (L778) or 'almost absent' (L780-781), especially when finding differences up to 9%! (L729-730).	As indicated in the summary: It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. We agree on the comment on 'relatively minor' and have revised the text. As shown by Postma et al. (2015, referred to in the document) the SPC dosing given for a substance and form for pigs for a country can be substantially higher or lower than the average (mean) DDDs (range 71.1-202.4%). This demonstrates (and is also indicated in the summary of the

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		Finally, a clear conclusion is lacking on the issue of making the mean for oral DDDAs over premixes, oral solutions and oral powders. This is also not clearly mentioned in chapter 9, only in the summarizing table it is mentioned. **Proposed change**: Define benchmarks of acceptable differences. Provide clear conclusion on the use of mean DDDA for premix, oral solutions and oral powders.	principles) that a pragmatic approach has to be applied for the assignment of DDDvet and with as few exceptions as possible. This is also the case for the assignment of human DDDs. Note that some of the DDDvet and DCDvet values given in Appendix 1 have changed in the revised principles; this is due to further validation and revision of the data in particular for one of the participating MS. The main aim of establishment of DDDvet and DCDvet is to establish a fixed unit of measurement that can be used to report consumption across times. The following conclusion is now added: The same DDDvet will be assigned by substance and species for all oral forms.
815-816	4	**Comment**: Again 'minor differences' are mentioned, while it is not clear how this was objectively determined. Looking at Figure 15 and 16, the differences do not look to be minor for several products!	We agree on the comment on minor differences and have revised the text.
Table 14, 15 and 16	4	**Comment**: It is unclear how the shown average values have been established **Proposed change**: provide additional information to allow to assess how the values were established	Due to the huge amount of data the calculation as such is performed by running an R-script developed based on what is described in Chapter 1.4 and in the principles; the outputs from running the R-script are the DDDvet and DCDvet values. The R-script handles data on dosing filled in by the nine MSs in a template and revised by ESVAC together with the individual MS when required (missing information, lack of standardization etc.). The final data sets have been approved by the data provider of the individual MSs.

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Figure 24 and 25	4	**Comment**: These figures seem to be identical? Proposed change (if any): check whether there was no copy/past error?	It is corrected in the revised principles.
1016-1026	4	**Comment**: The statements made in this section seem to be contradictory. **Proposed change**: clarify text	We agree and this text has been revised.
1140-1141	4	**Comment**: What is meant with 'different definition'? Different assignment of LA-factors or truly different definition of an LA factor? What definition does ESVAC use then? **Proposed change**: provide clear guidelines / definitions for the determination of LA-factors	These sentences have been deleted as it is clarified that the same definitions on duration of effect have been used by Postma et al. (2015) and ESVAC.
1144	4	**Comment**: A group of researchers is currently finalising a review paper describing all possibilities for the reporting of antimicrobial consumption (will hopefully be published soon). In this paper it is very clearly demonstrated that based upon the DDDA and DCDA there are several possibilities to define the consumption. It would be beneficial to include the several options an discuss the advantages and disadvantages of the different systems before concluding on what system ESVAC would propose to use.	The aim of the principles is to provide a clear methodology for the assignment of DDDvet and DCDvet to be applied for reporting of consumption data obtained through ESVAC or national (public) monitoring. In Chapter 6 of the principles it reads among others:"…it is important to also reflect on which indicators to be used for the reporting of data. Further discussions are needed on this subject…" Discussion on the indicators is out of scope for the principles document. Note that this topic is intended to be further addressed by ESVAC in collaboration with the ESVAC experts and the ad hoc WG TU.

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		Proposed change: Indicate that the used methodology is only one of the different options available.	
1163-1164	4	**Comment**: DDD/1000 inhabitants/ day per year is a very confusing notation of the used unit. It should be DDD/1000 inhabitants per day and this for a specific year or determined over one specific year. E.g. in 2015 the use of amoxiclav was 15 DDD/1000 inhabitant/ per day. Indicating that in 2015 daily 15 persons per 1000 (1.5%) received a dose of amoxyclav. **Proposed change**: change description into DDD/1000 inhabitants/day determined during one year.	Per year is deleted.
1187-1191, Table 21, 22, 23, 24	4	**Comment**: the obtained result DDDA/1000 finishers/year is an unclear figure? How should this be interpreted? Does this number means that throughout the year 2013 daily 503 out of the 1000 finishers present were treated with a defined dose of OTC? This would be an incredibly high treatment number. Or does it means that 503 pigs out of 1000 had been treated for one day in 2013 = every finisher on average treated for 0.5 days in a year with OTC? **Proposed change**: please provide a more clear interpretation of the used units of measurement. Preferably in the sense of: “this results indicate that a pig is on average treated …X per year with a DDDA of the specific product”	The main aim of the principles is to provide a transparent methodology for the assignment of DDDvet and DCDvet values. The aim of this chapter is to present some examples of calculations. See also previous comments on this subject. It reads that the tonnes and numbers of pigs are invented figures and should be interpreted as such. Examples of interpretation have been added in the revised principles.

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1200-1212	4	**Comment**: This is a very confusing section! It seems very imprudent to create another definition that closely resembles DDDA, i.e. DDDA (kg). The use of it is also not clear. **Proposed change**: provide more clarifications on the used calculation methodology. Avoid confusion with the used definitions	See previous comments.