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Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on ''Reflection paper on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation' (EMA/CVMP/849775/2017)

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

Stakeholder no.	Name of organisation or individual
1	Federal Office of Consumer Protection and Food Safety (BVL) (Department "Veterinary Medicines")
2	Pestizid Aktions-Netzwerk e.V. (PAN Germany)
3	ÚSKVBL, Hudcova 56a, 621 00 Brno, Czech Republic
4	EGGVP – European Group for Generic Veterinary Products
5	AnimalhealthEurope

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1. General comments – overview

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1	The BVL would like to thank the authors for their extensive and pioneering work on "dose optimisation of established veterinary antibiotics in the context of SPC harmonization". The BVL fully welcomes and supports the development and introduction of non-experimental approaches to modify SPCs of well-established veterinary antibiotics. Concepts based on PK/PD, and PK or PB/PK modelling can be powerful and very useful tools helping to revise label instructions of established veterinary antibiotics, while avoiding the conduct or duplication of experimental animal studies. However, as with any new concepts, their acceptance and implementation in practice largely depends on the level of confidence in the validation results, the appropriateness of underlying assumptions and a clear communication of potential limitations and uncertainties. In our view, and as will be discussed in more detail in the comments below, the proposed methodologies could clearly benefit from further clarification and discussion on those aspects as well as from addition of clear(er) definitions. Also, the number and relevance of the case studies might currently not be sufficient, to allow for robust conclusions on the general applicability (generalizability) of the methodologies and their suitability for routine use. The paper might also benefit from critical discussions and additional considerations about how to proceed with antimicrobials, when PPHOVA approach is not applicable or fails in producing meaningful results (e.g., when underlying assumptions are not satisfied), what the (non-experimental) alternatives could be, or where combinations of proposed approach with limited (bridging) experimental data could potentially be used.	The CVMP appreciates the positive feedback on the use of non-experimental approaches for established veterinary antibiotics. The CVMP is aware of the limitations of the use of models and the fact that the model outputs do contain uncertainty. It is also acknowledged that the quality of the model predictions largely depends on the amount and quality of the data that is used as input (this is of course also true for existing *in vivo* experimental procedures). The CVMP realises that the amount and quality of the available data for established antibiotics will vary. "Generizability" and "routine use" will therefore not be CVMP's ultimate goal of the development of the modelling approaches. To the contrary: each practical situation might require a specific approach. We will need to realise that there is an issue with a number of established antibiotics which needs to be fixed. As the data available for the various antibiotics may differ, we will need to be flexible with respect to the tools we use for repair. With the reflection paper, the CVMP intended to provide tools that are versatile and can be adapted to the situation, as needed. For this reason, standard alternative approches for when the modelling approaches fail, cannot be developed: solutions will need to be found on a case-by-case basis. As the generalizability was not the goal, the number of case studies is felt adequate. As explained in the paper, the case studies were done in the context of a pilot project, and are

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	When drafting comments, we were well aware that the paper has the status of a "reflection paper", which is understood as an invitation for discussion and further in-depth analysis, rather than a definite proposal for scientific or technical requirements. It is currently not clear, if the paper is intended to be further developed into a guideline to replace the "reflection paper" or, if the intention of the pilot project is to gain experience with applying the principles directly to product data before drafting a formal guideline. In addition the regulatory pathways for the SPC harmonisation via non-experimental models still need to be defined. With this in mind, we wish our review of the paper to be regarded as a supporting and critically constructive contribution to an ongoing important project, rather than an argument against it.	intended to illustrate how the methods could work. They were certainly not intended as the final outcome for these cases, and they were based on a limited number of studies. If these cases were assessed with all data from all dossiers, the outcome will likely be different. Iindeed, as indicated by BVL, this is a reflection paper and not a guideline. The CVMP feels that some comments made would be more relevant if it was a guideline. In particular, some of the detailed comments on the case studies are felt to go beyond the scope and intention of the reflection paper, but are nevertheless appreciated as supporting and critically constructive. At this point in time, the CVMP has not decided on whether development of further guidance would be desirable.
	Ad chapter 3. PK/PD approach for dose optimisation: The description of the PK/PD approach for dose optimisation is not yet sufficiently clear and a defined consistent and transparent algorithm is missing, in particular with regard to step 6. The 8 steps of the approach are sometimes fragmentary explained and the requirements on the data to be used in the PK/PD integration should be elaborated in more detail. Which data feeding into the PK/PD integrations are appropriate and eligible? For example the use of old MIC data (older than 5 years) in PK/PD integrations does not appropriately take into account the actual susceptibility situation. Besides, the use of wild type MIC distributions in PK/PD integrations would likewise not be 'dose optimising' as bacterial populations with decreased susceptibility or acquired resistance that may have developed after a substance has been used	Thanks for the comment. We have limited the technical description of step 6 which can be performed using two approaches. The 1st is to determine the distributions of clearance and bioavailibility (for an extra-vascular dose) to establish a daily dose based on the concentration levels reached at steady state according the formula Dose=(clearance/bioavailability)*(MIC/f)*(AUC/MIC) Where f corresponds to the binding and (AUC/MIC) is the target value. Using the mean and standard deviation of clearance, bioavailability and f and their distribution function, we can generate by Monte Carlo Simulation (MCS) the distribution of dose and estimate the dose needed to reach the target for 95 % of the population for a MIC value. We have

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	for a long time are not considered. It is acknowledged that PPHOVA is a pragmatic approach using existing data and does (currently) not intend to aim guideline status by defining clear data requirements. Nevertheless, at least minimal requirements on the quality and quantity of data should be defined for each data set that will be applied in the PPHOVA approach (PD, PK, PDI, PDT, PTA etc.). In addition, it should be explained how the PK/PD integrations could be applied in case underlying data are not sufficient, inappropriate or data are not available at all. Next to that, some of the issues outlined in chapter 3 were not considered/applied in the case studies and vice versa; general principles were applied in the case studies that have not been mentioned in chapter 3 (e.g. the use of MIC distributions of the target pathogens instead of single MIC values, introduction and use of compartment models, etc.). Thus, some principles of the PPHOVA approach are not evident from the main text of the paper but are first understood when reading the case studies. The 'core' part of the PPHOVA approach (step 6) lacks sufficient details of the models proposed. The purpose and the defined course of action of the two proposed approaches that are based on different PK data sets appears not comprehensible as well as the embedding of meta-analyses and Monte Carlo Simulations. Moreover, inconsistencies are noted when applying the PK/PD approach e.g. in the amoxicillin case study: - in 3.3.8 (step 8) it is stated: "For each case, the new daily dose will be defined as the one able to reach a PTA of 90 % for the least susceptible target pathogen". This principle was not respected in the case study: "With the proposed dose and due to	detailed the approach with the case study amoxicillin. The second approach is based on the population PK analysis of raw data to select the best PK models and estimate the parameter distributions, their covariance and the possible covariables (weight, sex, formulations, etc). The algorithm follows the recommendations in scientific literature. As it was a little more complicated, we do not described it in details. We can add in a new version references about the process and a figure of the algorithm. Based on this population PK analysis, we can simulate individuals to compute the different PDI and use them to analyse their distribution and simulate the dose needed to reach the target. We choose to apply the two concepts on our case studies to explain the process through examples. We agree with the comment that we applied a pragmatic approach to test the feasibility of the approach on selected cases and we share your opinion about the need to better define the conditions of application that requires an expert group work for a guideline. We share your concern about the needs of definition of the minimal requirements to apply the approach that can be done in the context of guideline development. Thanks for the comment. We will add a sentence to explain why Bordetella bronchiseptica was rejected as a target organism for amoxicillin because the cut-off value (32 µg/ml) is too high to be reach by the range of dose that we can explore. Sentence : The wild type population of Bordetella

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	the high MIC values for *B. bronchiseptica*, this target pathogen never reaches the PK/PD objectives. *B. bronchiseptica* is out of the therapeutic indication of amoxicillin administered by oral route to pig when one is optimising the dose." This deviation from the PK/PD approach was not sufficiently discussed, is it a limitation? What are the consequences resulting from this finding for this specific case study as well as for the PPHOVA approach in general? - PDTs reported for calves instead of PDTs of pigs were used although information of 3.3.4 (step 4) does not mention that PDTs from non-target animals can be used. This inconsistency was neither justified nor discussed or outlined as limitation.	bronchiseptica is ranged between 4 and 32 mg/L (Median=16 mg/L) which are very far from the range of concentrations reached with a dose of 20 mg/kg of amoxicillin (Figure 12, AUC_{24h} : 6 or 12 mg.h/L). For the purpose of the pilot study, we have excluded this bacterial species from the list of our target species. Thanks for this comment. We did not provide the criteria to select a PDT. We used a PDT derived from in vitro studies of the activity of amoxicillin on pasteurellaceae isolated from calves. As the pharmacodynamics activity is against bacteria, we have assumed that the potency of the drug on the wild type population is the same and independent from the animal origin of the isolates. This point must be mentioned in the document. Added sentence : The PDT was derived from time kill curve studies performed in vitro allowing characterization of the whole concentration-effect relationship between amoxicillin and target pathogens. We used PDT determined on bacterial isolates from calves in the lack of equivalent study performed with isolates from pig, considering that pharmacodynamics parameters of antimicrobial action are independent from the animal origin of isolates.
	Ad chapter 4. PK approach for withdrawal period adjustment: The formula used for extrapolation of withdrawal periods in itself considered mathematically correct, but results will only be reliable if certain preconditions are met. These preconditions are only partially mentioned and discussed in the text. In particular, we would like to	It is acknowledged that the methods are described in general terms. The reason for a more general approach in this reflection paper this is, that in the situation of the future project on dose optimization of the old antibiotics, the generated data

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	have some more information and guidance given concerning the following aspects: The most important information needed to use the approach are probably the tissue half-lives (terminal half-lives) and dose-linearity. Both terms need to be properly defined and explained in the context of their use. Differences in the set of information that underlie the computations may have a huge influence on the results, leading to inappropriate withdrawal periods and therefore to consumer risks. It should be made entirely clear to the reader, which precondition(s) must be met before the approach can be used – and in which cases the approach should not be used. If preconditions are not met (or necessary data to show this are not available), extrapolation of withdrawal periods would not be possible without further consideration. It should be discussed which alternatives exist and in which cases (supplementary) residue depletion data for the higher dose are necessary. In the current version of the reflection paper, the proposed approach was applied to two substances only (amoxicillin and oxytetracycline). The examples used are not fully valid based on the requirements given in section 4.4 of the text (see comments on the case studies). Further validation (i.e. comparison between predicted and real withdrawal periods) needs to be done before applicability for antibiotics in general can be considered as proven. **Ad chapter 5. Approach for addressing the risk for the environment:** Comments on ERA were provided by the German Environment Agency (Umweltbundesamt – UBA): This pilot project on dose optimisation is a necessary initiative – but there is some inconsistence with regard to the environmental assessment.	(hourglass approach) could vary enormously in quantity as well as in quality. Therefore the methods and strategies for every assessment would differ from case to case. This requires a versatile approach. Full residue studies becoming available is considered unrealistic. The need for supplemental studies may however emerge during the assessment of a specific case. This would largely depend on the quality and completeness of the submitted data package. We would like to avoid mentioning many requirements up front, which would restrict the versatility of the proposed methods. In the executive summary it was acknowledged that depending on whether more data would be available, the outcome of the test cases would differ from the present outcome. We believe a validation between predicted and real withdrawal periods using in vivo residue studies would be unrealistic. The number of case studies was necessarily restricted to two, which is limited, for reasons of feasibility and resources within the pilot project. It should be noted that the case studies were not meant to cover all situations (see also chapter 9), but rather as a test and an illustration. It is

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	One of the main critic point is that the pilot study is based just on 2 examples of antibiotics (AMO & OTC). Just 2 out of 5 "chemical classes of antibiotics" are met and it seems so that the project results shall be used (or extrapolated) for all antibiotics on the marked for which such dose optimisation would be necessary. **Ad chapter 6. Approach for addressing the risk for the target animal:** The proposed approach for the evaluation of target animal safety including the 7-step-model is supported in principle. A re-evaluation of the MOS, reassessment of the safety of the product in the target species under the condition of the optimized dosing regimen and the identification of toxicity target organs are considered as the three essential pillars, necessary to ensure target animal safety. However, while the principles can be supported, there are several concerns pertaining the implementation of those principles as exemplarily done for amoxicillin and oxytetracycline. Although, it is agreed that the total dose administered over a given period of time is essential to estimate adverse effects on target animal safety, the impact of treatment duration and the dosing interval on TAS is considered similarly relevant for different antimicrobials. Dosing intervals and dosing duration, therefore, should be taken into account for the re-evaluation of target animal safety under the condition of improved dosing and addressed in chapter 6 and in the examples on amoxicillin and oxytetracycline. As in the scope of this paper, target animal safety considerations are based on a re-evaluation of older studies and published literature, minimal requirements on data quality and quantity should be defined	acknowledged that there is no guarantee that the proposed method for the ERA will work in every situation. Amendments have been made in Chapter 6.2 to address the potential impact of a change of dosing frequency. As PKPD cannot be used to determine the duration of treatment, it is explained that generally this will not be changed except for circumstances such as described in the oxytetracycline case. At high level, the requirements for published literature

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	to enable a valid assessment. When possible, available guidelines like VICH 43 should be taken into account. As the evidence levels of the used data might differ significantly, it should be described, how results based on different data qualities have to be weighted. Therefore, a worst case approach might be prudent. If the available dataset does not meet the minimal qualitative and quantitative requirements, e.g., if margin of safety studies, data on reproductive safety or local tolerance are missing, it should be critically discussed, how target animal safety can be ensured. It seems that the appraisal of target animal safety in both examples could not be done with sufficient elaborateness due to a lack of primary data as e.g., for OTC, TAS studies in the target animal species only covered local tolerance. Therefore, it is the more concerning that in conclusion, the applicability of the proposed evaluation scheme was deemed adequate in both examples. The lack of crucial data or insufficient data quality in the examples should be critically addressed in order to ensure valid and reproducible results. If sufficient data in the target animal species are unavailable, the implementation of a safety factor might be prudent, e.g., if data gathered from laboratory animals and humans are transferred to farm and companion animals. The idea to pool studies and products has merit, unfortunately, a clear definition of what products can be considered "similar" and, therefore, for which products data can be pooled, was not given. Especially in the examples, it seems that data were not pooled according to the requirements previously specified in chapter 6, e.g., different routes of administration were not evaluated separately. It should be ensured that general recommendations/ requirements specified in chapter 6 are met in the examples and when not	references should not be any stricter than those required for a 'well-established use' application, as laid out in Volume 6B of Notice to Applicants. In addition, in regard to reporting requirements for studies, quality criteria could impact more widely beyond the scope of the pilot project. In practice, assessors refer to relevant guidelines (e.g. VICH, OECD) as a basis for evaluating study quality. Possible risk mitigation measures that may be implemented if a risk is identified are stated in Chapter 6 under individual steps. The conclusions for each of the case studies are set out in guarded language in Chapters 6.2 and 7.2. The limitations of the approach are discussed in Chapter 9.4. Limitations also related to the circumstances of the pilot project itself, with limited access to industry data and time available to complete the task (see comments above). It is noted in the RP that outside the pilot project further data would be sought to give greater confidence in the conclusions, but concluded that the data review approach would in principle be feasible for both cases.

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	possible, reasons, why exceptions can be made, should be given. **Ad chapter 9. Discussion and conclusions:** In general, this section could benefit from a more detailed discussion of the proposed approach and potential limitations: It is understood that the PPHOVA approach is extrapolating human PK/PD approaches to animals. PK/PD concepts established for humans have been used by CVMP to review dosing regimens in referral procedures but have always been considered together with clinical data. No explanation is provided in the report, if and how reliable PK/PD concepts established for humans can be used to predict clinical efficacy in animals without correlation to clinical data. In addition, PK/PD concepts are not established for all substances/classes of antimicrobials even in human medicine. In particular, for older substances/classes of antimicrobials information is missing on which PDI would be best to predict clinical efficacy. Thus, the limitations of this approach should be further discussed. In the report it is further stated that the PDI: AUC/MIC will be used as 'a point of departure' for all antimicrobial classes. This approach would need reliable scientific clinical data in support. It is noted that this approach would be equivocal at least for those antimicrobial classes where PDIs other than AUC/MIC are established to predict clinical efficacy e.g. C_{max}/MIC in aminoglycosides. In such situations PDTs for AUC/MIC will not be available. How can the PDT then be determined? Next to that, it is noted that there is very likely a substantial lack of information about PDTs in animals and target bacteria. Considering	Some amendments have been made to Chapter 6.3.1 to supplement the guidance advising when the pooling of data is rational. The correlations between the PK/PD indices and the clinical efficacy of different classes of antibiotics have been determined from experimental infection models developed in rodents (rats, mice), for human antibiotic therapy. Clinical studies in humans, whether prospective or retrospective, have helped quantify their levels of correlation with efficacy (clinical, microbiological) and propose threshold values (or critical values) for these indices associated with high cure probabilities (> 80-90%). This is already discussed in the chapter 9 as a limit of the proposed methodology. In the section, "need for a clinical confirmation" we aknowledge that one challenge in the application of PK/PD modelling in dose optimisation would be to have robust information on PDI and PDT in each drug/bug/animal species combination.

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	this aspect it appears that the PDTs used in the case studies have not been sufficiently justified (e.g. the use of PDTs derived from calves for use in the amoxicillin case study in pigs). The PDT is the key factor related to clinical efficacy. Consequently, lack of information or extensive extrapolation of this parameter is considered a substantial limitation of the PPHOVA approach. In addition, the recommendation to consider solely free plasma concentrations appears not to be sufficiently discussed. Depending on the clinical indication and the target pathogens, free plasma concentrations may not always be the appropriate surrogate for the target tissue biophase and this should also be considered as a limitation of the PPHOVA approach. As already mentioned by the authors, a limitation of the PPHOVA approach is that no recommendation on the duration of treatment can be made. With regard to the aim of the project to use the dose optimisation in the context of SPC harmonisation suggestions should be made/discussed how the duration of treatment can be addressed. Finally, a discussion/conclusion is missing whether the case studies under these conditions are representative to extrapolate the PPHOVA approach to different situations i.e. different substances/classes of antimicrobials, animal species, clinical indications, routes of administrations, pharmaceutical forms. For different situations it is very likely that there will be considerable	This point will be clarified in the general approach and in the case study. Sentence proposed. Protein binding of antimicrobials may affect the clinical efficacy of therapy. Only the non protein bound fraction of a drug in plasma can penetrate and equilibrate with the extravascular space. Penetration into the extravascular space is important as the majority of bacterial infections occur in the interstitial fluid of tissues or in other body fluids than blood. Moreover, it was shown that only the non protein bound fraction of an antimicrobial is microbiologically active. Standardized MIC determination were performed with a protein binding close to 0. [Zeitlinger, M. A., H. Derendorf, J. W. Mouton, O. Cars, W. A. Craig, D. Andes and U. Theuretzbacher (2011). "Protein binding: do we ever learn?" Antimicrob Agents Chemother **55**(7): 3067-3074.] The work was only a pilot project perform to explore the way to revise old drugs posology. Our conclusion is not extrapolable for all compounds and antibiotic classes. The purpose of the document was to define a process and to test it on 2 cases. The range of application and the conditions of applicability of the process will require more discussion. But basically, the concept can be applied on

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	data gaps leading to limitations already mentioned (e.g. the need for consolidated data, scientific evidence supporting the setting of PDI and PDT etc.). Thus, a prospect is missing whether the PPHOVA can finally be applied/recommended as a standard approach for future dose optimisation of established antimicrobials for use in animals. Concerning target animal safety and withdrawal periods, please be referred to the specific comments. **Ad chapter 10. CVMP Recommendations:** The recommendations 5, 6 and 7 are not supported based on the issues raised in the "Specific comments" section of this document.	pharmaceutical drugs used by intravascular and extravascular routes for treatment of acute and systemic infections where classical pharmacokinetics pharmacodynamics approach are used to design treatment or to perform bioequivalency studies between formulations.
2	Since the risk posed by antimicrobial resistance (AMR) is a growing threat on global scale, PAN Germany welcomes EMA's initiative for dose optimisation of veterinary antibiotics in terms of maintaining their use efficiency. However, we would like to point out that dose optimisation based on the PK/PD analysis, while serving the objective to ensure treatment efficacy in animals, is not an appropriate approach to prevent the emergence, selection and/or dissemination of resistant micro-organisms in bacterial populations in all compartments, including the environment. We agree that dose optimisation, which is mainly considered as an increase in dosages and application events, can lead to improved efficiency in animals and thus reduce the risk of AMR development in animals as well as reduce the risk of AMR transmission from animals to humans. However, in the worst case this benefit occurs at the expense of the environment. Higher dosages and longer treatment periods are likely to have a higher environmental impact, since a higher amount of substances and their residues are released into the air, water and	The CVMP agrees with these points. An optimised dose, leading to better efficacy and possibly a reduction of the risk for resistance in the target animals, will often lead to a higher total dose and therefore a higher exposure to the environment. However, in cases where the current label dose is not efficacious, there can be two situations in practice at present: (1) a higher dose is already applied (off label), which would mean that dose optimisation is basically an update of the label and will not increase the (environmental) exposure in practice; (2) the label dose is used which will not lead to cure and therefore further antibiotic treatment may be necessary, leading to further (environmental) exposure. Therefore, the CVMP believes that in practice, dose optimisation of certain veterinary antibiotics will not have a major impact on environmental exposure. The CVMP acknowledges that AMR in the environment is a

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	ground via stable and exhaust air, slurry and manure. Consequently, the risk of AMR development in the environment increases. The conflict of interests between maintaining the availability of old antibiotics for the treatment of bacterial infections and a consistent environmental protection should be communicated as a limitation to the overall objective of this pilot study. However, the fact that possible negative effects of dose optimisation on AMR development in the environment are not taken into account due to insufficient data is not justifiable and is not in line with the One-Health approach (https://www.who.int/features/qa/one-health/en/). Even if in both cases of the pilot study (AMO and OTC) an increase of efficiency can be achieved, while no unacceptable environmental risk is to be assumed, an increased dosage might result in an unacceptable risk to environmental compartments in other cases. AMO and OTC just represent 2 out of 5 antibiotic classes. Therefore, the results are not suitable to serve for an extrapolation to other authorized veterinary antibiotics, for which dose optimisation is considered necessary, without any further test methods have been applied to exclude environmental risks with a higher accuracy.	relevant issue to consider, however more work needs to be done in order to provide data and tools for evaluation, which would eventually facilitate a risk characterisation. The issue may be relevant for all veterinary antibiotics and not only for those where dose optimisation is needed. Therefore, consideration of AMR in the environment should be considered generally, and was therefore not included as a specific item in this reflection paper.
	PAN Germany has been campaigning for better protection of the environment from veterinary drug entries and AMR development for more than six years and has critically accompanied the revision of the veterinary medicine law at EU level (https://pan-germany.org/tierarzneimittel-uebersicht/). We are committed to ensuring that precautionary measures are the most important for effective control of AMR from animal husbandry. The avoidance and reduction of veterinary medicinal products through an increase of animal health can evidently lead to a relief of the environment and	The reduction of antimicrobial use in veterinary medicine required to limit their use when necessary to treat and cure bacterial infections to protect animal health and welfare. Use of optimised old drugs in a context of better veterinary diagnostic will probably contribute to reduce exposure of environment.

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	thus to a reduction of the risk of AMR development in the environment. Preventive measures to promote animal health mainly relate to the adaptation of improved husbandry practices and thus also affect related policy areas.	
3	**Safety of consumer:** When any new system is introduced it should be ensured that the new system gives results comparable to those of the existing system. This system was used when the statistic approach was introduced by guideline EMEA/CVMP/036/95 (Approach towards harmonization of the withdrawal periods). According to EMEA/CVMP/036/95 for old chemical entities the withdrawal time corresponded to the time point at which the concentrations of residues in all tissues for all animals fall below the respective MRLs. For new chemical entities withdrawal periods were calculated in accordance with Volume VIII of the Rules governing Medicinal Products in the European Community, data should be sufficiently adequate to use a statistical method. Conclusion: When the statistical method of calculation of the withdrawal period began to be used, an assessor could (and can) check whether the data in the calculated withdrawal period are (with some probability) below MRL, i.e. the statistical method ensure at least the same standard of establishment of the withdrawal period as the old method of establishment of withdrawal period. The project followed the establishment of the WDI (withdrawal interval) by PK/PD modelling, which is used by FARAD in the U.S.A. That PK/PD modelling provides a rough estimation of the WDI (withdrawal interval) for substances with linear kinetics, and is intended for veterinarians, who use products with those substances off label. WDI is established for substance, dose and route of administration and not for specific product and value of WDI is	The Comment is noted. It is agreed that the methodologies of the guideline and of this RP are different. Of course the outcome of the modelling approach is as good as the data that are used as the input. The same is true for the conventional methods. The question is however, whether or not the proposed approach to extend the authorised WP will provide sufficient safety. The CVMP is convinced that it will. The collection of all available data from dossiers and literature will allow a reliable estimation of the parameters. Moreover, within the approach one may select the parameters on worst-case considerations. In addition, it may be possible to add safety spans in cases where the data leaves significant uncertainties. Moreover, the CVMP believes that the methodology needs to provide an adequate prediction of a safe WP, and this does not necessarily mean that it should aim at comparable results (when compared to the conventional studies). For example, if the new method gives a better prediction than the conventional method, then the result will be different but acceptable. The CVMP wishes to point out that the current procedures for establishing WPs also uses a model with various assumptions in relation to PK processes, and has been accepted since the 90's (without having studied the predictive value of its results in field situations).

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	recommendation only and WDI does not replace the withdrawal period for the product. It is theoretically possible, if PK/PD modelling is used for determination of the withdrawal periods, to use the high safety span for consumer's safety in cases where the data leave significant uncertainties, but on the other side this approach can lead to the determination of unnecessarily long withdrawal periods and thereby to increase costs for farmers. **Precautionary principles:** From view of food law - Commission Regulation No. 178/2002 article 7 – the precautionary principles **are valid**. Following information are mentioned in point 15 of the Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance: "RECOGNISES that due to the complexity of the problem, its cross-border dimension and the high economic burden, the impact of antimicrobial resistance goes beyond its severe consequences for human and animal health and has become a global public health concern that affects the whole of society and requires urgent and coordinated intersectoral action, where necessary based on the precautionary principle". http://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-antimicrobial-resistance/ From view of the safety of consumer PK/PD modelling could be used for a rough estimation of the "withdrawal period" which may not provide consumer safety in all cases. Therefore, standard or at least the restrictive confirmatory study (according to valid VICHs) should be performed for verification of the PK/PD modelling – for example: performance depletion study 3 time point / 3 animals / point, or	The comments are noted The performance of a confirmatory study for tissues and full residue studies for milk and eggs, would of course be preferable, but this pilot project was aimed at testing non experimental methods in the context of the dose optimisation of the established antibiotics.

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	specific approach could be used for injectable product in some cases (mentioned in the current guideline VICH GL 48). For milk and eggs - the standard depletion studies should be performed. **The view of safety of the consumer the Commission could provide the financial support to the industry for products where needed from view of antimicrobial resistance.** At the present time there is valid system of cascade (in conformity with the article 10 of Commission Directive 2001/82 EC); which enables veterinarians to use VMP off label, if desirable. The cascade system is also mentioned in the new veterinary legislation - REGULATION (EU) 2019/5 that follows in principles of the article 10 of Commission Directive 2001/82 EC, it would be possible and useful to develop the cascade system similarly as it is carried out within the scope of FARAD. At more – if veterinarian uses the veterinary product in cascade system - zero tolerance in monitoring system is not valid yet and according to Commission Implementing Regulation (EU) 2018/470 valid limit is established by the legislation. **Responsibility:** According to valid EU rules a marketing authorisation holder (or an applicant) is currently responsible for the veterinary medicinal product. If withdrawal period is established by PK/PD modelling, who will have the legal responsibility for results? Who will be responsible, if positive findings of residue concentrations are determined at monitoring for residues presence? Which of the following subjects: Commission, CVMP, the marketing authorisation holder or a farmer?	A change in dose may have implications for target animal safety (TAS), withdrawal periods (WP) and the environmental risk assessment (ERA). This implies the need for many studies, which is unrealistic for the reasons mentioned in the report. The aim of the project is to find alternative, non-experimental approaches. Requiring data may lead to decreased product availability, which could have a negative impact on the antimicrobial resistance problem. It should be noted that the cascade does not provide for the possibility to use a higher dose for an authorised product used in the authorised target species for the authorised indication. It is our understanding that the responsibilities will not change as a result of the methods used for the WP calculation. The discussion on data gathering has indeed to be held, but is not considered within the scope of this RP. It is acknowledged that the methods and the algorithm are described in general terms. The reason for this strategy, which seems to be in contrast

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	Quality on input data and guideline: the reflection paper mentioned "hourglass approach" of collection of data. The system of collection of data, quality of input data and methodology of all steps for established withdrawal periods on basis of PK/PD modelling should be clearly described in guideline. If the new withdrawal period is calculated by PK/PD modelling and WP is used for the product, will the marketing authorisation holder be able to submit a new depletion study indicating a shorter withdrawal period according to valid guideline VICH 48, which is internationally harmonized and will that shorter withdrawal period be accepted? Possible consequences: If the new depletion study is accepted, discrepancy of the two withdrawal periods will occur. **User safety:** The text does not contain any comment on possible impact on user safety caused by the possible changes of the doses of the veterinary medicinal products. Dose optimisation of established veterinary antibiotics and possible higher doses should also concern user safety assessment as it depends on the dose of the veterinary medicinal product. There is the CVMP „Guideline on user safety for pharmaceutical veterinary medicinal products" (EMA/CVMP/543/03-Rev.1) that has been in place since 2010 and „Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014) since November 2018. The quantitative risk assessment consists of comparing the levels to which the user is exposed with the levels when no adverse effects are expected to occur. Therefore, with changed posology, there will be changes in the risk for the user of the veterinary medicinal products	to the situation in guidelines where explicit requirements are described in great detail is, that in the case of dose optimisation of the old antibiotics, the generated data (hourglass approach) could vary enormously in quantity as well as in quality. Therefore the methods and strategies of choice for any assessment will differ from case to case. An in depth discussion/description was therefore avoided. For a MAH the submission of new residue data in order to further refine the WP would of course be possible The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and the user safety assessment is necessary. This aspect should also be taken into account in the document, the group should consult experts to address the user safety and the text of the reflection paper should be amended, i.e. a chapter on approach for addressing risks for the users should be added. **Risk for the environment** Optimised dose will lead to higher PECs and this will anyway lead to ERA Phase II assessment. **Target animal safety – local tolerance** In reaction to the part of the reflection paper "When pooling studies within different product groups as outlined above, some attention may need to be given to the relative bioavailability and **differences in the PK profile for the active substance** from different product formulations (for example, long-acting compared to immediate release injections). When calculating the MOS, studies from different products should only be pooled if the PK profiles are similar (also considering that TAS studies are not anyway able to determine a precise MOS due to the dose multiples used). Relevant information may be found in the pharmacokinetics studies for the individual products." – we would like to comment as follows: This above text cannot be supported, as the examples are not considered as fully relevant. Even in same group of active (e.g.	It is not correct that any increase in dose would automatically lead to a phase II assessment. It is still possible that the assessment remains in Phase I and stops there. However, it is expected that most of the established antibiotics are already in Phase II with the current dose and that therefore Phase II data will be normally available. The population PKPD approach is able to manage and integrate data from different routes of administrations and formulations. The approach can distinguish the different profiles of absorption (as shown for amoxicillin) and will help to reveal the dose (range) necessary to have a correct potency against the targeted pathogen. So different formulation with different PK will be considered independently even if the pop PKPD will consider the similarity in term of distribution, metabolism and excretion to determine the clearance parameters. The quoted text is included in '*Step 1: Determine the TAS profile for the **active substance** …according to the revised dose, pharmaceutical form and **route of administration**'*.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	amoxicillin trihydrate) administered as suspension for injection with LA properties there are significant differences in chemical composition (excipients e.g. aluminium stearate, different oils, differently fractioned) and physico-chemical properties, that influencing local irritability. And also vice versa – local irritability influencing also PK profile (at least absorption) and finally also efficacy (levels achieved, speed of absorption/penetration) and also residue depletion mainly at injection site and surrounding. The question is if we could make pooling studies in such cases – considering MOS for amoxicillin as active. Also different exact routes of administration and irritability should be considered (e.g. IM vs SC) and also differences across the species.	It is proposed to pool studies from groups of products as indicated in 6.3 (same active substance, target animal species, route of administration and pharmaceutical form). It is noted that when calculating the MOS for the active substance, '[TAS] *studies from different products should only be pooled if the PK profiles are similar*.' Further information has been added regarding the acceptable level of PK variability. The example given is relevant, but not exclusive. In relation to the impact of differences in excipient formulation on local tolerance/irritability, this is addressed in Step 6 of the process: '*Further considerations for the conclusion on the safety and benefit-risk for* ***individual products***' , where it is stated that '*Consideration should be given to the systemic and* ***local safety of the excipients*** *in the individual formulation in relation to any impact of the concurrent dose increase*.' An additional sentence has been added: '*Product-specific studies, e.g. injection site safety, should be reviewed*.' Further, in the case study relating to oxytetracycline injections, it was noted that although oxytetracycline itself is plausibly an irritant, excipients may also impact on local tolerance and that this should be taken into account on a product-by-product basis. It was the purpose of the investigation. Even if different

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Dose optimisation – example of amoxicillin: There should be taken into account not only PK for single dose of certain amount (e.g. 40 mg of active/kg bw/day), but different regimen of dosing should be considered (according clinical studies performed and available PK data might be more appropriate to dose amoxicillin 2 (or may be 3 times) per day to achieve the most proper dosing –please refer to table with the respective pathogens/timing of dosing (Table 12) . Also total duration of the treatment is not involved in simulation model properly – so different scenarios should be performed ref PK (total dose once, total dose divided 2(3) times per day, "new" dose established and administered 2 (3) times per day, days of total treatment duration in different scenarios of dose/interval combinations) – and this is not covered by proposal. **Questions as a conclusion:** How it can be concluded, that the dose simulated is really the most proper one? Why not (based even on the data submitted as an example) conclude that can be sufficient/effective lower dose administered twice/three times daily for the respective respiratory swine pathogens? How we can consider/address specific cases of certain antimicrobials: e.g. macrolides vs respiratory tract infections – and specificities of their PK and affinity to macrophages interference with immunodeffensive mechanisms etc.?	dosage regimen leads to the same exposure, the question is about the practicability of the administrations. (to be introduced in the text). As discussed before. The question of practicability The pilot study was limited to 2 cases. The considerations of the approach for the other antimicrobial classes requires going a step further to establish guidelines and review the different classes.
4	EGGVP welcomes this reflection paper and fully agrees and supports its rationale, problem description, project objectives and approach.	The positive feedback is much appreciated.

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	The paper uses balanced and pragmatic approaches under a robust way. Implementing it would allow keeping a broad arsenal of safe and effective treatment options available in the future. The draft is written in a deeply professional way; the principles are well designed, logically and intelligibly described in the draft proposal, while applying scientifically sound methods. EGGVP has no additional comments or remarks to this reflection paper.	
5	AnimalhealthEurope welcomes this well-written and balanced Reflection Paper and appreciates the opportunity to provide comments. This reflection paper is very technical and the pharmaceutical industry recognises the effort done for proposing a global approach trying to avoid the generation of new data. It is understood that as with the amoxicillin and oxytetracycline studied cases, data that might be provided to support such an *in-silico* set-up of the dose, are often limited and may be far from the applicable current standards: such data package should suffice for applying the proposed methodology and this could be reiterated in the reflection paper. AnimalhealthEurope supports the hour glass approach to the issue, which will help ensure the best use is made of available information. Lastly AnimalhealthEurope suggests a reminder in the preamble to the impact dose optimisation may have on Animal/Public Health due to decreased availability of antimicrobials for animal health, if full updated data packages were required for this process.	The positive feedback is much appreciated. It is acknowledged that the dossiers of the established products may originate from several decades ago and will almost by definition not be up to current standards. It is also acknowledged that requiring full data packages would not be feasible at all and would impact on the availability of veterinary medicines. Indeed, label doses need to be correct and harmonisation of SPC will take place under the new veterinary legislation, and that means that we will need to address dose optimisation in any case in one way or the other. Therefore, it follows that any dose optimisation approach should be able to deal with less-than-optimal data sets. On the other hand, this will not automatically imply that the proposed methodology will work in each and every situation. In cases where one or more of the non-experimental approaches fail, other approaches may need to be found where possible, and this will require a careful case-by-case assessment.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6	1	Comment: The term 'antibiotics' does not include semi-synthetic or synthetic substances e.g. fluoroquinolones or sulphonamides. Thus, it is proposed to replace 'antibiotics' by 'antimicrobials' both, in the title and in the entire document. This would be in line with the wording of current CVMP guidelines e.g. EMA/CVMP/627/2001-Rev.1, EMA/CVMP/AWP/706442/2013. In addition, an explanation of the term 'antimicrobial' should be included either in the glossary or as a footnote: a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Antiparasitics and substances classed as disinfectants or antiseptics are excluded from this definition OIE Terrestrial Animal Health Code definition). In the context of this report, the focus is on compounds acting against bacteria. Proposed change: Reflection paper on dose optimisation of established veterinary ~~antibiotics~~ **antimicrobials** in the context of SPC harmonisation	Agreed.
15-16	1	Comment: Changes in dosage may not only have an impact on efficacy, withdrawal periods and ERA, but also on user safety. According to current guidance, user risk assessment (URA) has to be conducted product-based rather than substance-based. A 2-4 fold increase in dosage should not generally be considered as irrelevant in terms of user safety concerning the active substance(s) as well as the excipients. Higher doses might necessitate some kind of revised user safety assessment and maybe changes in user warnings, especially for injectable	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products. This aspect should be added to the reflection paper and some guidance may need to be given. Proposed change: Please modify the text as follows: "However, a change in dose may have implications for target animal safety (TAS), withdrawal periods (WP), ~~and~~ the environmental risk assessment (ERA) **and user safety (URA)."**	the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
16	3	Comment: The user risk assessment is based on the dose of the veterinary medicinal product; therefore the change in dose will lead to change in user safety that needs to be reassessed and this aspect also must be implemented into the reflection paper. Proposed change (if any): the following text should be added: (ERA) **and user safety (URA)**.	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor

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			quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
30-33	1	Comment: We do agree that PK/PD and PK modelling in itself are well-established scientific approaches, but they have so far not been validated for dose optimisation and for determination of withdrawal periods for VMPs, respectively. E.g. Equation 2 provides a quantitative approach using some PK parameters rather than a full PK model. To establish a validated model for determination of withdrawal periods, it would be necessary to compare WPs predicted by the model with those derived from study data (residue depletion data at different dosages would be needed). This should be done for various substances as also mentioned by Martin-Jimenez et al. 2002. Proposed change: Please modify the text as follows: "Non-experimental approaches ~~based on well-established scientific principles~~, were used, namely PK/PD modelling for dose optimization, PK modelling for WP adjustment,..."	The comment is noted. Text has been adapted.
30	3	Comment: PK modelling for WP adjustment is not standard principle for establishment of the withdrawal period for the veterinary medicinal product for major species in EU. In connection with availability of the product for minor species the setting of a	The comment is noted. Text has been adapted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		withdrawal period in the minor species is possible based on overall pharmacokinetic parameters (e.g., plasma terminal elimination half-life) could be an option for certain compounds (e.g., compounds distributed mainly in extracellular fluids/plasma only) - EMA/CVMP/SWP/66781/2005–Rev.1. – Note: this guideline is not internationally harmonized. Proposed change (if any): text "based on well-established scientific principles" should be deleted.	
43	1	Comment: There is no clear definition if "amoxicillin" or "amoxicillin peniciloic acid" was used for this project. The peniciloic acid would be the more relevant compound with regard to the environmental risk assessment (because of fast transformation). Proposed change: Please clarify.	The substance used for the case study is amoxicillin.
59-61	1	Comment: The two examples of AMO & OTC do not result in an unacceptable risk to environment by doubling of the doses; but risks from antibiotic authorisations (florfenicol, thiamulin) are known and it might be (and will be) possible that doses change will result in unacceptable risks to environmental compartments. In all these cases the benefit risk has to be revised. Proposed change (if any): -	This is acknowledged. Indeed, any increased risks will ultimately need to be considered in the benefit-risk evaluation. This is explained in paragraph 5.3.8.
129-131	2	Comment: PAN Germany calls for a strict ban on the use of such antibiotics in animal husbandry, which are of priority importance for human medicine. Since the new EU regulation on veterinary medicines, which is not yet implemented, gives the possibility to reserve certain antimicrobials for humans only, we	The comment is noted, however considered outside the scope of this particular reflection paper.

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		demand a prompt consistent EU-wide implementation (https://oeilm.secure.europarl.europa.eu/oeil-mobile/summary/1559301?t=d&l=en). Proposed change (if any): In addition, due to concerns about antimicrobial resistance (AMR) in humans, **animals and the environment, there is an urgent need to ban the veterinary use of antibiotics with priority importance for human medicine** (e.g. fluoroquinolones, 3rd- 4th-generation cephalosporins, and colistin).	
140-143	2	Comment: The objective of reducing AMR should be tackled by a comprehensive approach considering the AMR development in animals, humans and the environment. In case of dose increase, an increased burden on the environment with residues of active substances and their degradation products is to be expected. Thus, the risk of AMR development in the environment will be increased.	Point noted. However, limitation of AB use should not be accomplished by using doses that are too low to be efficacious. Responsible use of ABs also includes that animals that are treated receive the appropriate dose.
147-150	1	Comment: See comment on lines 15-16. Proposed change: "A change in the posology of a product, in particular an increase in the dose or in the dosing frequency, can have implications for target animal safety (TAS) and also, in the case of food producing species, for the withdrawal periods (WP), ~~and~~ the environmental risk assessment (ERA) and **user safety (URA)."**	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some

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			scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
150	3	Comment: please see the comment for line 16 and general comment on user safety Proposed change (if any): the following text should be added: (ERA) **and user safety (URA)**.	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover

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			the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
156-165	1	Comment: In general, non-experimental approaches might not be possible in situations when the underlying data are inappropriate, insufficient, or data are not available at all. Proposed change: The following sentence should be modified as follows: "However, such approaches might not be possible in all situations or for all veterinary antibiotics ~~(e.g. in the case of non-linear PK~~) **when the underlying data are inappropriate, insufficient, or data are not available at all**."	Text has been changed.
170	3	Comment: please see the comment for line 16 and general comment to user safety Proposed change (if any): the following text should be added: safety of consumers, target animals, **users,** and the environment;	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor

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			quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
176-202	1	Comment: The aim(s) of the project including specific objectives is clearly outlined in the introduction chapter 1. A corresponding discussion and conclusion on whether these aims are met or not is, however, missing in chapter 9. Proposed change: It is proposed to include in chapter 9 a discussion and conclusion on whether the aims outlined in chapter 1 are met or not.	The chapter already described the conclusions, notably by presenting the 2 cases studies and their respective discussion/conclusions.
178	3	Comment: please see the comment for line 16 and general comment to user safety Proposed change (if any): the following text should be added: depletion data**, URA data,** ERA data	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some

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			scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
204-205	1	Comment: "The non-experimental approaches developed were based on scientific considerations, and on well-established modelling techniques." Proposed change: This sentence might need modification. Please see previous comment on lines 30-33.	Text has been modified.
208	3	Comment: please see the comment for line 16 and general comment to user safety Proposed change (if any): amend the line accordingly: address the safety of ~~both~~ **users,** environment**,** and target animals	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products

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			will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
264	3	Comment: please see the comment for line 16 and general comment to user safety Proposed change (if any): the following text should be added: approaches (**URA,** ERA and TAS)	The CVMP does not consider it necessary to develop specific methodologies for the URA, because there will be no issue regarding replacing "new studies" by modelling approaches. It is expected that the relevant toxicity data will already be available and that any increase in exposure can be compared to the PODs of the existing data. Moreover, the CVMP notes that the formulations and strength of the products will not change and that therefore some scenarios (e.g. spilling of droplets on skin) will change neither qualitatively nor quantitatively. It is also expected that the most important risks have already been identified on the label and that the

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			existing label warnings would also cover the situation where a higher dose is used. Of course, there is always the possibility to further address the URA where needed, but the number of cases where this is needed is expected to be quite small.
270-272	1	Comment: In the example provided, a 2-fold increase in dose requires an extra 3 days withdrawal period. These extra 3 days would then be added to all other products, whose dose is 2-fold increased. However, other products may have a different posology and/or bioavailability (also in regard to the dose change) leading to differences in half-lives. This would not be taken into account if only one mean half-life is used in Equation 2 and the same number of days is added to all products, which might result in inappropriate withdrawal periods. In our opinion extrapolation of withdrawal periods should be conducted for each product separately (as also mentioned in lines 633-637). Proposed change: The text should be amended to explain that extrapolation of withdrawal periods should be conducted for each product separately taking into account differences in posology and/or bioavailability.	As explained in chapter 2.2, the pilot project, was aimed at the dose optimisation and harmonisation at the level of the veterinary medicinal product, not at the level of the pharmacologically active substance. Nevertheless, the modelling and review approaches will benefit from the input of all relevant information across products, and in addition the information from other sources such as published papers. Therefore, the data will be collected at the level of an *animal species-disease indication-route of administration-pharmaceutical form* level (as in the case studies). The information will be integrated in the review approaches (ERA and TAS) and in the selection of model parameters (dose and WP). Of course, the applicability of data across products will need to be considered. It should be noted that one of the conditions for using the WP model is that

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			distribution is complete at the MRL level. The influence of absorption processes on the plasma-time profile at this later phase will be negligible. Using multiple data sources for the estimation of the PK parameters will actually strengthen the reliability of these estimations and will result in more reliable WP extrapolation as compared to using data on a single product basis.
299-376	1	Comment: This chapter is on the appropriateness and the applicability of (modelling) approaches to address doses in human medicine. It reviews PK/PD approaches that have been used in human medicine and gives examples for PDIs established for beta lactams, fluoroquinolones and aminoglycosides in humans. It is noted that even in human medicine PK/PD relationships are not established for all antimicrobial substances/classes. In particular for older antimicrobials information on potential PDIs to predict clinical efficacy is not available. This is of concern and should be addressed in this chapter. For target animals species distinct PK/PD approaches have not been established, yet – Are there any? - This should be also mentioned for reasons of completeness. It is understood that the PPHOVA approach is extrapolating human PK/PD approaches to animals. Thus, a rationale should be included to explain why PK/PD approaches established for humans can be extrapolated to animals. In particular, it should be explained how human derived PDIs can be used to predict clinical efficacy in animals without any correlation to clinical data. Proposed change:	A chapter on the applicability of the method is already presented in the report. The beginning of the PK/PD even for human medicine was develop on animal models, notably in rodent and in mice, given weight to extrapolate the approach in veterinary medicine. Also, a chapter on the limit of the methodology is also already included.

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		The chapter should be revised taking into account the comments made above. It is suggested to include a paragraph on the appropriateness and the applicability of (modelling) approaches to address doses in veterinary medicine. The limitations of this approach should be outlined.	
301-312	1	Comment: PK/PD approaches are used pro- and retrospectively, this should be supplemented. Proposed change: In the last 20 years, the **prospective** PK/PD approach has … In human health, the PK/PD approach is also used **retrospectively** …	Agreed.
346-349	1	Comment: It should be taken into account that other authors considered also the PDI C_{max}/MIC (i.e. a C_{max}/MIC >10) as a relevant clinical predictor for FQs (e.g. Schentag, J.J, 2000; Clinical pharmacology of the fluoroquinolones: studies in human dynamic/kinetic models; Clin Infect Dis. 2000 Aug;31 Suppl 2:S40-4) Proposed change: It is proposed to include also the C_{max}/MIC > 10 as relevant clinical predictor for FQs.	Agreed.
355-357	1	Comment: The best PK/PD index … the three PK/PD indices. Proposed change: Please provide a reference for this statement.	Agreed.
393-394	1	Comment: Antimicrobial concentrations in relevant biophases may be different to that in plasma. Concentrations in the biophase may be higher in respiratory infections e.g. macrolides in pulmonal epithelial liquid linen (PELF) or they may be lower in	Agreed.

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		gastrointestinal infections when excretion of parenteral administered antimicrobials into the GIT is low. Thus, the general conclusion 'So the PK/PD integration is appropriate for acute infections in vascularized tissue' is not agreed to. Proposed change: It is proposed to replace ~~…So the PK/PD integration is appropriate for acute infections in vascularized tissue.~~ … by **Irrespectively, using plasma concentrations for PK/PD integration is a simplified approach that may not always be the appropriate surrogate for the target tissue biophase**. This limitation of the PPHOVA approach should also be addressed in the chapter 9.1.3 Limitations of the modelling approach.	
403	1	Comment: It is recommended to use one term in line with the glossary and avoid confusion. Proposed change … ~~threshold value (or critical value or PDT) of the PK/PD index~~ … … **target value of the PK/PD index (PDT)** …	Agreed.
409-411	1	Comment: Can the PPHOVA approach be applied when one or all questions (Is there a dose linearity? Is there a difference in bioavailability between products? Is the free plasma concentration representative for the target tissue biophase?) will be answered with 'no'? Proposed change: A respective conclusion should be drawn at the end of this chapter with regard to which PK data are appropriate and viable for the PPHOVA approach. It is also suggested to address potential limitations on PK data in the chapter 9.1.3	The capacity to analyse a range of dose with the simplest model (equation 1) requires a dose linéarity. If the PK is non linear, a PK model to describe the time concentration according dose should be used if available. We assume the dose linearity for the PPHOVA. As stated in the text, the differenceof availibility between formulations can be

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		"Limitations of the modelling approach".	taken into account as we do for oxytetracyclin. We assume that plasma is representative of extravascular phase. We add a sentence for special case which can necessitate a more sophisticated PK model to perform the analysis.
416-418	1	Comment: The explanation on the mode of action and its relation to the pharmacological class is not fully comprehensible. Proposed change: The mode of action of the active substance ~~and~~ **depends on** the relationship between concentration and bacterial killing rate ~~must be defined.~~ ~~According the pharmacological class of the active substance, the mode of action~~ **and** can be defined as time-dependent or concentration-dependent.	Agreed.
420-421, 426	1	Comment: The explanation of ECOFF is not in line with the definition provided in the glossary: 'measures of a antibiotic MIC distribution that separate bacterial populations into those representative of a wild type population, and those with acquired or mutational resistance to the molecule.' Proposed change: (ECOFF), which is the MIC value **separating** ~~the identifying the upper limit of~~ the WT population **from that with acquired or mutational resistance (non-WT population)**. The ECOFF definition in line 426 should be revised, accordingly.	Agreed, an harmonisation of the ECOFF definition will be done, as follows: "Measures of a antibiotic MIC distribution that separate bacterial populations into those representative of a wild type population, and those with acquired or mutational resistance to the molecule"
434-441	1	Comment: Guidance is needed on how answers to the questions raised in lines 434 to 441	Such information would need to be

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		can be interpreted. Which PD data are appropriate and eligible for the PPHOVA approach? It is noted that use of MICs at or below the ECOFF in PK/PD integrations would not be 'dose optimising' since bacterial populations with acquired resistance can be expected following the use of established antimicrobials for a long time. If the ECOFF is used bacteria with decreased susceptibility are not taken into account that may have developed after a substance has been used for a long time. Proposed change: A conclusion should be drawn at the end of this chapter on which PD data are appropriate and viable for the PPHOVA approach e.g. recent MIC values (most preferable from the last 5 years) should be considered which are representative for the respective bacterial population that is intended to be treated. It may also be useful to address potential limitations of PD data in the chapter 9.1.3 Limitations of the modelling approach.	presented if a guideline is developed, but is considered beyond the scope of this Reflection Paper.
442-462	1	Comment: Reference is made to comment above on lines 299 – 376. Proposed change: For target animals species distinct PK/PD approaches have not been established, yet – are there any? - This should be mentioned for reason of completeness. It is understood that for the PPHOVA approach human PK/PD should be extrapolated to animals. Thus, a rationale should be included to explain why PK/PD approaches established for humans can be extrapolated to animals. In particular, it should be explained how human derived PDIs can be used to predict clinical efficacy in animals without any correlation to clinical data. The limitations of this approach should be outlined and should also be addressed in the chapter 9.1.3 Limitations of the modelling approach.	Comment noted. It should be noted that the human PK/PD models were originally developed from animal models.

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459-462	1	Comment: The suggestion to use the PDI: AUC/MIC as 'a point of departure' for all antibiotic classes is not agreed to. This simplified approach would need scientific clinical data in support. It is noted that this approach would be equivocal at least for those antimicrobial classes where PDIs other than AUC/MIC are established to predict clinical efficacy e.g. aminoglycosides. In such situations PDTs for AUC/MIC will not be available. How can the PDT then be determined? Proposed change: The suggestion to use the PDI: AUC/MIC as 'a point of departure' for all antibiotic classes should be critically reconsidered unless the approach is supported by sound scientific clinical data.	Please refer to Toutain et al., 2017 and Nielsen and Friberg, 2011/2013. AUC/MIC is used as point of departure, however in our case study we consider also T>MIC when it is considered as best predicator. Regarding the need for clinical confirmation, this point is discussed at the end of the report.
479-481	1	Comment: In case of lack … in human medicine. The sentence is not clear as data from experimental or pre-clinical trials in the target animal species also relate to "veterinary pharmacology". It is further noted that there is very likely substantial lack of information about PDTs in target animal species and target bacteria. This is a considerable limitation of the PPHOVA approach because the PDT is the key factor related to clinical efficacy in animals. This substantial limitation should be outlined in this chapter as well as in chapter 9.1.3 Limitations of the modelling approach. In addition, justification should be provided to explain why the PDT can be derived from experimental or pre-clinical trials in the target animal species or can be supported by data obtained in human medicine without any correlation to clinical data in the target animal. Proposed change: In case of a lack of available information ~~from veterinary pharmacology~~, the PDT can be derived from available data from experimental or pre-clinical trials in the	Comment noted, however this point is already aknowledged in the report in the "feasibility section" where we clearly mention that "For old antibiotics, the PK/PD integration approach is eligible to dose optimisation". In the treatment of acute diseases in animals when the substance belongs to an antimicrobial class with scientific evidence from experimental and clinical trials supporting the setting of PDI and PDT.

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		target animal species or supported by pharmacological and clinical data obtained in human medicine. Please revise the chapter by taking into account the comment above.	
491-492	1	Comment: Please see previous comment on the MIC cut off (lines 434-441). Use of MICs at or below the ECOFF in PK/PD integrations would not be 'dose optimising' since bacterial populations with decreased susceptibility/acquired resistance are not taken into account that may have developed after a substance has been used for a long time. Recent MIC values (most preferable from the last 5 years) should be considered which are representative for the respective bacterial population that is intended to be treated. Proposed change: … and ~~the~~ **recent** MIC distribution **profiles** ~~of the wild type population with a MIC below or equal to the ECOFF~~ **that are representative for the target bacterial population intended to be treated**.	Agreed, an harmonisation of the ECOFF definition will be done, as follows: "Measures of a antibiotic MIC distribution that separate bacterial populations into those representative of a wild type population, and those with acquired or mutational resistance to the molecule"
493-494	1	Comment: This "core" part of the PPHOVA approach is very hard to understand, the purpose of this step becomes not entirely clear and the algorithm of the procedure is not comprehensible. It is understood that depending on the availability of PK data the first approach will be applied when" summary PK parameters" are available and the second approach will be used if "pharmacokinetic raw data" are available. Nevertheless, it is unclear why the first approach is related to the PDI: AUC/MIC and the second approach is related to the PDIs: T>MIC, C_{max}/MIC. If the decision on which approach will be used is dependent on the availability of PK data, then it appears illogical not to consider all three PDIs in each approach.	We have introduced text modifications to be more precise about the different approaches. As explained, the first approach can be used to estimate a daily dose based on PK parameter summary (AUC, Cmax). The second can be used to analyse the effect of dosage regimens on the distribution of PDI (AUC/MIC, Cmax/MIC, T>MIC) for different time period (1^{st} day, x day). .

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		In other words, why does the first approach apply only for AUC/MIC and the second to only T>MIC, C_{max}/MIC? In addition, for both approaches it is stated "…to estimate the distribution of the PDI values" and "to calculate the PTA of the PDT". Are these different aims? The purpose of the calculations needs to be clarified. Next to that, a meta-analysis can be performed for the first approach but a meta-analysis is not proposed for the second approach. Is there a reason for that? Moreover, a Monte Carlo Simulation should be performed in both cases, but it is not explained what is simulated in which way and for which purpose. Proposed change: It is highly recommended to revise this chapter for a better understanding of the algorithm of the step 6. It is also suggested to include simple examples for the first and second approach, each with an example for Monte Carlo Simulations together with a graph (if appropriate) to describe the modelling process. Examples could be provided as annexes as they may hinder readability. Definitions for "summary and raw PK data" should be provided (please include definitions also in the glossary). The differences should be exemplified and it should be explained why summary data are eligible/appropriate for AUC/MIC and raw data for T>MIC, C_{max}/MIC.	
498	1	Comment: a meta-analysis <u>can</u> be performed… Proposed change: Please explain in which situations a meta-analysis "can" be performed. In addition, quality standards for the data to be included in the meta-analysis should be specified.	Text modified
499	1	Comment:	Not modified. Mean and standard

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		"… mean and standard deviations…" is only meaningful for normally distributed parameters but most PK parameters are not normally distributed Proposed change: Please specify which means are calculated.	deviation can be derived from different distribution law in function of the parameter and data source. The statistical law for MCS must be chosen according the parameter.
499-501	1	Comment: This sentence is unclear (see comment on lines 493 – 494 above). Proposed change: A ~~model~~ **formula (equation 1)** ~~of~~ **for** the relation between dose and PDI can be used to ~~estimate distribution of the PDI (equation 1) and~~ calculate the PTA of the PDT **(C_{target}).**	Partially agreed. The sentence has been revised in order to improve the understanding. However it is important to keep the "estimate distribution".
505-506	1	Comment: … non-linear mixed effect algorithm. It should be specified more in detail what type of non-linear model will be used and why. Proposed change: Details should be given for the non-linear mixed effect algorithm (perhaps in an annex?). Please clarify whether a meta-analysis will also be applied?	Population pharmacokinetics must fulfilled good practices in this field. The non-linear model must documented. The meta-analysis is used to combine different mean and variances. For a population pharmacokinetics, the different dataset can be analysed together using a PK model and covariates (formulations, animals).
505-507	1	Comment: This sentence is unclear (see comment on lines 493-494 above). Proposed change: A population pharmacokinetic analysis based on non-linear mixed effect algorithm can be performed to ~~estimate distribution of the PDI and~~ calculate the PTA for a PDT.	Partially agreed. The sentence has been revised in order to improve the understanding. However it is important to keep the "estimate distribution".

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507-510	1	Comment: This sentence is unclear (see comment on lines 493-494 above). Proposed change: This approach is applied to analyse the ~~other~~ PDI**s** (T>MIC, C_{max}/MIC~~)~~ chosen in function of the antibiotic class**)**, ~~because it requires to estimate the distribution of their values~~ in function of the population distribution of key pharmacokinetic parameters (bioavailability, volume of distribution, clearance).	Agreed.
511	1	Comment: … of 5000 cycles… Proposed change: If a number of cycles is proposed justification should be provided for it.	This is a Reflection Paper rather than a guideline.
521-523	1	Comment: to set the clinical cut off clinical data are necessary Proposed change: …MIC value reflecting clinical outcomes ~~and able~~ to discriminate between clinical failure and success. It requires **clinical** data ~~able~~ to discriminate clinical case outcomes according the MIC of isolates and the level of exposure.	Agreed.
536-552	1	Comment: It is mentioned in the text that large amounts of residue depletion studies would be needed in order to cover the variation under field conditions, such as different breeds, different animal life stages with different ages and body weights, different housing and feeding conditions, and different health status, which is considered as not practicable. However, it is in line with current legislation and guidelines to conduct residue depletion studies in a limited number of healthy animals (in most cases) from one breed and kept under identical conditions.	The comment is noted. The CVMP would like to point out, that this is a general description of the present situation. Variables are mentioned that could influence the WP for one dosing level. Stating that varying the dose would also influence the WP is considered not appropriate here.

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		In our opinion, dosage is unquestionably one of the most important influencing factors on the length of withdrawal periods, followed by administration route and product (formulation, excipients). The variations under field conditions may be important in certain cases but are not feasible to be taken into account to establish WPs. One important aspect missing in the considerations under 4.1 is that according to current requirements separate (individual) residue depletion studies have to be conducted for different products. Proposed change: The text should be modified/amended accordingly to emphasise dosage as the most important factor influencing length of withdrawal periods.	
553-569	1	Comment: This section presents a description of shortcomings of old residue studies. It does not become entirely clear to the reader, in how far this would help to justify that the resulting "old" WPs can form a reliable basis for the extrapolation. The way it is written would rather suggest that results of old residue depletion studies are not suitable to be used for extrapolation, as extrapolation adds an additional layer of uncertainty. The message of this section should rather be that despite some shortcomings available ("old") residue depletion studies might be suitable to be used as a basis for extrapolation under certain conditions. Furthermore, we would like to make the following comments on the bulleted list: First bullet point: In how far do the old residue depletion studies represent field conditions? According to our experience they include smaller numbers of animals as well as the other shortcomings mentioned, but the variety of animals does not differ from those in more recent studies. Either some kind of explanation should be added or the point should be deleted. Second bullet point: The message of this sentence is unclear. To establish consistent withdrawal periods, analysis of the data based on current guidelines	Comment is noted. This section is a general section describing the present situation. We disagree that the message of this section is that 'old' studies could not be suitable. The comments on the bullet points are noted, but did not lead to changing the text of this segment.

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		would be sufficient. Fifth bullet point: Recent studies contain larger numbers of animals based on requirements laid down in the applicable guidelines. Although their age, weight, race and housing conditions are similar, the larger number of animals yields a larger variety of outcomes that better reflects the underlying population and therefore leads to an increase in reliability of results. Proposed change: Please amend/modify the text accordingly.	
574	3	Comment: the text - calculating withdrawal periods in case- should be deleted Proposed change (if any): the text should be now read: calculating "withdrawal interval (WDI)" in case…	See adjusted text In fact new withdrawal periods are estimated using the calculated WDI. So in principle the text is considered to be correct and does not have to be altered.
576	3	Comment: the text - new WP - should be deleted. Proposed change (if any): the text should be read: "withdrawal interval (WDI)".	In fact new withdrawal periods are estimated using the calculated WDI. So in principle the text is correct.
580ff	1	Comment: The withdrawal periods derived from the proposed algorithm (Equation 2) are considered correct in principle, provided the assumptions of dose proportionality (linear kinetics) and complete distribution are met. As acknowledged in line 611f, Equation 2 neglects the convex nature of tolerance limits leading to a potentially underestimated WP. In order to avoid this, we would like to propose another approach based on individual animal data, if for the corresponding WP these data are available and dose proportionality is given: If dose proportionality is given, the WP for the k-fold dose could be determined	It is acknowledged that the current guideline on the calculation of WPs provides a statistical approach that takes into account a 95% confidence limit on the 95th percentile. Due to the convex nature of the 95/95 interval curve, there is a probability of a slight increase of the WP (when using the statistical method), on top the WP calculated, even when dose-linearity is assumed. Theoretical

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		by applying the guideline's approach to the k-fold of the individual residue concentrations. Such a procedure is preferred over applying the formula since it incorporates the residue variability and the uncertainty in the terminal half-live resulting from this variability. Thus it avoids the systematic error that arises by ignoring the convexity of the tolerance limit curve. If results from a residue depletion study in tissues did not allow for use of log-linear regression analysis and the alternative approach was used to derive withdrawal periods, this study would also no be suitable to derive reliable half-lives for use in Equation 2. In these cases other data would have to be used for calculation of half-lives. In these cases data from different sources would be used in Equation 2 (withdrawal periods established via the alternative approach from one study and half-lives from another study). Some experience would be needed to see whether this might have an impact on the resulting withdrawal periods and thereby also on consumer safety. Proposed change: Explanation needs to be provided how to assess whether linear kinetics does apply and whether tissue distribution at MRL level is complete. The impact of the use of different data sources for WPs and half-lives on the resulting WPs for the increased dose needs to be explored and discussed.	calculations suggest that this additional increase is around 5%. Whereas the current statistical method and the proposed algorithm cannot be fully compared, the addition of a safety factor to the selected worst-case half-life in tissues may be considered. It is further acknowledged that, depending on the nature/quality of the available data, other more or lesser sophisticated statistical methods could be used to determine the new withdrawal period. Further restricting the proposed methodology would make the hourglass method less versatile. It is agreed that indeed, depending on the data available, several other approaches can be followed to determine the terminal half-lives. we consider the remarks made very valuable. We would like to emphasize that in an individual case assessment these could be considered depending on the data available.

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581	3	Comment: $T_{1/2}$ - Terminal half time in tissues – formula for calculation of terminal half-life is not mentioned in the reflection paper and principle of own calculation of terminal half-life is not mentioned too. How many sampling points are needed for establishment of $T_{1/2}$? Some studies have more sampling points and different $T_{1/2}$ is calculated, if the sampling points are combined. Why the worst case scenario of calculation of $T_{½}$ is not used for calculation? How mean half time in tissues (after distribution is complete) will be calculated for injectable product where injection site is not target tissues for the establishment of the withdrawal period (example of this situation: referral of gentamycin)? Will the data from non GLP or old studies be actually used for calculation of $T_{½}$? Will data out of validation range of method be actually used for calculation of $T_{½}$? Will data without stability be actually used for calculation of $T_{½}$? Proposed change (if any): -	The comments are noted. The hourglass method would consider all available data. We believe that further elaboration on how the specific kinetic variables would be calculated is beyond the scope of this reflection paper.
585	1	Comment: What is meant by "mean half-live in WP determining tissue" to be used in Equation 2? Since in residue depletion studies for each tissue there is only one regression line, there is also only one such half-life. If the mean of distinct half-lives for the critical tissue from several studies is meant: shouldn't it be the longest such half-life (worst case)? If "mean" half-life is stated having in mind applying Equation 2 also for milk/eggs (with regression lines for each individual animal): also, a worst case should be used since else one cannot be confident that almost all residues are below MRL. Proposed change: Please add some explanation concerning this aspect.	It is meant: the half-live of the WP determining tissue. Depending on the kinetics/tissue distribution/inj site residues, the tissue that determines the WP indeed could change, depending on the size of the dose adjustment. The word 'mean' is now deleted. Further elaboration of methods to determine dose linearity or half-lives is considered beyond the scope of this reflection paper.
602-610	3	Comment: the Figure 4 and 5 should be deleted. Linear kinetics should be described only.	We don't agree. We feel these figures provide a significant visual contribution to the text

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606-610	1	Comment: Figure 5 shows an example where Equation 2 cannot be used as tissue distribution is not completed at MRL-level, which results in a disproportional increase of WP at higher doses. As complete distribution has to be proven before extrapolation can be applied, this should also be mentioned in section 4.4 point 1 as an important prerequisite and should also be discussed in the case studies. Therefore, Section 4.4 point 1 should be reworded. This should also be included in the case studies. Proposed change: Please add to 4.4. Point 1: d. Is tissue distribution completed at MRL-level (yes/no) The issue of possibly incomplete distribution of residues at MRL-level should also be discussed concerning the examples used in the two case studies.	Text as suggested was added. There is no explicit need to further address the issue in the case studies.
614-615	1	Comment: As acknowledged in the reflection paper, the convex (non-linear) shape of the tolerance limit curve is not taken into account in Equation 2, which might lead to an underestimated WP. However, the exact shape of the tolerance limit depends on several factors: - the uncertainty resulting from the variability of the data - the sample size of the study the original WP estimation is based on - the amount of extrapolation beyond the last slaughter time in that study Therefore, also the discrepancy between the tolerance limit curve and the straight line implied by Equation 2 depends on these factors. Hence, a universal maximum upper bound for this discrepancy cannot be derived. Proposed change:	This comment is noted and the text is slightly amended and the safety span is no longer 'concrete'.

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		It is preferred not to state a concrete safety span here but to request for a justified safety span from case to case.	
618-639	1	Comment: Although it is noticed that the document is not a guideline, in our view clearer definitions and instructions are needed in this section to make the approach more transparent and usable as well as to allow for conclusions on reliability of the case studies. In particular, the following aspects need to be taken into account to give clear information on how to handle the points mentioned in this section: – Half-lives of substances: o Tissue half-lives may significantly differ from plasma half-lives and may also differ from each other, i.e. for each tissue only tissue specific half-lives should be used. Therefore, half-lives used in the calculation need to be half-lives of the substance in the relevant target tissues (WP determining tissue for the specific product). o It should be clearly pointed out that only terminal half-lives are relevant, i.e. from a time span when distribution processes are finished and depletion of the substance results from excretion only. Guidance or reference to existing guidance would be needed on how to establish terminal half-lives in tissues for the purpose of withdrawal period determination. In particular, the following points need to be addressed: ▪ To establish terminal half-lives, data from all time points in the terminal phase should be used. At least data from three time points are necessary to allow for estimation of reliable half-lives. Furthermore, the terminal phase has to be log-linear. There should be some guidance on how to show the log-linearity. ▪ Some instructions should be given on how to choose the starting point for a terminal half-life from a residue depletion curve.	The points made are comprehensive and scientifically sound. Indeed this document is a reflection paper, not a guideline. Depending on the availability and quality of the data that would be gathered from all sources (hour glass approach) one would have to take a specific approach to determine the various parameters needed. Therefore the conditions and methodology are described in general terms. This was done in order to keep the approach versatile. An extensive description of each of the points mentioned would go beyond the purpose of this reflection paper.

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		▪ Also instructions are needed on how to assess study data concerning reliability. Will data from non-GLP studies, older studies or studies with parameters out of validation range of the method or without stability data be actually usable for calculation of T½? ▪ How to handle aggregated data? Half-lives should be calculated based on regression analysis of the arithmetic mean of the logarithmized individual data or equivalently on the logarithm of the geometric mean at each time point $\frac{1}{n}\sum_{i=1}^{n}\ln(y_i) = \ln(\sqrt[n]{\prod_{i=1}^{n} y_i})$ Using the logarithm of the arithmetic mean at each time point is not equivalent and may result in a wrong half-life. The reason is that residue data are assumed to be log-normally distributed. In order to fulfil the assumptions of linear regression, individual data therefore have to be logarithmized before regression analysis. In case of the same number of observations at each time point, this is equivalent to computing the half-lives from a regression of the logarithm of the geometric means at each time point. The size of the error in estimates for half-life resulting from using the logarithm of the arithmetic means depends on how much the arithmetic mean and the geometric mean differ. This in turn depends on the individual data. Therefore, it should be clearly stated how the calculation should be done. Otherwise the determined half-life might differ from the real one only because of the calculation procedure. It should be addressed what to do if only aggregated data (in particular arithmetic means) are available, as this is the case in many publications. ▪ It is at least questionable, whether reliable terminal half-lives can be calculated for injection site tissues.	

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		▪ How to deal with different terminal half-lives for the same tissue resulting from distinct residue studies? – dose linearity: Explanations needs to be given in particular concerning the following aspects: o some kind of definition for dose linearity o how dose linearity can be shown o It needs to be considered whether plasma values only would be sufficient (see also comment to lines 621-625). It might be the case that plasma levels show linear kinetics, while tissue levels do not. Therefore, some instruction is needed on how to check for dose-linearity in tissue and potentially also in milk and eggs. o How to deal with absorption? How can saturated absorption be predicted for higher doses? o Linear kinetics may be a property of the active ingredient but not necessarily remaining in the formulated product. Does this aspect need to be taken into account? – complete distribution: Some explanation needs to be provided how complete distribution can be checked. It should be made entirely clear to the reader, which preconditions must be met before the approach can be used. If preconditions are not met (or necessary data to show this are not available), extrapolation of withdrawal periods would not be possible without further consideration. It should be discussed which alternatives exist and in which cases (supplementary) residue depletion data for the higher dose are necessary. Proposed change: Include more information concerning the above mentioned points.	
621-625	1	Comment: In point 1. a., it should be stated that linear kinetics should apply for the	The condition of linear kinetics is mentioned and is valid for tissues as well

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		intended dose range in each target tissue as plasma kinetics does not represent the conditions in tissues. This might lead to wrong conclusion from plasma kinetics, especially for lipophilic substances which accumulate in fat. The request for complete tissue distribution at MRL-level is missing here (see comment to line 606-610). For all listed assumptions it should be checked whether they are applicable in the case studies (examples). Proposed change: Please amend the text accordingly.	as for plasma. We see no need to further specify.
629-630	3	Comment: Public assessment reports should be listed before FARAD database. Proposed change (if any): ii. Public Assessment Reports (if available) iii. FARAD database	Text is adjusted.
635-637	1	Comment: Whether another tissue than the original WP-determining tissue may become critical for the withdrawal period should be checked **before** Equation 2 is applied. In addition, some information should be provided on how to deal with the use of Equation 2 in cases when the withdrawal period determining tissue for the old dose is unknown. We propose to give some more emphasis to this aspect, since changes in the WP determining tissues might result in large differences in WPs. Proposed change: Some more explanation should be provided to the reader on how to become aware that other than the original WP-determining tissues become critical for the WP, including some information on the importance of this aspect.	Comment is noted. Depending on the kinetics/tissue distribution/inj site residues, the tissue that determines the WP could in principle change, depending on the size of the dose adjustment. When putting this method into practice, assessment would obviously be done by experts in this field, taking this phenomenon into account.
638-639	1	Comment:	Indeed no specific examples are

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		No information is given in the reflection paper on how "further kinetic modelling" could be conducted. While it is acknowledged that the current document is not a guideline, at least some information should be given on this to give the reader an impression how it might work. Proposed change: Please give instruction to the reader in which cases Equation 2 is usable/not usable and how "further kinetic modelling" can be conducted. Would it also be possible to use, in certain instance, mixed non-experimental (modelling) and experimental approaches; i.e. small (bridging) experimental studies which could complement and validate the modelling results?	mentioned, and this section was described in general terms. This was done in order to keep the approach versatile. Kinetic modelling is a term that is generally accepted.
638-639	3	Comment: It is mentioned in Reflection paper that PK/PD modelling will be used for linear kinetics only (on page 7) but in connection to point 4 it seems that calculation of the WP will be also performed probably for non-linear kinetics probably too therefore the text on the lines 638 and 639 should be deleted, therefore approach for linear kinetics should be described only.	It is acknowledged that linear kinetics are implied for the use of the algorithm mentioned in lines 638-639.
640-641	3	Comment: Injection products – withdrawal period is established on basis of inj. site: It is known that some generic VMPs prepared in injectable formulation intended for intramuscular and subcutaneous administration have longer withdrawal periods than is the withdrawal period of respective reference product. These differences in withdrawal periods for those generic products vs. reference product are due to different residue depletion rates from injection sites of the generic and the reference products. Therefore Commission Directive 2009/9/EC rightly requires as follows: "For generic veterinary medicinal products intended to be administered by	The comments are noted. The hourglass method uses all available relevant data that can contribute in the estimation of the necessary parameters. The Farad calculation is noted. We could unfortunately not compare the results of both methods, but are convinced (since the algorithms are similar) that when the input parameters are the same, both

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		intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided: — evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies ….” The question arises from the different WPs for the approved VMPs containing the identical active substance. How the $T_{½}$ will be calculated? Will the data obtained for generic and for respective reference VMP indiscriminately utilized for PK approach for withdrawal period adjustment? In context of the sentence ….Doubling the dose by injecting.. For product with oxytetracycline for cattle - dose 20 mg/kg bw (IM) - withdrawal period 35 days for meat and offal is authorized in the EU and the withdrawal period max. 38 days is proposed in the pilot project for double dose (line 2107) and max. 41 days in case of increased volume of injection (line 2113) but FARAD calculated withdrawal period 50 days for dose 40 mg/kg (IM) as a single dose – see below:	methods would generate comparable results.

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		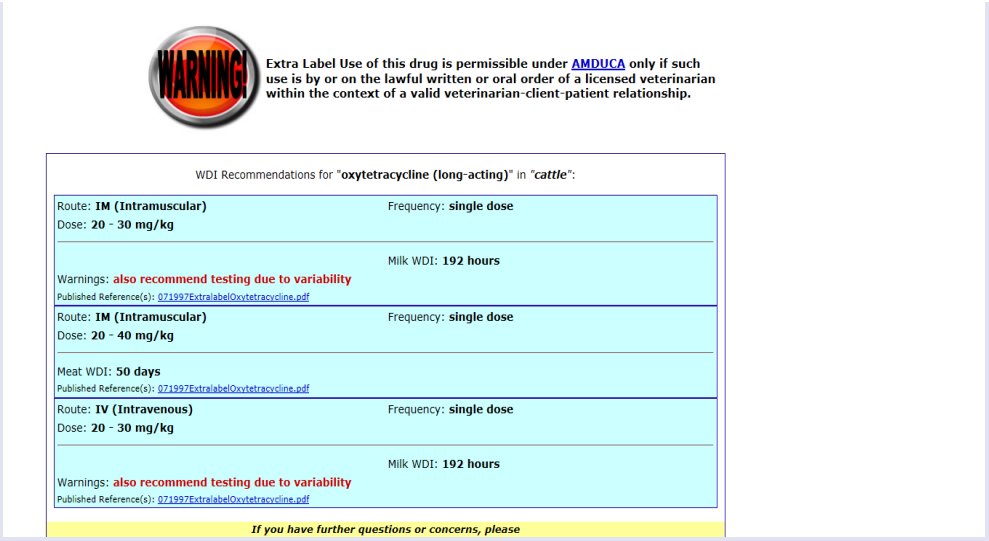	
641-645	1	Comment: Based on our experience in evaluation of residue depletion data from studies in injection sites, we would consider it questionable whether linear kinetics apply to injection sites and whether an extrapolation for this tissue based on a linear extrapolation is possible. Absorption and depletion of residues from injection sites is in most cases not linear, but depends on factors like formulation of the product, blood flow at the particular injection site and the amount of product administered. Based on this we would propose to clearly exclude products for intramuscular and subcutaneous use from the approach to extrapolate withdrawal periods using Equation 2. Proposed change: The text should be amended to explain the above described issues with non-linear depletion kinetics in residues from injection sites and to exclude products	Opinion is noted. It is agreed that the sampling of the injection site might lead to data that show a high variation. We don't agree with the thesis that absorption processes from the injection site are non-linear in most cases. In order to keep the method versatile we don't think it is appropriate to limit the applicability of the model. If during an assessment the situation would occur where significant non linear absorption from the inj. site becomes relevant, this would then have to be dealt with.

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		for intramuscular and subcutaneous use from application of Equation 2.	We propose to leave the text as it is.
643	3	Comment: the information regarding steady state in tissues should be proven. If steady state in tissues is not proven the accumulation in other tissues is possible and other tissues can be main for determination of the withdrawal periods and target tissues Proposed change (if any): the following text should now read: … (see Figure 6)" provided the information regarding steady state in tissues has been proved".	The algorithm can (in theory) only be used when distribution is complete. This was already described.
644-645	3	Comment: on the basis of comment mentioned concerning line 643 Proposed change (if any): the text within the lines 644-645 should be deleted.	We propose to keep the lines in.
647	3	Comment: Proposed change (if any): the text should be now read: …can be used "(in case of linear kinetics)".	We propose to keep the text as it is.
653	3	Comment: Example on residues in eggs – amoxicillin was used Example on residues in milk – gabapentin was used In EU MRL´s for amoxicillin in eggs and gabapentin (for all tissues and milk) are not established. These examples are perhaps good in terms of pharmacokinetic models, but these examples are erroneous from the point of view of valid European legislation – Commission Regulation (EU) No 37/2010 and as it is mentioned on page 23 .. "this project only dose variations are considered and no extra label use" …. These examples should be changed. Proposed change (if any):-	Comment noted. The examples were only used to illustrate the principles. We propose to keep them in.
653-708	1	Comment: General comment on the use of Equation 2 for calculation of withdrawal periods	Comment is noted. These examples in milk and eggs are

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		in milk and eggs (for more specific comments on methodologies and examples, see subsequent comments): Only one example each was used for eggs and for milk to show applicability of Equation 2 also for these food commodities. The example for eggs is dealing with amoxicillin which is not allowed for use in birds producing eggs for human consumption and the example used for milk was not an antibiotic substance. Section 4.6 should contain examples of residues of antibiotic substances with MRLs for the food commodities milk and eggs set in Europe. No MRLs from other regions, e.g. from Japan as in the amoxicillin example in milk, need to be used as there should be a suitable number of residue studies on antibiotic substances with numeric MRLs is available in the European network of authorities. Furthermore, appropriate methods for the calculation of withdrawal periods in eggs and milk should be used to allow for a reliable comparison with results from Equation 2. In milk and eggs, residue data are not independent from each other, as several samples taken from the same animal are included in one dataset. Applying linear regression analysis would result in autocorrelation, i.e. correlated residuals. Therefore, estimates for regression lines are in fact undistorted but not efficient. As a result, variance is underestimated in case of positive correlation as covariance between residuals is not taken into account. This leads to too small tolerance limits and, therefore, underestimated withdrawal periods. The strength of this effect depends on the extent of correlation. Although this issue is addressed in line 664, it is not clear why no attempts were made to model withdrawal periods in milk (or eggs) using the established standard methodology (e.g. TTSC). Proposed change: Please modify and amend the text as stated above.	included to show that in principle the algorithm can also be used in these food commodities. So when for example via existing residue studies WP's for these commodities are calculated for a certain dose (using preferably recommended methods like TTSC), Extrapolation using equation 2 would in principle be possible. It should be noted that further elaboration on this is not considered necessary within the context of this reflection paper.
653-708	1	One might discuss WP extrapolation for eggs and milk more in detail: Assume dose proportionality, and assume $Dose_{new} = Dose_{old} \times k$ (i.e. $\log_2(k)$	Comment noted. Using the hourglass approach, there are

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		half-lives are added in Equation 2 to WP_{old} to obtain WP_{new}). There are four possible levels of information on $Dose_{old}$: 1. individual residue concentrations $conc_{old}$ at all time points are known; 2. individual $TTSC_{old}$ and individual $t_{1/2}$ are known; 3. individual $TTSC_{old}$ and just one (mean? / worst-case?) $t_{1/2}$ are known; 4. just WP_{old} and just one (mean? / worst-case?) $t_{1/2}$ are known. Note that the information content is decreasing from level to level. Therefore, one can go from a low level to a level with a higher number by appropriate calculations, but not the other way around. Depending on the level of information, different procedures for estimating WP_{new} are possible: In **1.**, one can apply the TTSC approach as described in the GL to $conc_{old} \times k$ (note: this is only possible, if $conc_{old} \times k <$ MRL at the last time point); i.e. one does not make use of Equation 2. At this level of information individual variability is taken into account and WP_{new} is derived from a proper tolerance limit. In **2.**, one can apply Equation 2 to each individual animal using their individual $TTSC_{old}$ and individual $t_{1/2}$; i.e. add to each individual $TTSC_{old}$ $\log_2(k)$ times the individual $t_{1/2}$ to obtain $TTSC_{new}$ – from these, WP_{new} can be determined using the TTSC approach as described in the GL. There is no information available on how far $conc_{old}$ is below MRL at $TTSC_{old}$. Therefore WP_{new} might be too long. In **3.**, one can apply Equation 2 to each individual animal using their individual $TTSC_{old}$ and the one $t_{1/2}$; i.e. add to each individual $TTSC_{old}$ $\log_2(k)$ times the one $t_{1/2}$ to obtain $TTSC_{new}$ – from these, WP_{new} can be determined using the TTSC approach as described in the GL. If $t_{1/2}$ is not a worst-case half-life, individual $TTSC\_{new}$ will be too short in some cases. Furthermore, since for all animals the same half-life is assumed, individual variability might be underestimated. Overall, this can lead to a too short WP_{new}.	indeed many levels of information/data possible. In our opinion, discussing each of them in great detail in this reflection paper should be avoided. The points mentioned here are valid. These would obviously be part of the assessment of a particular case, depending on the available data and their quality.

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		In **4.**, one can apply Equation 2 to WP_{old} and the one $t_{1/2}$; i.e. add to WP_{old} $\log_2(k)$ times the one $t_{1/2}$ to obtain WP_{new}. At this level of information individual variability cannot be taken into account and WP_{new} cannot be based on the computation of a new (adjusted) tolerance limit. Applying Equation 2 might lead to a too short or too long WP_{new}. Thus, depending on the information available, up to four different extrapolated WP_{new} can be obtained. Note that using less information might lead to a shorter (!) extrapolated WP_{new} (e.g. this might be the case in 3. vs. 2. if the one $t_{1/2}$ in 3. is not a worst-case half-life). This shows that further discussion is needed on the extrapolation of WP for milk or eggs. Proposed change: It is proposed to add a new section and discuss the distinct possibilities for WP estimation in eggs or milk depending on the available information.	
656-689	1	Comment: The example for residue depletion in eggs was taken from a publication on oral application of amoxicillin to laying hens (Liu et al., 2016). 25 resp. 50 mg/kg body weight were applied once per day for five consecutive days. The authors of the study used WT1.4 for analysis of data and presented two separate calculations, one for amoxicillin (AMO) only and one for amoxicillin plus amoxicilloic acid (AMA) and amoxicillin-diketopiperazine-20,50-dione (DIKETO). In Europe, no MRL for amoxicillin residues in eggs was set and also no marker residue was defined. Liu et al. calculated withdrawal periods based on an MRL of 10 µg/kg in Japan. For AMO withdrawal periods of 5.21 and 7.67 days were derived for the 25 mg and 50 mg/kg bw group, respectively, based on regression analysis. Calculation of WP for the sum of metabolites (AMO + AMA + DIKETO) resulted in somewhat longer WP of 8.00 and 9.11 days following	It should be noted that these examples were presented as an illustration of how the methodology could work. In our opinion the algorithm would also work for eggs and milk.

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		treatment with 25 mg or 50 mg/kg bw, respectively. As mentioned in line 664, linear regression analysis is not a suitable method to calculate WP for eggs as data are not independent from each other. The fact that the inappropriate use of regression analysis and Equation 2 came to the same result does neither imply the adequacy of the regression analysis nor the validity of Equation 2 – both methods might have produced the same wrong result, or results might have coincided just by chance. Furthermore, only the WPs calculated for AMO were taken into consideration. As no marker residue for amoxicillin residues in eggs was established and to cover the allergic risk for AMA and DIKETO, the sum of metabolites should be used as also indicated by Liu et al. Proposed change: Proposed changes are included in the comment above. In addition, as TTSC is considered to be the more suitable method for residues in eggs, the program Melk 14 should be used to calculate reference withdrawal periods in eggs for the evaluation of results from Equation 2.	
671-683	1	Comment: Results from the application of the PB/PK model for eggs developed by Hekman and Schefferlie (2011) were used to show that the final phase of the residue depletion curve is log-linear and that there is dose-linearity at the dose range of 25-50 mg/kg. According to their publication, "the model is to be used as a tool to obtain an insight into those properties of a drug which are responsible for the amount of residues in eggs and it could help in the design of critical studies for determining withdrawal periods for eggs". Here, the PB/PK model and the WT1.4 model are used to check the assumptions of Equation 2 on log-linearity in the final phase and dose-linearity. This raises two concerns:	It should be noted that this example is presented as an illustration of how the methodology could work for residues in eggs.

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		First, as outlined in the comment to lines 656-689, WT1.4 is not appropriate in the context of milk/eggs and the results of WT1.4 are therefore not reliable to check the assumptions of Equation 2. Second, it is questionable whether the PBPK model is suitable to derive log-linearity and dose-linearity, since no goodness-of-fit measures of the model curves are provided. According to Figure 8: The goodness-of-fit of the model curves is not obvious since for the higher dose all measurements are above the corresponding curve, and for the lower dose consecutive residuals are not independent either (first the measurements are below the curve, than above, than below again, thus the shape of the curve seems to be incorrect). Therefore, it is not obvious that the data can be described by parallel curves (indicating dose-linearity). In addition, it might be preferred to demonstrate dose-linearity more statistically than just by visual inspection (e.g. by determining confidence intervals for ratios of dose-normalized PK parameters). The model fit is also addressed by the developers of the PB/PK model themselves: Schefferlie and Hekman (2016) mention in their more recent publication that more data and studies are necessary to further calibrate this theoretical model. "At present, the model seems able to predict the excretion into albumen and yolk for a limited number of drugs." The authors of the reflection paper therefore might wish to show that the PBPK model is validated for the examples used. Proposed change: In accordance to the comment to lines 618-639, we suggest that some instruction is provided on how to properly check the assumptions on log-linearity and dose-proportionality (dose-linearity). This requires a proper definition of both in the first place. It should then be stated which information/data is necessary to draw conclusions on the two assumptions and which statistical	

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		approach could be used (e.g. determining confidence intervals for ratios of dose-normalized PK parameters to derive dose-linearity). It should be addressed whether a different approach has to be taken to show dose-linearity in eggs and milk than in tissue or plasma. The examples should follow the instructions carefully in order to provide guidance to the reader. In case the two assumptions are not met or no conclusion can be drawn, some guidance should be provided on how to proceed.	
673	1	Comment on Figure 7: Some text is considered useful to explain the message of Figure 7 to the reader. As yolk and albumen are not assessed separately, it remains unclear why this analysis is necessary here and what the outcome for the withdrawal period would be. Proposed change: Please add some text to clearly explain to the reader the message of Figure 7.	Comment noted text is slightly amended.
679	1	Comment on Figure 8: Some additional labelling of the figure would be useful to make it more readable. E.g. the time period of treatment should be clearly marked and numbering of days should start again after the end of treatment. Proposed change: The labelling should be amended as described above.	Comment noted.
685-689	1	Comment: From Liu et al. (2017) one **cannot** conclude that - the final phase of the residue depletion curve is log-linear: Only arithmetic mean concentrations are given in the publication. Depletion curves are estimated from log-transformed residue data. If means are used they should be means of the log-transformed residue concentrations which correspond to geometric means on the original scale, and these are not reported in Liu et al.	Comments noted. It is acknowledged that with more data a better indication would have been obtained. However as an example of the pragmatic use of data from literature, we consider

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		(2017). See also comment to lines 618-639. - one has dose proportionality: First, in the paper this issue is not discussed (only a positive correlation between dose and residues is mentioned). Second, this cannot be decided based on the published arithmetic means – analogous to above, geometric means are necessary for this. Here, doubling the dose should lead to doubled geometric mean residues in case of proportionality. (Mathematical proof: proportionality means $residue_i \sim \alpha \times dose \times \exp(\varepsilon_i)$ for some proportionality constant α and for a normally distributed error ε with expected value 0 and all measures i = 1,...,n; thus $\log(residue_i) = \log(\alpha) + \log(dose) + \varepsilon_i$; averaging implies $mean(\log(residue)) = \log(\alpha) + \log(dose) + mean(\varepsilon) = \log(\alpha) + \log(dose)$ since $mean(\varepsilon) = 0$; anti-log leads to $geomean(residue) = \alpha \times dose$, q.e.d.) Proposed change: Please add a statement that for the purpose of this example dose proportionality and complete distribution were only assumed to be checked successfully, since the necessary data to actually check these assumptions were not available.	this use of data a relevant example here. We agree these data are limited.
691-705	1	Comment: The substance used as example for residues in milk (gabapentin) is not within the scope of this reflection paper. Data were taken from an article published by Malreddy et al. (2012) which is dealing with pharmacokinetics and depletion into milk after co-administration of gabapentin and meloxicam in cows. It does not become clear, neither from the reflection paper nor from the article,	Comment noted. The example is indeed using a fictive WP, and is merely to underpin the theoretical possibility of using the algorithm also for the food commodities: egg and milk.

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		how the WPs in milk were set. It seems that the time point, when the residue depletion curve met the fictive MRL of 0.1 µg/ml, was used without taking into account confidence limits and tolerance intervals. If that was the case, this wouldn't be an appropriate method to derive WPs. Also, the TTSC method, which is normally to be used for milk samples, was not used by the authors as no single animal data were available from the article. It cannot be observed from Figure 9 that the final phase of the residue depletion curve is log-linear. Rather deviation from linearity seems to occur at the last sampling time (approximately 48 hours after treatment). However, as no SDs are given in the figure, the variation of values per time point remains unknown. SDs are given in the original figure in the Malreddy paper and should be included in Figure 9. Proposed change: The text should be modified/amended accordingly.	
712-718	3	Text requires rewording as follows: In Phase I, products with a low environmental exposure are filtered out; these products do not need further assessment and substance related environmental fate and effect data are not strictly required. Examples of products with a low environmental exposure are products for companion animals only and products that result in a Predicted Environmental Concentration in soil (PEC_{soil}) of less than 100 µg/kg, based on a worst-case estimation. In Phase I can also terminate compounds with PEC_{soil} above 100 µg/kg if data show extensive metabolism in the target animal (ADME study) or complete degradation in manure (EMA/CVMP/ERA/430327/2009).	Text changed as suggested.
721-723	2	Comment: A risk assessment for substances with PECgw <0.1 µg/l is not sufficient to prevent all environmental risk, because cumulative and synergistic effects of multiple residues are not taken into account.	The comment is noted, however cumulative and synergistic effects of multiple residues are not included in the

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			current risk assessment methodology, as agreed internationally and laid down in VICH Guidelines. It is therefore not possible to include this within the scope of this reflection paper.
721-726	3	Text should be reworded as follows: PECs for these compartments are also calculated. When the PECs are for all environmental compartments below the relevant PNECs, no further assessment is needed. If any of these PECs is above the PNEC for that compartment and therefore possible risk is identified as RQ is above 1, then PEC refinement based on metabolism, excretion and the environmental fate of the substance can be taken into account. When the PECs after refinement are below the relevant PNECs, no further assessment is needed. If no data for refinement are available or if PECs after refinement is still above the PNEC for that compartment then further data on fate and effects are required for the relevant environmental compartment(s) in Tier B. It should be noted that a PEC in groundwater (PEC_{gw}) ≥ 0.1 µg/l triggers further risk assessment also taking into account guideline on assessing the environmental and human health risks of veterinary medicinal products in groundwater (EMA/CVMP/ERA/103555/2015).	Text changed as suggested.
728-731	2	Comment: Under current legislation, the authorisation of a veterinary medicinal product may be prohibited, if an unacceptable risk to the environment is presumed. It remains unclear how to proceed if a change in dosage of an established veterinary medicinal product results in an unacceptable environmental risk. In this context, PAN Germany sees the need to considering a withdrawal of the authorisation, if suitable risk mitigation measures (RMMs)	Point noted, however, the reconsideration of the authorisation is part of the overall benefit/risk balance for the product. CVMP guidance on B/R evaluation already exists and does therefore not need further explanation in the context of this

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		cannot be established or if their positive effect on the environment is not certain. Proposed change (if any): In the situation where following a full ERA a risk for the environment cannot be ruled out, i.e. the PEC is higher than the PNEC, this should be considered in the overall benefit/risk balance for the product, and risk mitigation measures (RMMs) may need to be recommended in the product literature **or the authorisation may even need to be reconsidered.**	reflection paper.
734-736	2	Comment: The lack of adequate monitoring data of AMR in the environment is a crucial point and cannot be neglected under any circumstances, when it comes to tackle the growing problem of AMR with respect to the One-Health approach.	Point noted, however considered outside the scope of this reflection paper. Text related to AMR in the environment is already included in paragraph 5.1.
778-780	2	Comment: The current legislation is not sufficiently protecting the environment from adverse effects of veterinary medicinal products containing PBT and vPvB substances. According to the new EU regulation on veterinary medicines, which is not yet implemented, an authorisation for a new product can be denied, if the active substance meets the criteria of PBT or vPvB (https://oeilm.secure.europarl.europa.eu/oeil-mobile/summary/1559301?t=d&l=en). Thus, especially in the case of old antibiotics PAN Germany recommends to consider PBT/vPvB criteria in the ERA for a dose optimisation to ensure adequate protection of the environment.	The CVMP acknowledges that PBT and vPvB properties of veterinary medicines are important to consider within the context of the environmental impact assessment. However, as explained in paragraph 5.3, this point is considered to be outside the scope of this particular reflection paper.
785-786	1	Comment: Juridical issue: There might be strong and fundamental legal problems with the ownership of the data if one wants to use the information from public assessment reports considering several authorisation procedures.	As explained in paragraph 2.2, this can be overcome by using a community interest referral to the Agency.
793-796	1	Comment: This is a theoretical consideration – as there are no science based QSAR	Change not accepted. The intention of the reflection paper is to explore non-

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		approaches for environmental side effects of antibiotics known. If such QSAR approaches would be developed, the next step would be to validate them with "real data" Proposed changes (if any): It would be more appropriate to acquire the ecotoxicity data directly by performing effect (or even fate) tests.	experimental approaches.
802-803	1	Comment: Please keep in mind the new Groundwater Guideline coming into effect in November 2018.	This is already mentioned in paragraph 5.2.2.
811	1	Comment: Correct is RQ 1 or higher.	Text amended.
825	1	Comment: Correct is RQ 1 or higher.	Text amended.
827- 829	1	Comment: In such case it might be possible that unacceptable risk after doses change occurs without any appropriate RMMs. Would that result in non-approval of authorisation? CVMP should reflect on these consequences.	As explained in the Reflection Paper, in case serious risks are not excluded and cannot be mitigated, the B/R balance of the product needs to be reconsidered on a case-by-case basis, taking into account regulatory options.
882-885	1	Comment: In agreement with the current state of knowledge, the target animal safety of a product depends foremost on the administered dose, the number of treatments and the intervals between each single administration. Based on the PK/PD modeling, administered doses as well as dosing intervals might be optimized within the scope of this reflection paper. Therefore, it would be prudent to discuss the impact of both, increased dosage and reduced dosing	Section 6.2 has been amended as follows: *On the basis that, in the context of this project, any change to the dose of an antibiotic will be based on PK/PD modelling, then it is assumed that any adverse impact on safety will be in most cases as a consequence of an increase in*

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		intervals on target animal safety. Furthermore, depending on the interpretation of "unchanged treatment duration" (see line 2823), the number of individual administrations within the treatment period might increase as well, and may be important for the revaluation of target animal safety. If an unchanged treatment duration means that the number of treatment days is adopted from the initial registration, the number of single doses would increase, if treatment intervals have to be shortened based on the PK/PD model. Shortened dosing intervals reduce the time period for regeneration of toxicity target organs between two treatments and might cause more severe tissue damage. Damage to the gut microbiome for example due to oral antimicrobials is a function of dosage over time. Higher dosages as well as prolonged treatment durations may lead to an increase of adverse effects. On the other hand, subinhibitory doses may also affect the gut microbiom and facilitate the selection of antimicrobial resistances. Proposed change: It is proposed to amend this paragraph and the related paragraphs on the two examples on amoxicillin and oxytetracycline and include reduced dosing intervals and prolonged treatment durations caused by dose optimization in the revaluation of target animal safety. Considering this paragraph, the following change might be suitable: "On the basis that, in the context of this project, any change to the dose of an antibiotic will be based on PK/PD modelling, then it is assumed that any adverse impact on safety will be a consequence of an increase in the dose (mg/kg), an increase in the duration of dosing and a reduction of dosing intervals."	*the dose (mg/kg) administered ~~in a given period~~ and/or an increase in the frequency of dosing.~~, as opposed to an increase in the duration of dosing.~~ An increase in total dose over a given period of time will result in a reduction in the MOS for a product. In some cases the frequency of administration may impact safety, for example a high dose of gentamicin administered once daily has been recommended compared to administration at more frequent dosing in order to limit nephrotoxicity (EMA/CVMP/298167/2014) ~~with some exceptions possible (e.g. gentamicin, where frequency of administration may also impact safety)~~. PK/PD modelling cannot be used to determine the duration of treatment to achieve a clinical cure; hence treatment duration generally will not be changed unless the PTA is reached for only a very short time (see oxytetracycline case example). In each case it would be necessary to assess if an acceptable MOS for each product can be retained with the new dose/regimen*. These issues are addressed as required in the case studies and no changes are

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			proposed.
892	1	Comment: No explanation is given on what is meant by "similar products". Necessary requirements that products have to fulfil in order to be considered similar, however, are essential to understand the proposed approach. The definition of "similar products" might even differ depending on whether it refers to the evaluation of TAS, PK/PD, ERA or withdrawal periods. Proposed change: It is proposed to include a definition of "similar products" either in the body of the manuscript or in the Glossary. If requirements for "similar products" differ within the manuscript, depending on the focus of the revaluation, e.g., TAS or ERA, an explanation on what is summarized as "similar products" should be given at the appropriate paragraph.	This sentence includes a reference to chapter 2, General Considerations, where it is already stated that 'data will be collected at the level of an *animal species-disease indication-route of administration-pharmaceutical form* level… The information will be integrated in the review approaches (ERA and TAS) and in the selection of model parameters (dose and WP)' (2.2). More specifically in section 6.3.1. it is stated 'Review the TAS studies for **all products with the same active substance and pharmaceutical form that are administered by the same route of administration**.' Later, it is noted that 'studies from different products **should only be pooled if the PK profiles are similar**'. Further explanatory text has been added in this regard. Step 6 advises that attention should be paid to the excipient formulation when concluding on the safety of individual products. It is considered that in each step of this

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			section sufficient guidance is provided on requirements for 'similar products' to allow extrapolation of information when possible.
893	1	Comment: "Toxicity syndrome" is no standard term used in target animal safety evaluations. Consequently, "syndrome" should be deleted. Proposed change: In this respect, pooled studies will be useful for establishing the toxicity ~~syndrome~~ and MOS.	Thank you; an amendment was made prior to the public consultation.
893-896	1	Comment: As mentioned previously the approach to pool data is encouraged and the proposition that the relationship between formulation, pharmaceutical form and route of administration with bioavailability, as well as pharmacokinetics should be considered, is highly appreciated. However, no explanation is given what these considerations might entail, neither in Chapter 6, nor in the examples on amoxicillin or oxytetracycline. Proposed change: It is proposed to further elucidate on the methodology on how the aforementioned relationships shall be considered for the evaluation of target animal safety.	As outline in chapter 6.3.1, the criteria for pooling studies are that products have the same pharmaceutical form, are administered by the same route of administration and have similar PK profiles. It is stated that relevant information can be gained from the PK studies for individual products. The following guidance has been added: 'Strict bioequivalence is not necessary also considering that TAS studies are not anyway able to determine a precise MOS due to the dose multiples used. However, the degree of pharmacokinetic variability that can be accepted will be dependent on the (new) therapeutic index of the active substance. Relevant information may be

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			found in the pharmacokinetics studies for the individual products. Assumptions may also be made regarding the relative bioavailability of different formulations based on the principles for biowaivers outlined in the CVMP's Guideline on the conduct of bioequivalence studies (EMA/CVMP/016/00)'. The following amendment is made in the amoxicillin case study (7.5.1) '*Aqueous oral solutions may be eligible for a biowaiver from bioequivalence studies (EMA/CVMP/016/00) allowing extrapolation of TAS data between different formulations'* In regards to the oxytetracycline case study, the PK of different formulations was reviewed in chapter 8.2.1, with the conclusion that no major differences in PK would be expected*. The following text has been added in 8.5.4: In regards to extrapolation of safety data from formulations used in literature studies, it has to be considered that the exact formulation of these products is not be available; however, the PK of several oxyteracycline 'solution for injection'*

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			formulations was reviewed in chapter 8.2.1, with the conclusion that no major differences in the PK would be expected.
904-1018	1	Comment: While the strategies and data used to appraise TAS are described sufficiently and pooling of data is a feasible method to broaden the available dataset, it is difficult to understand, on which level data can be pooled for each individual step. It furthermore seems, as if general requirements pertaining the comparability of data mentioned under 2.2 are not always met by data pooled for the exemplary evaluations of amoxicillin and oxytetracycline. The following questions might be considered in order to define groups for which data can be pooled depending on the different steps: • Is bioequivalence necessary in order to pool data? • Is it necessary that the products have an identical composition (active substance and/ or excipients) to pool data, or what kind of variations are allowed? • Is it necessary that the products have the same route of administration and/ or pharmaceutical from? • Is it necessary that data have been generated in the target species or can data gained from other species or even in vitro data be used equivalent? Proposed change: It is proposed to precisely define, which requirements have to be fulfilled in order to pool data for each step used to evaluate target animal safety. A table or picture might be helpful to illustrate, which data can be grouped. Moreover, requirements proposed in section 6 should be met in the examples or explanations should be given, on why exemptions can be allowed.	Although it is considered that these points are already largely addressed, some amendments have been made to supplement the guidance provided. 6.3.1. Step 1 Review the TAS studies for all products with the same active substance and pharmaceutical form that are administered by the same route of administration to the concerned target animal species/category…. should only be pooled if the PK profiles are similar. Strict bioequivalence is not necessary also considering that TAS studies are not anyway able to determine a precise MOS due to the dose multiples used. However, the degree of pharmacokinetic variability that can be accepted will be dependent on the (new) therapeutic index of the active substance. See also the final paragraph of chapter 6.3.1, where the use of TAS studies conducted with products of different pharmaceutical form, or different routes of administration, is discussed.

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			6.3.2. Step 2 Review the safety data from the clinical field trials for all products with the same active substance and pharmaceutical form that are administered preferably by the same route of administration…. Although formulation differences should be taken into account when extrapolating data especially for local safety, in regards to the systemic MOS, variability in population characteristics may have a greater impact. Step 1a advises on use of data from non-target species. Within the limitations of the pilot project, it is considered that these issues are adequately addressed in the case studies.
920-921	1	Comment: While the same pharmaceutical form, route of administration, but also the same target animal species are necessary to define the MOS, toxicity target organs are mostly the same irrespective of the aforementioned characteristic. This should be made clear in the manuscript. Furthermore, it might be beneficial to not only describe, which product characteristics have to correspond, but also which characteristics (e.g., target animal species or disease indication) are not relevant, for TAS studies to be pooled. As the requirements for pooling of TAS studies to determine toxicity target organs and the new MOS differ, it might help the understanding of the concept,	The following sentence has been added under Step 1a: Data from non-target species will provide additional information on target organs and toxicity profile.

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		if both evaluations are done separately. Subheadings may be useful tools to improve clarity. Proposed change: The following rephrasing might be considered: 6.3.1.1 Toxicity profile Review the TAS studies for all products with the same active substance, irrespective of the target animal species, disease indication, their pharmaceutical form, the route of administration and excipients in order to confirm the target organs and toxicity profile of the active substance. 6.3.1.2 Margin of safety Review the TAS studies for all products with the same active substance, tested in the target animal species and with the same pharmaceutical form and route of administration in order to determine the new MOS. TAS studies can be pooled irrespective of disease indication. When pooling studies within different product groups as outlined above, some attention may need to be given to the relative bioavailability…	It is preferred to maintain an approach as similar as possible to that in the current Part IV.I.B of the dossier, whilst not ignoring that data from other target species/pharmaceutical forms/routes may provide additional valuable information in a step-wise approach if there are limited data.
925-927	1	Comment: PK profiles and relative bioavailability are important factors influencing the comparability of MOS studies. While the authors state that attention needs to be given to these factors, it remains unclear, how this might be done, and if there are limits to the extent of differences in PK profiles and bioavailability that still allow pooling of study data. Proposed change: It is proposed to rephrase the sentence, focussing on explaining what is meant by "give attention to", and if necessary to include limitations for the pooling of studies.	This section is amended as follows: 'When calculating the MOS, studies from different products should only be pooled if the PK profiles are similar. Strict bioequivalence is not necessary also considering that TAS studies are not anyway able to determine a precise MOS due to the dose multiples used. However, the degree of pharmacokinetic variability that can be accepted will be dependent on the (new) therapeutic index of the active

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			substance. Relevant information may be found in the pharmacokinetics studies for the individual products. Assumptions may also be made regarding the relative bioavailability of different formulations based on the principles for biowaivers outlined in the CVMP's Guideline on the conduct of bioequivalence studies (EMA/CVMP/016/00)'.
941	1	Comment: Referring to the comment made for line 920, a subheading with a consecutive numbering would improve the clarity of this paragraph. Furthermore, it might be beneficial to indicate, which requirements studies have to fulfil, in order to be pooled for the re-evaluation of reproductive safety. Proposed change: It is proposed to further structure this paragraph by including: 6.3.1.3 Reproductive toxicity Additionally, it is proposed to include the following sentence: "Reproductive safety studies for all products with the same active substance, pharmaceutical form and route of administration, indicated for the same target animal species, should be reviewed in order to confirm reproductive safety.	Additional numbering has been included, partially as requested. The additional information requested is already included at the start of 6.3.1.
942-943	1	Comment: The assumption that there is no reproductive toxicity at 3x ORTD, if a product is approved for use in breeding animals is highly speculative. As most products that are re-evaluated under the scope of this reflection paper have been initially registered at a time, when requirements for target animal safety studies were	Amendments agreed.

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		more lenient, it cannot be ruled out that there is a negative effect on either pregnant animals or offspring, especially considering higher doses. Therefore, it is proposed to reconsider this assumption and only determine the margin for reproductive safety based on available study data. If reproductive safety studies are neither available for target species, nor for laboratory animals, the SPC should be amended, stating that reproductive safety has not been demonstrated and the product should only be used according to the benefit/risk assessment by the responsible veterinarian. Proposed change: It is proposed to delete the sentence: "It is assumed… at 3x ORTD". In agreement with the following comment on line 944, it is furthermore proposed to amend the last sentence of this paragraph as follows: "If there is a lack of reproductive safety studies or the a margin of safety of the improved dose is below 3, additional risk management measures should be implemented, including strengthening of warnings in SPC 4.7 (NtA, Volume 6C) e.g., restrictions on use in breeding animals or only according to the benefit/risk assessment by the responsible veterinarian."	
944-945	1	Comment: According to VICH 43, reproductive safety studies should be conducted with 3 x ORTD in order to ensure that safety is guaranteed despite accidental overdosing, higher doses due to the pharmaceutical form (e.g., tablets) or increased susceptibility for adverse effects due to physiological variations of the treated animal. Following the explanations of the authors, who state that reproductive safety can be assumed, if the improved dose is lower than 3 x ORTD and safety was shown for 3 x ORTD, the actual margin of safety for the improved dose could be as low as 1. Based on Guideline VICH 43, reproductive safety studies, however, require treatments with 3 times the recommended dose in the treatment group.	

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		Albeit this reflection paper adopts a pragmatic approach, unconditional reproductive safety should only be indicated in the SPC, if it was demonstrated with a sufficient margin of safety. Therefore, it is proposed to adjust the SPC, if reproductive safety has not been shown for 3 times the improved dose similar to products for which reproductive safety only has been demonstrated in laboratory animals. Proposed change: The authors are asked to consider the following wording: "If this dose is lower than the margin of safety demonstrated in reproductive safety studies, then it is probable that reproductive safety could be accepted for the improved dose, albeit with a lower margin of safety." In agreement with the previous comment on line 942 the following changes are proposed for the last sentence in this paragraph in order to underline that risk management measures might be essential, if the margin of safety is low. "If there is a lack of reproductive safety studies or the margin of safety of the improved dose is below 3, additional risk management measures should be implemented, including strengthening of warnings in SPC 4.7 (NtA, Volume 6C) e.g., restrictions on use in breeding animals or only according to the benefit/risk assessment by the responsible veterinarian."	Partially accepted. Part of the original text is maintained as it is possible that a MOS <3 was accepted from the studies.
950	1	Comment: In alignment with the previous comments about structuring of this paragraph by using consecutive numbering, "Local tolerance" should be preceded by the corresponding numbering. Furthermore, it might be beneficial to indicate, which requirements studies have to fulfil in order to be pooled for the re-evaluation of local tolerance. Proposed change: It is proposed to further structure this paragraph by including "6.3.1.4 Local tolerance"	Additional numbering has been included, partially as requested. The additional information requested is already included at the start of 6.3.1. A cross-reference is made to Step 6 for consideration of impacts of the excipients.

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		Additionally, it might be beneficial to indicate, which requirements studies have to fulfil in order to be pooled for the re-evaluation of local tolerance.	
954	1	Comment: In alignment with the previous comments about structuring of this paragraph by using consecutive numbering "Palatability" should be preceded by the corresponding numbering. Proposed change: It is proposed to further structure this paragraph by including "6.3.1.5 Palatability"	As above.
956	1	Comment: It is not clear, why there is a "Step 1a", if it is not followed by "Step 1b". However, referring to the comment on line 920 and the proposed inclusion of subheadings, it might be considered to include "additional considerations" as a further subheading followed by the paragraph now following "Step 1a". Proposed change: It is proposed to further structure this paragraph by including "6.3.1.6 Additional considerations"	Step 1 is a review of classical TAS studies for the specific target species under consideration, as would be included in Part IV.I.B of the dossier. Step 1a relates to studies that could be used from other parts of the dossier, or from different product 'groups' or from species or routes of administration other than the one of concern. It is proposed not to amend the numbering of Step 1a.
966-967	1	Comment: Referring to the comment on line 920, an unambiguous and uniform description of requirements for pooling of studies is recommended. Proposed change: The following change is proposed: "Review the safety data from the clinical field trials in the target population for all products with the same active substance	Amended as follows: '…by the same route of administration to the concerned target animal species/category.' Additional information has been included: 'Although formulation differences affecting bioavailability should not be overlooked,

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		and pharmaceutical form that are administered preferably by the same route of administration.	the main purpose of field data is to investigate the potential impact of a dose/regimen change on safety across the diversity of the target population characteristics and in the presence of disease'.
981-988	1	Comment: In the examples on amoxicillin and oxytetracycline "grey literature" and text books are cited and used to evaluate TAS. It is not clear, why both are not mentioned in this general part. Furthermore, there is no information on quality requirements for references, and how these references should be assessed. Proposed change: It is proposed to include sub paragraphs on grey literature and text books, including quality requirements and necessary considerations for using them in TAS evaluations.	At high level, the requirements for published literature references should not be any stricter than those required for a 'well-established use' application, as laid out in Volume 6B of Notice to Applicants. In regards to reporting requirements for studies, quality criteria could impact more widely beyond the scope of the pilot project. In practice, assessors refer to relevant guidelines (e.g. VICH, OECD) when assessing study quality. In Step 4, use of reports from scientific institutions and textbooks has been added.
986	1	Comment: Referring to a previous comment (i.e., line 892), an explanation on what requirements products have to fulfil, in order to be considered similar, might be essential, to understand the proposed approach. Proposed change: The authors are kindly asked to further elucidate what is meant by "similar products".	The broad requirements are laid out throughout the chapter, but at Step 4 more flexibility may be required therefore no further specification is made.

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992-994	1	Comment: It is not clear, how it is possible to conclude on the safety in step 5 and consider step 5 at the same time. This is most probably a typo and should be corrected. Proposed change: The sentence should be revised.	Typo corrected. Thank you.
1021	1	Comment: It is not clear, why Ampicillin is mentioned in this introductory sentence, as the whole chapter is on amoxicillin. Proposed change: The authors are kindly asked to explain, why ampicillin should be included in this sentence, else it is proposed to delete it in order to prevent confusions.	Agreed.
1041	1	Comment: 7.2.1. Determination of the PK parameters Information on PK data relating to chapter 3, step 2 is missing. Proposed change: Please clarify whether there is dose linearity, a difference in bioavailability between products and if the free plasma concentration representative for the target tissue biophase?	Please note that all information used for the amox case study came from published literature.
1047 Table 4	3	Another new reference available: J Vet Pharmacol Ther. 2018 Jun;41(3):356-368. doi: 10.1111/jvp.12482. Epub 2018 Jan 19: Amoxicillin-current use in swine medicine. Burch DGS, Sperling D.	It is acknowledged that the information used for the case studies is not complete, and this was also not the aim. More information may be available e.g. in registration dossiers and public literature.
1042-1088	1	Comment:	Agreed.

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		It is understood that text in lines 1042 – 1056 relate to "summary PK data" and lines 1057 -1088 relate to "raw PK data". Proposed change: For clarification, please include sub- headings. At the beginning of chapter 7.2.1: "summary PK data (first approach according step 6 in chapter 3)" and replace in line 1057 ~~Population Pharmakokinetics~~ by "raw PK data (second approach according step 6 in chapter 3)"	
1048-1054	1	Comment: Arithmetic means and standard deviations are only meaningful for normally distributed parameters but some PK parameters such as AUC are not normally distributed Proposed change: Please state the correct means for each parameter.	Agree. For MCS, the log normal law is used for AUC but the mean and var used were those described in the scientific papers which is arithmetic. For the PK model, the mean are geometric mean.
1049	1	Comment: … clearance, the bioavailability and the apparent clearance. Proposed change: Please clarify the meaning of "apparent clearance".	Not modified. It means clearance observed.
1055-1056	1	Comment: For amoxicillin … 0.6 to 0.8. Proposed change: please add units for bioavailability and free fraction amoxicillin plasma concentration	Not modified. It is a fraction (no unit).
1065-1066	1	Comment: It is a two-compartment model with a zero order input rate (K_0) between lag time (T_{lag}) and end time (T_{end}).	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were

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		Proposed change: Please explain why a two compartment model was used in this case study. In addition, the use and choice of compartment models and its purpose is not mentioned in chapter 3.3.6, yet. This should be supplemented in step 6 of chapter 3.	based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1076	1	Comment: … non-linear mixed effect model… Proposed change: It should be specified more in detail what type of non-linear mixed effect model was used and why.	Not modified. The model is described in the text (see ref).
1079-1084	1	Comment: The graph and the table seem not to fit: the graph shows that the curves for formulations 1-3 are identical although AUC_{24} for the formulation 3 is about twice that of formulation 1 or 2. Proposed change: Please clarify.	Thanks for the comment. Graph revised
1099	1	Comment: … between 2002 and 2016… It is noted that MICs older than 5 years were considered that may not appropriately reflect the current susceptibility situation. Proposed change: The fact that the MICs may not appropriately reflect the current susceptibility situation should be noted in the conclusions to define an optimal daily dose (7.2.7) of this case study.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1107	1	Comment: … Define the PK/PD index…	Please consider Toutain et al., 2017 and

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		Further justification should be provided to use the PDI AUC/MIC instead of the PDI T>MIC that is typically reported to be the index best predictive for clinical efficacy in beta-lactam antimicrobials including amoxicillin. Proposed change: It is suggested to mention in the first place that the PDI T>MIC that is the index best predictive for clinical efficacy in beta-lactams together with PDTs that have been proposed for this PDI followed by a justification why to use the AUC/MIC for amoxicillin instead.	Nielsen, Friberg 2011
1124	1	Comment: … target values for a target attainment… Proposed change: … ~~target~~ values for ~~a target attainment~~ **the PDT**~~-~~..	Done
1124-1126	1	Comment: … derived from a study performed in calf with amoxicillin against Pasteurellaceae (Lees *et al.*, 2015). It is assumed that no data on PDT values for AUC/MIC are available for pigs and therefore PDTs reported for calves were used. However, this is not in line with chapter 3.3.4, where no information is provided that PDTs from non-target animals can be used. Thus, the use of non-target PDTs should be properly justified in this case study and chapter 3.3.4 needs to be revised, accordingly. Moreover, in the publication of Lees *et al.*, 2015 *in vitro* data with no correlation to clinical efficacy are reported. This should be reflected and a justification for the appropriateness of the proposed PDTs should be provided. Thereby, considering also that the publication of Lees is about bovine target pathogens i.e. Pasteurellacea. Pharmacodynamics effects of amoxicillin on Pasteurellacea may be different from on swine target pathogens, in particular for *A.pp.* that can be located and survive intracellular in alveolar macrophages.	Partially agreed, the sentence has been revised to improve the understanding.

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		Proposed change: Please revise the paragraph according to the comment above. In addition, chapter 3.3.4 needs to be revised, accordingly. Moreover, the limitations with regard to the used PDTs should be mentioned in the conclusions of the case study (7.2.7).	
1141-1142	1	Comment: … a PDT such as 40% (static PDT) to 60%... In lines 342 to 345 of the report is stated: In general, beta-lactams require 40-80% $fT>MIC$ of the dosage interval to achieve bactericidal activity depending on the individual class and the target bacterial species (Ambrose, Bhavnani et al., 2007). Proposed change: Please explain why PDTs lower than 80% were considered appropriate for this case study.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1186-1197	1	Comment: Table 10… two different values for the PD parameters can be selected, (i) a single MIC values … (ii) a distribution of MICs ... According to previous comment on line 1199 it is noted again, that MICs older than 5 years were considered that may not appropriately reflect the current susceptibility situation. In addition, in is stated that the whole distribution of MICs for each species was used. Even if not mentioned in the text it is assumed that MIC distributions below the ECCOFFs (wild type MIC distributions) rather than whole distributions were used. If this assumption is correct PK/PD integrations would not be 'dose optimising' since bacteria with decreased susceptibility are not taken into account. Proposed change:	In the introduction it is aknowledged that for amoxicillin the PDT between 40% and 80% is recognised. In this table we consider only 60% as the PDT representative of bactericidal activity (reduction of 2 log), the value of 80% could correspond to a higher therapeutic objective of 4log reduction.

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		Please clarify whether whole MIC distributions or MIC distributions below the ECCOFFs were used. The fact that the MICs used in this case study may not appropriately reflect the current susceptibility situation should be noted in the conclusions of the case study in chapter 7.2.7. Next to that, information on which MIC data are eligible and are appropriate is missing in the introductory part of the PPHOVA approach (chapter 3). The pros and cons to use single MIC values or whole MIC distributions /wild type MIC distributions should be introduced, discussed and supplemented there.	
1214-1216	1	Comment: Monte Carlo simulations … were performed using simulX of R software implemented with the package mlxR. Proposed change: The modelling process should be described more in detail.	This document is a pilot project on the feasibility of such modelling approach not a guideline on how the modelling have to be done. If such guideline is proposed, then more details of the modelling may need to be presented.
1219-1221	1	Comment: … PTA to maintain concentration above the MIC with the wild type distribution of the susceptible bacterial species were estimated from the simulations …. The use of wild type distributions in PK/PD integrations cannot be considered as 'dose optimising'. Please see previous comments. Proposed change: Justification should be provided how a doses can be optimised when only wild type distributions are considered in the PK/PD integrations and this should be noted in the conclusions of the chapter to define an optimal daily dose (7.2.7).	The objective of an antimicrobial ltherapy is to treat WT population, increasing the dose to be able to treat non susceptible bacteria is not under prudent and rational use. In this situation, the better option is to select another antimicrobial.
1255-1257	1	Comment: … results in Table 12 revealed that fractionation of the dose increases the	It should be noted that the case studies

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		probability to attain the target value of the PDI …mainly due to the short half-life. As shown in chapter 7.2.5.2, favourable results considering the T>MIC are only achieved when the daily dose of 40mg/kg bw is fractioned i.e. the daily dose of 40mg/kg has to be divided into 5 mg/kg/3h. This clearly indicates that even if the daily dose is increased to 40mg/kg (based on PK/PD modelling of the PDI AUC/MIC), the dose interval (based on modelling of the PDI T>MIC) plays an important role, at least when the half life is short as demonstrated here for amoxicillin. In this case study this result may be "compatible with an administration via drinking water and could be viable under field conditions where pigs have *ad libitum* access to water". However, this may not be applicable (impractical) for other administrations e.g. in feed formulations where the daily dose can hardly be split in such short dose intervals. In such situation what would be then the outcome of the PPHOVA approach? Proposed change: With regard to the comment made above the limitations of the use of the PDI AUC/MIC are shown. Thus, the use of AUC/MIC as a point of departure in the PPHOVA should be carefully reconsidered or at least critically discussed.	were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1269-1271 (also once more cited in lines 1287-1288)	3	"A recent paper (Burch & Sperling, 2018) reviewed the use of amoxicillin in swine looking at the various formulations and routes of administrations in regards to clinical efficacy. **They considered epidemiological cut-off values in their PK/PD correlation and concluded that an oral dose of 20 mg/kg bw might not be suitable and should be increased."** For which type of infection there was extracted this "reformulated" conclusion from the article? And was the dose 20 mg amox/bw/once daily … or divided i.e. 10mg amox	Thank you for providing the reference to this paper. It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		/bw/twice daily ? Not agreed to use this statement above in the reflection paper as the conclusion in our opinion differs from the conclusions of the authors of the article. Based on the article from Burch and Sperling, where is written - citation word by word: *"Amoxicillin given in feed at 20 mg/kg bodyweight were highly effective in controlling A. pleuropneumoniae infections."* And it should be also noted another part of Burch and Sperling article – citation word by word: *"A PTA rate of 90% was never achieved with the breakpoint recommended of 0.5 µg/ml (Schwarz et al., 2008) when administered at a single dose of 20 mg/kg bodyweight orally on a daily basis."* This part is related to simulations and modelling made by Rey et al (2014) and does not represent the clinical results. There should be also distinguished/considered different pathogens and different dosing schedules (20 mg/bw/daily for **X** consecutive days) vs (10 mg/bw/ twice daily = 20 mg of total daily dose but divided for X consecutive days). Please also read the part of the Burch and Sperling article from the perspective of clinical considerations, which is very important.	
1282	1	Comment: 7.2.7. Define an optimal daily dose In lines 1177 to 1180 it is stated: "With the proposed dose and due to the high MIC values for *B. bronchiseptica,* this target pathogen never reaches the PK/PD objectives. *B. bronchiseptica* should be deleted from the therapeutic indication of amoxicillin administered by the oral route to pigs when one is optimising the dose.	Agree. Done

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		Proposed change: This finding should mentioned and discussed in this chapter.	
1289-1297	1	Comment: … optimized dose …is 40 mg/kg bw … fractionating the dose of 40 mg/kg bw newly defined, during the day in function of the drinking rhythm and behaviour of the treated animal. For the Amoxicillin case study products with approved doses of 10 – 20 mg/kg bw given once or twice daily for 3-7 days (line 1032) were considered. With regard to the approved doses of products considered in this case study the conclusion in 7.2.7 is not fully consistent/sufficient. What is the consequence for products with dosages below 40 mg/kg bw? With regard to a once or twice daily application, it should be clarified whether 1 x 40mg once daily and/or 20mg twice daily is recommended? In addition, the PPHOVA approach does not take the entire treatment duration into account. It should be explained how one should proceed with the different treatment durations (3-7 days) of the products included in this case study. Proposed change: Please clarify and amend the conclusions according to the comment made above.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. Regarding the duration of treatment we clearly indicate in the document that this is one of the limitation of this approach.
1302-1304	1	Comment: It is not clear how the information on posology and withdrawal periods for different products containing amoxicillin has been gathered. However, checking the data for products authorized in Germany using our national product database, there seem to be some mistakes (see comment on line 3185, Annex 3), which might put the reliability of the data source into question. The differences in data do not result from the 8 years passed by since 2010 as some	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		of the products listed in Annex 3 were never authorised as they are listed there. Proposed change: Please correct data listed in Annex 3 and accordingly adapt Table 13.	
1308-1309	1	Comment: No information is provided on the criteria used for selection of amoxicillin products used for this compilation. Inclusion as well as exclusion criteria used should be provided to make the approach used transparent to the reader. Proposed change: Please provide the criteria used for the products listed in Table 13.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1330	1	Comment: The text "...in pigs after i.v. and i.m. administrations presented in Table 14..." does not match with the labelling of table 14 "... in pigs after oral administration..." (line 1332) Proposed change: Correct the text or the labelling to ensure consistency of the information provided.	Text is amended appropriately.
1368-1383	1	Comment: The study description is difficult to read and also seems to contain some inconsistencies. It does not become entirely clear which value of T_{max}, $t_{1/2}$ and C_{max} or which statement concerning linearity/non-linearity corresponds to which route of application (feed or drinking water). Furthermore, the dosages used are inconsistently listed as 11.6 and 23.2 mg/kg (line 1370) and as 14.5 and 29 mg/kg in line 1383. The T_{max} for the higher dosage is missing in line 1373. Proposed change: Please rephrase the paragraph to increase readability, e.g. by insertion of a	Text is amended appropriately. It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		table listing the relevant parameters.	
1401	1	Comment: Concerning dose linearity only plasma values were taken into account. As mentioned in the comment on lines 618-639, it needs to be considered whether using plasma values only would be sufficient. There might be cases when plasma levels show linear kinetics, while tissue levels do not. Can Equation 2 be used in these cases? Proposed change: Please include a discussion concerning this point.	Comment noted. Depending on the data that were available. It was already mentioned that if more data would have been available the outcome of the test cases could have been different.
1406-1408	1	Comment: Godoy et al. (2010) discussed in their paper that the dose-linearity shown is not in agreement with results from other papers, which in their opinion is attributable to nonlinear absorption and they stated that the dose level which saturates the absorption in pigs is not clear. Proposed change: The critical discussion of Godoy should be mentioned in the text to provide a complete picture.	Comment noted. We believe that a further discussion of that paper would not improve the test case as it is presented here as an example.
1409-1410	1	Comment: It does not become entirely clear how the cited references would support the assumption of dose linearity. Both papers are only dealing with an "assumption of dose linearity" without providing any proof. Proposed change: Please delete this sentence, as it does not contribute to show dose linearity for the amoxicillin example.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1427-1429	1	Comment: This paragraph is a citation from an SPC for a human medicinal product (dosage	It should be noted that the case studies were presented as an illustration of how

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		form: capsule). It seems questionable in how far this citation proves/supports the linearity assumption for different dosages of amoxicillin in pigs using powder which is solved in drinking water. Although the dose range based on a 60 kg person (4.1 to 50 mg/kg bw) includes the dose range used in pigs, it seems questionable whether the comparison based on similarities in GI tract only (ignoring the different application forms) should be used as supporting evidence for dose linearity of amoxicillin in pigs. Proposed change: This paragraph should be deleted or, alternatively, further data showing comparability of human and pig data (including discussion of different application forms, e.g. capsule versus drinking water solution) should be added.	the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1435	1	Comment: Linearity is shown for concentrations in plasma only. As this is an important information (please also note comment to lines 621-625), this should be added to the summary Proposed change: The text should be amended accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1499-1508	1	Comment: It seems that the calculations were based on arithmetic means, which would not be correct from a scientific point of view (see comment to lines 618-639). For muscle and fat tissues data for two time-points only are available. Terminal half-lives based on two time-points only are rather questionable, i.e. not meaningful, since log-linearity cannot be assessed. This should be clearly indicated in the text/tables, similar to the comments given in table 18. Proposed change: Please change the text in accordance with the above mentioned pitfalls,	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		especially including a critical discussion on the use of arithmetic means and a recommendation on how to proceed if only aggregated data are available.	
1509-1528	1	Comment: Again, calculations seems to be based on arithmetic means, which is not correct from a scientific point of view (see comment on lines 618-639). Additionally, the information provided in the Figure 20 does not match with Table 19. Values for liver and skin/fat tissues presented in Figure 20 seem to be roughly the same and data points at days 1, 2, 4, 6 and 8 are shown for residue concentrations in both tissues. As only one LOQ value is mentioned in the caption, 20 µg/kg seem to be applicable for all edible tissues. Figure 20 seems to contradict with the comment listed in Table 19, that in fat only two slaughter times with residue concentrations above the LOD were available. As this is not mentioned for liver tissues, data from more slaughter times seem to be available. To ensure consistency, the number of slaughter days with residue concentrations above the relevant analytical limit should be clarified. The figures are dealing with values above the LOQ whereas the tables comment on values above the LOD. Proposed change: Please change the text in accordance with the above mentioned pitfalls, especially including a critical discussion if the arithmetic means were used.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1534	1	Comment: One prerequisite that needs to be fulfilled before extrapolation of withdrawal periods can be applied, is completeness of distribution at MRL level. However, this aspect was not considered for the amoxicillin example. Proposed change: Please include a paragraph on tissue distribution at MRL-level.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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1538ff	1	Comment: As mentioned in section 4.4 No 3 "There should be a check whether other tissues (other than the original WP-determining tissue) may become critical for the WP, as a result of possible differences in $t_{1/2}$ between the tissues." Even if this is not the case in the example here, this point should be checked and discussed in all examples since this is of high importance for the applicability of Equation 2. Proposed change: Please include a discussion concerning possible changes of WP determining tissue.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1540-1541	1	Comment: Linearity was only shown for a dose range up to 20 mg/kg. In section 4.4 line 623 it is stated "Do linear kinetics apply for the intended dose range (yes/no)". Therefore, as the intended dose is 40 mg/kg the answer to this question will be "No" and there should be a statement/discussion how this will be handled in the context of this exercise and what the impact will be if linearity over the whole dose range cannot be shown. This should take also Figure 17 into account, as it seems that the variance of data points increases with dose. Additionally, it is stated in line 633 that Equation 2 should be used only if the condition of linear kinetics is fulfilled. Furthermore, as mentioned in the comments to 4.4 (lines 621-625) dose linearity needs to be shown for the target tissues and not for plasma only. Proposed change: It is proposed to amend this paragraph with the applicable dose range for which dose linearity has been shown. It should be clearly stated, that Equation 2 may only be used if dose linearity is shown for the target tissue and for the respective dose range.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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1548-1550	1	Comment: The longest half-live estimated in section 7.3.6 was 2.7 days. Therefore, it seems questionable whether 48 h indeed represent the worst case. Proposed change: The selection of a "worst-case" half-life should be discussed.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1552	1	Comment: As mentioned in the comments above not all conditions are fulfilled or not even checked and a discussion of this is missing. It raises concerns that Equation 2 was simply used without any discussion of uncertainties involved. Proposed change: Include a discussion/explanation why Equation 2 can be used although not all preconditions are fulfilled and what might be the implication for the outcome.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1600	1	Comment: Overall, the whole chapter on TAS evaluation for amoxicillin would be easier to understand, if the scheme presented in chapter 6.3. would be applied in the examples as well. For Step 1, e.g., target organs and the toxicity profile have to be determined and a new MOS has to be defined. Reproductive toxicity, local tolerance and palatability have to be evaluated. If the examples would follow the same structure including subheadings as part 6.3., it would be easier to notice, if data are missing. Furthermore, if there is a lack of sufficient data e.g., on palatability, this would be an essential information as well, and therefore, should be addressed in the manuscript. Proposed change: It is proposed to revise the structure of this paragraph following the example	General comment Detailed comments have been received on the case studies. It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. Please also note that within the scope of this reflection paper, reporting of studies, discussions and conclusions have been

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		given in chapter 6.3. If data are missing, this should be stated and implication for the validity of the target animal safety evaluation should be discussed.	kept at high level focused on the key issues relating to the practicability of the approach for necessary brevity of the report and for data confidentiality reasons. Some amendments have been made as requested. The impact of missing data on the TAS assessment is further discussed in chapter 9.4 of the report.
1604-1614	1	Comment: While the authors present the key facts of the provided TAS studies, comparability and clarity of the results may be improved by following a well thought-out scheme including those factors that are important to interpret the study results. Maybe a kind of checklist might be beneficial. Proposed change: The following scheme may be considered in order to improve clarity of the presented results. Active substance: Formulation (e.g., excipients, name of the product or a consecutive number for the product to allow anonymity): Pharmaceutical form: Route of administration: Year the study was conducted in: Study animals (species, number, age, sex): Dose: Outcome variables:	See above. For the purposes of the reflection paper, the aim has been to provide a very concise summary of the studies and key information available. The proposed scheme is useful, but more appropriate for a detailed assessment report rather than this reflection paper.

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		Results: Study according to GCP: Study according to VICH43: Study limitations:	
1610	1	Comment: It seems as if target toxicity organs, the toxicity profile, palatability and local tolerance, have not been considered for the re-evaluation of amoxicillin, perhaps due to a lack of available data. Nevertheless these information are essential to estimate TAS and, if unavailable, this lack of pivotal data should be mentioned and the implications for the validity of the re-evaluation should be discussed. Proposed change: It is proposed to either include information on target toxicity organs, the toxicity profile, palatability and local tolerance or state that relevant information were not available. However, if data are missing, this should be discussed critically and may make it unfeasible to draw a final conclusion on target animal safety.	Not agreed. Specific palatability studies were not available – this is now addressed in Step 1. Local tolerance is not generally considered for oral formulations. Overall conclusions relating to the toxicity profile and MOS are drawn in Steps 1 and 4 and the conclusions laid out at step 5. For the purpose of the reflection paper, the aim has been to provide a concise summary of the studies and key available information. Further discussion on data availability, limitations of the approach and conclusions are given in chapter 9.4.
1622-1680	1	Comment: The paragraph on "published literature" is difficult to read as subheadings are missing. As briefly commented above (i.e., line 981), it seems that the quality of references was not evaluate for this exemplary re-evaluation of amoxicillin	Please see earlier comment to line 981. It was not within the scope of the project to develop a quality standard for literature references.

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		target animal safety. The validity of information, however, is deemed highly relevant as information drawn from peer-reviewed papers is likely to be more valid than from expert opinions or homepages. An adaption of the evidence pyramid might be useful to assess the quality of literature and decide the relevance of derived information. Proposed change: It is proposed to restructure this paragraph and include subheadings like "peer-reviewed journals", "text books", "grey literature" and so on. A concurrent numbering of these subheadings comparable to the one proposed for step 1 might furthermore improve understandability. In addition, it is proposed to assess not only the content of the literature provided for Step 4, but also indicate the quality and evidence level. This might also be used to formulate are decided conclusions on target animal safety and indicate, how well-founded these conclusions are.	The heading 'peer-reviewed journals' has been added. The other headings were already included.
1636-1648	1	Comment: Referring to older SPCs of EU-authorized products might lead to citation bias, as SPCs cannot be considered primary literature. Furthermore, if SPCs are cited for the examples amoxicillin and oxytetracycline, they should also be mentioned in part 6.3.4 including benefits and risks associated with citing and referring to SPCs. Concerning this example, it would be helpful, if not essential to know, to which products and with which related dosage the statements refer to. Especially the information on no side effects at 5 times the recommended dose can only be interpreted, if the dosage is provided. Proposed change: It is proposed to revise this paragraph and include information on the products and related dosages, which these SPCs originate from. Furthermore, "Information from SPCs of EU-authorised products" should	The following statement has been added to 6.3.4: 'Information on target animal safety is available in the published SPCs of EU-authorised products. If supporting data are available (e.g. proprietary studies, pharmacovigilance reports, literature) they should be assessed in Steps 1 to 4. If the origin of the information is not verifiable, it should be reviewed critically'. For the purposes of this reflection paper for which the information available has been summarised, it is intended to retain

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		be listed at 6.3.4.	only a consolidated summary of the SPC information.
1658	1	Comment: Unfortunately, it is not clear, where the data mentioned under the heading of the JECFA meeting originate from, as the summary report of the 75th JECFA meeting does not include any NOAELs. While the quality and credibility of data presented at the JECFA meeting is most probably sufficient, it should be stated, what criterions are used to select appropriate literature. Overall, transparency about the origin of data, including the applied search criteria, the complete reference (according to a standard citation style), and how these data were interpreted is essential in order to increase transparency of the results. Furthermore, congress abstracts were not mentioned at 6.3.4 as eligible literature. Proposed change: It is proposed to revise this paragraph and include information on the origin and the evidence level of the cited data. Furthermore, "Congress Abstracts" should be listed and discussed at 6.3.4., including quality criteria.	The incorrect reference was included in the reference list. The correct citation is *Toxicological evaluation of certain veterinary drug residues in food / prepared by the seventy-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives* (JECFA).
1662-1664	1	Comment: The reference for the information on human toxicity is missing and should be added to this paragraph. Proposed change: It is proposed to include the appropriate reference for the data presented for "Human toxicity".	The underlined heading above is the correct reference (Toxicological evaluation of certain veterinary drug residues in food / prepared by the seventy-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).)
1673-1680	1	Comment: It is understood that the conclusion line 1673 only refers to the published literature presented in Step 4. As this literature at least partly does not refer to the target species and/or route of administration or pharmaceutical form, this	Some clarifications have been added. Within the context of this reflection paper, high level conclusions are provided.

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		facts should be discussed critically and be reflected in the drawn conclusion. Proposed change: It is proposed to revise the conclusion and provide more transparency especially concerning data limitations.	
1685-1687	1	Comment: Albeit limitations are mentioned as a general term, those were not discussed critically, e.g., there are no studies that fulfil the requirements of VICH43, as animals should be treated for 3 times the recommended treatment duration (15d) and with at least 8 animals per treatment group. Furthermore, at least in part, data do not refer to the target species pig, but to laboratory animals or humans. Some of the used references only have a mediocre evidence level. For some points, e.g., palatability, local tolerance and reproductive safety no data were available. Considering this lack of data and the limitations for a part of the cited literature, a final conclusion on the safety of the improved dose of amoxicillin can hardly be drawn, if scientific standards and well-established guidelines are applied. Proposed change: It is proposed to revise this paragraph and word the conclusion more carefully, addressing strengths of the evaluation as well as weak points.	Some amendments have been made, but within the context of this reflection paper this is a high level conclusion, the weaknesses indicated are essentially addressed (local tolerance is not generally assessed for oral formulations) and the conclusion is guarded. The conclusion is amended: 'Overall it is concluded based on the limited data available that the proposed dose of 40 mg amoxicillin/kg bw per day for 5 days in drinking water is likely to be adequately tolerated in pigs.'

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1698-1707	1	Comment: As not only the type, but also the dose of an excipient, might affect target animal safety, it would improve transparency to add the new maximum dosage of excipients to the manuscript. Furthermore, in Chapter 6, it has been mentioned that step 6 should be carried out on a by-product basis, therefore it might by relevant to matched excipients with the correspondent products. Finally, some information on safety of the individual excipients would help the reader to comprehend the conclusions drawn by the assessors. Proposed change: The following examples might be considered: - Pentasodium triphosphate, improved dose X – Y mg/kg, Product 1, 2 and 15, no negative effects on TAS known - Lactose monohydrate, improved dose X – Y mg/kg, Product 1,5 and 6, may cause dose-dependent lactose intolerance	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. It is not intended to provide this level of detail for each product in the context of the project and was not possible within the timeframe.
1712-1716	1	Comment: In agreement with the previous comments (e.g., line 1673, 1686) and following the same line of justification (e.g., missing data on palatability and local tolerance, validity of cited references), there are concerns that the conclusion drawn for target animal safety considering dose optimization of amoxicillin, do not reflect the deficits of this exemplary evaluation. A more careful wording might be indicated. Furthermore, there seems to be a discrepancy between the heading, which	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		states a product individual conclusion and the drawn conclusion below that includes all VMPs. Proposed change: It is proposed to add the following or a similar sentence to this paragraph. …indicated for respiratory disease. A final conclusion concerning each individual product cannot be drawn at the moment, as available data were limited for this exemplary re-evaluation of the target animal safety of amoxicillin.	The conclusion is amended as follows: Overall it is concluded, within the context of this pilot project, that VMPs administered at the proposed dose of 40 mg amoxicillin/kg bw per day for 5 days in drinking water are likely to be adequately tolerated in pigs for the treatment of the indication for respiratory disease. A final conclusion for individual products cannot be drawn at this moment due to limitations on available data.
1717-1744	1	Comment: 7.6. Overall conclusion and recommendations on amoxicillin The comment on lines 1289-1297 applies also to this chapter. Proposed change: Please consider to include respective conclusions also in this chapter with regard to the comment made on lines 1289-1297.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1727-1734	1	Comment: The short-comings mentioned for section 7.3 (lines 1308-1559) should be discussed in a clear and honest way in this section including an uncertainty	Comment noted CVMP considered amending the text but honestly believes no revision would be in

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		analysis. Proposed change: Please amend the text accordingly.	order
1742-1743	1	Comment: It is agreed that no specific safety issues were identified in this re-evaluation, however as elaborated above, the dataset was quiet limited and certain aspects like local tolerance, reproductive toxicity or effects of increased doses of excipients were not addressed at all. While the example of amoxicillin gives a first idea about the applicability of the proposed approach, it is not valid to deduce that target animal safety can be assumed based on the presented concept, as long as some relevant points like those mentioned above have not been fully assessed. Proposed change: It is proposed to rephrase this paragraph and underline the limitations of this example, including, but not limited to only fragmentary data from registration procedures, additional data with partly low evidence level, a lack of data e.g., for palatability or local tolerance. It is also proposed to explain, why, despite what is proclaimed in Chapter 6, no product individual considerations, e.g., concerning excipients were made, and what that implies for the credibility of this exemplary evaluation of amoxicillin target animal safety.	Please see all relevant responses in respect of your comments on lines 1684 to 1716. Further discussion on the value and limitations of the approach are given in Chapter 9.4.
1758-1759	1	Comment: In Annex 5, a 30% formulation is mentioned beside a 10% and 20%. Proposed change: It is proposed to rephrase this paragraph and include the 30% formulation.	Agreed, text amended.
1769	1	Comment:	Add text in chapter 3 step 3 to

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		8.2.1. Pharmacokinetics Information on PK data relating to chapter 3, step 2 is incomplete. In addition, it is stated that there are "differences in pharmacokinetics", which would preclude to apply the PPHOVA approach. Proposed change: Please clarify whether the PK data for both, LA and SA formulations are viable for the PPHOVA approach i.e. whether there is dose linearity, a difference in bioavailability between products and if the free plasma concentration are representative for the target tissue biophase?	recommend to check this point. OK Comments added in the text.
1797-1814	1	Comment: It is understood that text relates to "raw PK data". Proposed change: For clarification, please include a sub-heading in line 1797 and indicate that this chapter is on analysis of "raw PK data (second approach according step 6 in chapter 3)".	Agreed.
1801-1803	1	Comment: … analysed using a non-linear mixed effect model using Monolix® (Lixoft) … performed in R using mlxR package. Proposed change: It should be specified more in detail what type of non-linear mixed effect model was used and why. Please indicate the formula as well as dependent and independent variables.	This document is a pilot project on the feasibility of such modelling approach not a guideline on how the modelling have to be done.
1803-1804	1	Comment: The PK model was a mono-compartmental model using an extravascular administration route. Proposed change:	Agree.

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		Please explain why a mono compartment model was used in this case study. In addition, the use and choice of compartment models and its purpose is not mentioned in chapter 3.3.6, yet. This should be supplemented in step 6 of chapter 3.	
1810-1814	1	Comment: The headings of the graphs do not fit with the legend. Proposed change: Please correct.	Agreed, and corrected.
1821-1828	1	Comment: The same MIC references as in the amoxicillin case were used in the OTC case study. Accordingly, it is noted again that MICs older than 5 years were considered that may not appropriately reflect the current susceptibility situation. In addition, it is not explicitly mentioned what kind of MIC values are used for the PK/PD integrations. It is assumed that wild type MIC distributions were used. If this assumption is correct PK/PD integrations would not be 'dose optimising' since bacteria with decreased susceptibility are not taken into account. Proposed change: Please clarify which MIC values (single MICs, whole MIC distributions, MIC distributions below the ECCOFFs) were used for PK/PD integrations of this case study. The fact that the MICs used in this case study may not appropriately reflect the current susceptibility situation should be noted in the conclusions of the chapter to define an optimal daily dose (8.2.8) Information on which MIC data are eligible and are appropriate is missing in the introductory part of the PPHOVA approach (chapter 3). The pros and cons to use single MIC values or whole MIC distributions /wild type MIC distributions should	The Reflection Paper has a paragraph explaining the pros and cons of the use of single MICs values. It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		be discussed and supplemented there.	
1833-1842	1	Comment: … PDT is based on *in vitro* data and is not validated on clinical efficacy basis. Considering that the PDT is based on *in vitro* data with no correlation to clinical efficacy a justification for the appropriateness of the proposed PDT should be provided. Proposed change: Please provide a justification for the appropriateness of the proposed PDT and supplement a discussion/conclusion on the PDI in chapter 8.2.6, accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1844ff	1	Comment: Based on the PK profile… Are these that the PK profiles established on PK data as outlined in lines 1797 to 1814? If yes, these PK profiles have been established on "raw PK data". According to chapter 3.3.6 raw PK data should be used to determine PDIs other than the AUC/MIC. Thus, the method described in 3.3.6 3 would not have been not consistently applied in this case study. Proposed change: Please clarify by taking into account the comment above.	Agreed.
1844-1846	1	Comment: … the Monte Carlo Simulation was performed with SimulX implement in R with the package mxlR using 5000 random values. Proposed change: The modelling process should be described more in detail.	This document is a pilot project on the feasibility of such modelling approach not a guideline on how the modelling have to be done.
1848	1	Comment: 4 x IM administration of 10 mg/kg bw	Agree. Done

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		Proposed change: 4 x IM administration of 10 mg/kg bw **at a 24 h interval**	
1916-1918	1	Comment: "According to … the PK/PD breakpoint can be set at 2 µg/mL …" Proposed change: Please explain more in detail/provide a rationale why the PK/PD breakpoint can be set at 2 µg/mL given that in lines 1823 -1825 it is stated: "…all the criteria requested by EUCAST may not be fulfilled to use this tools with confidence…"	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1932-1934	1	Comment: … for the SA – 10% formulation, there is no need to increase the daily dose … provided a sufficient exposure for all the target pathogens tested. For the SA – 10% formulations approved doses are: 4 – 20 mg/kg bw i.m. daily for 1 to 5 days (line 1762). With regard to the approved doses of products considered in this case study the conclusion is not fully consistent/sufficient. What is the consequence for products with dosages below or above 10 mg/kg bw? Should the dose of these products be amended to 10 mg/kg bw? In addition, the PPHOVA approach does not take the entire treatment duration into account. It should be explained how one should proceed with the different treatment durations (1-5 days) of the products included in this case study. Proposed change: Please clarify and amend the conclusions according to the comment made above.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1952-1955	1	Comment: … for the LA – 20% formulation, there is no need to increase the daily dose of	It should be noted that the case studies

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		20 mg/kg ... with a second injection between 36 to 48h … Approved doses for the LA 20% formulations are: 20 or 30mg/kg bw, single injection or repeated after 48 or 72 hours (lines 1760 to 1761). With regard to the approved doses of products considered in this case study the conclusion is not fully consistent/sufficient. What is the consequence for products with dosages above 20 mg/kg bw? Should the dose of these products be amended to 20 mg/kg bw? Proposed change: Please clarify and amend the conclusions according to the comment made above.	were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
1970	1	Comment: An aspect which also needs to be mentioned here is the possible impact of different formulations, which might have an impact on absorption from the injection site and hence on WP. Different formulations might also explain identical withdrawal periods for products applied at different dosages. Proposed change: Please add some text discussing this aspect.	We propose to leave the text as it is. Plasma kinetics show that absorption rates were comparable for most of the 10% and 20% formulations.
1978-1979	1	Comment: As mentioned in section 4.5 there might be a point were another tissue becomes WP determining. Therefore a sentence should be included mentioning this point. Proposed change: Please modify the text as follows: Since the residues on the injection site determine the WP for tissues, increasing the dose (within limits) by simply increasing the number of injections would have no effect on the WP for tissues. **This would continue to be the case until, due to the increase of the overall dose, residues in one of the other tissues would become WP**	We propose to leave the text as it is. The subject of this comment was already discussed in the RP.

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		determining.	
2001	1	Comment: The scaling in Figure 24 does not fit with the scaling in the Figure published by Meijer et al. 1993, resulting in lower levels in Figure 24 than in the publication. Proposed change: Please correct Figure 24 in line with the paper by Meijer et al. 1993.	Figure 24 was redrafted.
2005-2009	1	Comment: We assume that Table 29 might be dealing with intramuscular application and not with intravenous treatment because values for relative bioavailability are listed in the last line. For product administered intravenously, bioavailability would be 100%. Some kind of legend explaining the abbreviations in Tables 28 and 29 would be useful and units of column headings should be added. Proposed change: Please check and amend the tables concerning the aspects mentioned above.	Comment noted i.v. was corrected to i.m.
2011-2012	1	Comment: For the cited paper this sentence is correct. However, there are other publications showing also lower bioavailability as well as differences between products (e.g. Toutain 1983, Mevius et al., 1986, Nouws et al. 1985), these findings should also be mentioned to provide a better overview of pharmacokinetics of the different products/formulations. Proposed change: Please add the information from other publications mentioned above.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2019-2021	1	Comment: Neither Oxytetracycline-20% formulations nor a dose of 11 mg/kg are	Correct citation was added.

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		mentioned in the cited paper. Maybe the paper by Mevious et al (1986) is meant here? Proposed change: Please correct the citation.	
2024-2025	1	Comment: Figure 26 is included in the reflection paper two times. The graphs seem to be the same whereas the captions differ. Proposed change: Please check whether one of the figures needs to be exchanged or whether only one caption is applicable and adapt numbering of figures accordingly.	Figure 26 was deleted 1 time
2049-2051	1	Comment: It seems questionable in how far the data used in Table 30 are suitable to serve as proof for dose linearity. First of all, different products were administered at various dosages and routes of application. Based on the data provided in Table 30, dose linearity is not shown for different dosages of one product and the possible impact of different doses could be co-influenced by different formulations and application routes. Only some of the studies from the papers cited are listed in Table 30: e.g. Toutain & Raynoud (1983) did not only present clearance data resulting from the dose of 20 mg/kg (long-acting formulation), but also described a study on i.v. application of 10 mg/kg ("conventional formulation") in calves. Nouws et al. 1985 described different formulations with different AUC and $t_{1/2}$ values, which should also be included in the table. As clearance values are not mentioned in most of the publications, they seem to have been calculated by the authors of the reflection paper. This should be clearly indicated and the method of clearance calculation including the parameters (AUC, $t_{1/2}$, V) used and also the impact on the comparability of the	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		values should be mentioned. Further on, there are huge differences in clearance values between studies. The high values resulting from two studies conducted with doses of 11 mg/kg and 40 mg/kg are explained with higher total body clearance values in calves compared to older animals. This argument seems to be incomprehensible as some other clearance values, which were also derived from studies in calves, do not show higher clearance values compared to adult animals (e.g. Achenbach 2000) and also compared to other animals with similar bodyweights which are not listed as "calves" (e.g. Toutain & Raynaud 1983). Therefore the term "calves" seems to have been used inconsistently between the publications and, therefore, body weight might be a better indicator of age. Comparison of animals of similar weights leads to the conclusion that clearance values in younger animals are not consistently higher. However, if the higher values (marked with "*" in the table) are not taken into account, only two dosages would be left, 5 and 20 mg/kg. In both publications dealing with the 5 mg/kg dose (Nouws et al. 1985 and Mevious et al. 1986), the VMPs were administered intravenously but resulting clearance values largely differ. If only the clearance value of 130 ml/kg*h from calves treated at 20 mg/kg (Meijer et al., 1993) is ignored, the mean clearance value at this dosage would be 83.11 ± 8.81 ml/kg*h (i.m./s.c). This is quite different to the mean calculated for animals treated at 5 mg/kg (i.v.) 59.5 ± 23.33 ml/kg*h. It should be carefully considered whether calculation of a mean clearance for such heterogeneous values would lead to meaningful results. In conclusion, the meaningfulness of Table 30 in terms of dose linearity seems to be weak and should be critically discussed including an uncertainty analysis (and also taking into account the comment to lines 2011-2012). Further on, if for the case studies the assumption of dose linearity is assessed based on these	

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		results, this would need to be justified. Proposed change: Please add explanations/discussions (including uncertainty analysis) as mentioned above.	
2052-5053	1	Comment: The mean clearance value of 88 ± 23 ml/kg*h mentioned here seems to be the arithmetic mean of all clearance values listed in Table 30 including adult animals as well as calves. This seems to be somewhat inconsistent with the footnote to Table 30, indicating that total body clearances in young calves are significantly higher than in older animals. Separate calculations for young and adult animals may be more appropriate to derive representative values. Furthermore, the calculated standard derivation of 23 ml/kg*h comprises more than one quarter of the value for total body clearance, clearly indicating a high variability of values from the various studies. Therefore, the validity of this mean total body clearance for conclusion of dose linearity seems to be questionable. Proposed change: Please, either delete this sentence or update the value in line with conclusions drawn after the discussion of the study results listed in Table 30.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2054-2055	1	Comment: To allow for reliable conclusions concerning linear kinetics, the available values for total body clearance should be presented grouped by dosages, formulations and routes of application as well as by age categories. The text should include a discussion on variability of values for total body clearance allowing to draw conclusions on uncertainties. Furthermore, as already mentioned in the comments to paragraph 4.4 (lines 621-625), dose linearity needs to be shown for the target tissues. Total body	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		clearance only takes plasma concentrations into account, which might not be representative for concentrations in target tissues, at least for some antibiotic substances. This should be discussed. Proposed change: Please amend the text taking into account the aspects mentioned above.	
2071-2073	1	Comment: Half-lives listed in Table 31 seem to have been calculated based on arithmetic means, as only these values were reported in the cited publications. This may result in wrong half-lives; for details please be referred to the comment on lines 618-639. Furthermore, it seems that there is a biphasic elimination of oxytetracycline (fast elimination at first followed by a terminal phase with slower elimination). Therefore, attention should be paid to the time span used for determination of half-lives, as including early time-points may result in too short half-lives. The authors should provide information on the time spans used for $T_{½}$ calculation as well as the estimation for all half-lives calculated by the authors of the reflection paper. It should be clearly pointed out, whether only the slow terminal half-live (as mentioned as prerequisite in Section 4) was considered. In addition, the data presented here indicate that half-lives differ between various formulations. This is also mentioned in a publication by Toutain and Raynoud (1983), who found differences in half-lives between long-acting and short-acting formulations. These aspects should also be discussed here. Proposed change: Please include explanations/discussion as mentioned above.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2074	1	Comment: Unlike in the amoxicillin example where the worst case half-life was considered	It should be noted that the case studies were presented as an illustration of how

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		appropriate, for OTC a mean half-life was calculated. As this is inconsistent between the two examples, some explanation should be provided. Furthermore, concerning the individual tissue half-lives it would be needed to check whether the WP determining tissue changes with higher doses. For details please be referred to the comment on section 4.4 point 3. Half-lives in tissues showed large variations between studies and also the tissues with the longest half-life differ. The authors should discuss possible reasons as well as the impact of different half-lives on determination of withdrawal periods. Different half-lives might result from: • different time spans used in the studies • distribution not completed • effects of different formulations (as described e.g. by Toutain and Raynaud 1983) • effects of different application routes • different values used (e.g. arithmetic means versus geometric means versus individual data) to calculate half-lives • combination of some of the points mentioned above It seems questionable whether one meaningful mean half-life can be calculated from these heterogeneous values. Some guidance should be provided to the reader in which cases scientifically justified half-lives for different tissues can be calculated and when the highest half-life available from study data as a worst-case should be used. Proposed change: Please include explanations/discussion as mentioned above.	the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2075	1	Comment: One prerequisite that needs to be fulfilled before extrapolation of withdrawal periods can be applied, is completeness of distribution at MRL level. However, this aspect was not considered for the oxytetracycline example.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please include a paragraph on tissue distribution at MRL-level.	states that the case studies should in no way be regarded as the final answer.
2075-2077	1	Comment: We do not agree with the conclusion drawn from data in Table 31. If the WP for tissues would be determined by the depletion of OTC from regular tissues (edible tissues other than injection sites tissue), the half-life of the respective WP determining tissue needs to be used. Here a mean half-life for all studies and all tissues was calculated, which might lead to an underestimation of the real WP and hence to MRL exceedance. Furthermore, a check whether the WP determining tissue changes at higher dose (see section 4.4 point 3) also requires use of half-lives for individual tissues. As an alternative the longest half-life of all tissues might be used. As this represents the worst case, it would also make the check of possible changes in WP determining tissues superfluous. Proposed change: Please correct this paragraph taking into consideration all comments concerning lines 2071-2077.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2079-2081	1	Comment: The OTC example given in Figure 30 shows (more or less) linear depletion kinetics in injection site tissues. However, there is no evidence provided that this would be similar for products with different posology and for other doses. As already mentioned in our comment to lines 641-654, absorption and depletion of residues from injection sites is not linear in most cases, but depends on formulation of the product, blood flow at the particular injection site, dosage per injection site etc. Even if linear depletion kinetics has been shown at the lower dose, it might not be applicable at the higher intended dose. Therefore, we propose to exclude products for use via intramuscular or	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. The terminal half-live was 6 days regardless of the formulation. The reason for this was explicitely discussed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		subcutaneous injection from the approach of extrapolation of withdrawal periods via use of Equation 2. Proposed change: Please change the text accordingly.	
2094-2095	1	Comment: An increase in total dose via increasing the number of injection sites might result in a change of the tissue determining the withdrawal period. Please be also referred to section 4.4 point 3 concerning this aspect. Proposed change: Please change the sentence as follows: "When a dose increase can be performed by increasing the number of injection sites, no change in WP for tissues would be necessary **as long as no other tissue becomes WP determining. Further** animal welfare could be at stake."	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2096-2098	1	Comment: Increasing the dose by increasing the injection volume might not only alter animal welfare, but also pharmacokinetics of the active substance. This needs to be taken into consideration for extrapolation of withdrawal periods. Proposed change: Please amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2099-2100	1	Comment: As a further possibility to leave the maximum volume unaltered, the authors propose to limit the maximal weight of the animals to be treated. However, no increase in withdrawal periods would only result, if the withdrawal period determining tissue would be the same at the lower and at the higher dose. If another tissues would become WP determining, this might result in a different WP.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please amends the text as follows: "Dose increase could also be achieved by limiting the maximal weight of the animal to be treated. In that case (if the max volume remains unaltered) no change in WP would be needed no change in WP would be needed, **as long as the increase in dose does not result in a change of the withdrawal period determining tissue**."	The theoretical possibility that another tissue could become WP determiningwas already discussed in the RP. No need to repeat
2103-2116	1	Comment: Different amounts of oxytetracycline as well as different excipients (in different amounts) are contained in the various injection volumes taken from a variety of products. In the current example the influence of the injection volume on the resulting withdrawal period seems to be marginal according to the authors of the reflection paper. We do not agree to conclude this from the dataset for the followings reasons: - There is only a very limited number of samples included and the low effect of injection volumes might just have occurred by chance. - As the sample contains various VMPs with different concentrations of OTC applied to animals of different weight, no information whether the amount of OTC per injection site differs less or even more than the injection volumes can be derived from the data. - The differences in formulations of the various products may also have an influence on the residue depletion from injection sites and hence on WPs. - Safety factors added to the withdrawal periods might also play a role. It appears to be likely that the influence of differences in amounts of OTC applied and the impact of different formulations do not allow to draw reliable conclusions concerning a possible impact of injection volumes on withdrawal periods. Data on injection site residues resulting from application of different dosages of OTC from one VMP would be necessary to provide evidence on the impact of different injection volumes on withdrawal periods.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please include a critical discussion whether Equation 2 can be used in case of an increase of volume administered per injection site.	
2118	1	Comment: Figure 32 was transferred from a publication by Nouws et al. (1985) without the standard deviations as given in the original figure. SDs would be useful to show the variability of residue concentrations. Data points show arithmetic means instead of geometric means and thus, may give a wrong picture of residue depletion. Proposed change: Please modify/amend figure, labelling and text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2121	1	Comment: The only information that can be taken from Figures 32, 33 and 34 is that from a certain time point after treatment residue concentrations in plasma as well as in milk continuously decrease. It would be going too far saying that the time dependent course of concentration of OTC in milk mimics the pattern in plasma. It remains unclear what the impact of the ratio of milk/plasma in terms of extrapolation of withdrawal periods would be. Proposed change: Please modify/amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2125 + 2128	1	Comment on Figures 33 + 34: It does not become clear from the legend that numbers 1 to 8 refer to different OTC products. The means mentioned in the labelling accordingly seem to be arithmetic means from several samples taken from animals treated with one product. As mentioned above, the SDs as given in the original figure from Nouws et al. (1985) should be included in the figures.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please modify/amend figure, legend, labelling and text accordingly.	We consider the figures 33 and 34 correctly described
2134+2137	1	Comment on Figures 35 and 36: It is mentioned in the labelling that data used for these figures were taken from study 6. As this study number is not mentioned elsewhere, origin of these data remains unclear. Please indicate from which source the residue depletion data in milk were taken. X-axis of both figures should have the same scaling to make it easier to compare data. Figure 35 shows that $t_{1/2}$ changes throughout the residue depletion from 13.4 h to 6.8 days at around 14 days after treatment based on data from one single animal. But also in Figure 36 from the same study with mean residue concentrations from all animals included in the study, a different $t_{1/2}$ (3.9 days) was computed during the terminal elimination phase. This may indicate (huge) differences between individual animals. Maybe not only data from one single animal (as shown in Figure 34) and means (as shown in Figure 35) but data from all individual animals should be used to derive some kind of worst case $t^1/_2$. Coefficients of determination should be given in the figures to show how well the regression line fits the data. Proposed change: Please modify/amend figure, labelling and text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. The source of study 6 would have to remain unmentioned.
2140-2142	1	Comment: Since the terminal half-life from Figure 34 (6.8 days) is longer than the one resulting from the mean tissue depletion data (6 days) it does not become clear why the last one is indicated as the worst-case and should be used in Equation 2. This aspect needs clarification. The reader would also need some instruction whether half-lives may be different based on the OTC product used and if so, when half-lives from one study may be used for extrapolation of withdrawal	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.

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		periods for other products. Proposed change: Please modify/amend the text accordingly.	
2144	1	Comment: As mentioned in the comments above not all conditions are fulfilled and a discussion of this is missing. It raises concerns that Equation 2 was simply used without any discussion of uncertainties involved. Proposed change: Include a discussion/explanation why Equation 2 can be used although not all preconditions are fulfilled and what might be the implication on the outcome.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2157-2160	1	Comment: The conclusion drawn concerning withdrawal periods in tissues supposes that no other tissue will become WP determining by an increase of the number of injections. Please indicate in how far this was checked for the different products. Furthermore, it seems to be the case that for some VMPs the duration of treatment might be increased. Please explain how increases in treatment duration will be taken into account. The terminal half-life for milk could be as high as 6.8 days (Figure 35), thus this value should be used. As only data from animal 6 are given in Figure 35, it remains unclear whether even longer half-lives might be applicable. Proposed change: Please modify/amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2159-2160	1	Comment: This sentence needs to be modified. Proposed change:	Text was corrected.

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		It is suggested that the text should read "leading to an addition of 6 days for each **doubling the dose**".	
2164-2166	1	Comment: It would be helpful for the reader, to provide the assumptions and calculations on which the proposed maximum injection volume for cattle is based. Please see also comments to lines 2096-2098 and 2103-2116. Proposed change: Please amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. A further explanation is not considered necessary.
2169-2170	1	Comment: It remains unclear how it was ensured that injection sites will remain to be the withdrawal determining tissue after increases in dose. There is also no explanation on this aspect provided in the previous sections. As this is an important precondition, it should be scientifically assessed and the underlying calculations should be discussed based on data from the case study. Proposed change: Include an explanation/discussion showing that the injection site will remain to be the withdrawal determining tissue.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. The issue of a possible change in WP determining tissue was already raised. No reason to repeat
2173	1	Comment on Table 35: It is assumed that the new tissue WP was calculated via Equation 2 using WP and $t_{1/2}$ for injection sites. However, it remains unclear whether the change in WP can be calculated in this way since the rate of depletion in the injection site might not depend on the volume but on the surface of the injected drug. If so,	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no

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		higher volumes would lead to a lower rate, i.e. longer half-life. Proposed change: Please provide explanations.	way be regarded as the final answer. The influence of injection volume on the rate of absorption depends largely on the nature of the active ingredient and the exipiënts. The absorption rate could be smaller or larger. In practice an moderate increase in the injection volume would have no significant influence. The number of injection sites however would. No need to amend the text
2179-2180	1	Comment: It is not clear why for the 20-30% formulations the repeated injection would not lead to changes in withdrawal periods. As mentioned before (comment to line 2169-2170), a scientific justification whether or not other tissue becomes WP determining should be included. Proposed change: Please modify/amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. The theoretical issue where another tissue would become WP determining was already raised in the RP.
2180-2181	1	There seems to be a mistake in this sentence, mixing up "doses" and "withdrawal periods". Proposed change: It is suggested that the text should read "leading to an addition of 6 days for each **doubling the dose**".	Text corrected.

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2181-2184	1	Comment: The influence of a second injection on withdrawal periods should be discussed in more detail. It should be described and justified that an increase of 6 days would represent the worst case. Visual inspection of depletion curves as well as half-lives indicate that at the time point the second dose is applied, a certain fraction of the first dose still remains. Therefore it seems questionable whether there is no further increase in WP necessary. As already mentioned, it seems to be questionable whether an increase in WP of 6 days would represent the worst case (see comments to lines 2117-2143. Proposed change: Please modify/amend the text accordingly.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer. The effect of the first injection, and a fraction of the dose still being present was taken into account.
2185	1	Comment on Table 37: It should be ensured that by repeated dosing the WP determining tissue does not change. Proposed change: Please modify/amend the text accordingly.	Comment noted. The issue was already addressed. In an assessment this risk would automatically taken into account. No need to amend the text.
2221-2257	1	Comment: While improved doses for 10% OTC formulations do not surpass the doses that have already been registered before and the current single dose dosage for 20% OTC formulations was confirmed as well by the PK/PD model, only dosing intervals for the 20% formulation were reduced to 36-48h. If a product is intended for a repeated treatment, this repeated administration has to be covered by target animal safety studies (see VICH 43). Especially, for the reduced dosing intervals for 20% oxytetracycline, those studies are crucial. No studies, however, covering two treatments 36h apart were presented within the scope of this re-evaluation. If there is a dearth of available or suitable	

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		studies, this fact should be critically discussed in the conclusions. Furthermore, it seems implausible to determine a margin of safety as data investigating overdosing according to VICH 43 were not presented. The presented data only back up the conclusion that local tolerance is a major concern pertaining oxytetracycline injections. If data on reproductive toxicity are not available, this should be commented as well. Proposed change: It is proposed to rephrase the conclusion of step 1 taking into account the aforementioned points.	Some amendments have been made as proposed. Although there was no VICH 43 study available investigating the 36 h dosing interval, several GLP studies that investigated doses up to 150 mg/kg, repeated at 72h intervals on 3 occasions are reported in section 8.5.4. In addition, some 10% formulations are approved for doses up to 20 mg/kg for up to 5 consecutive days (Table 26). The absence of a study with a repeat dosing interval of 36 h is now captured in section 8.5.7, where the impact on the conclusion is also discussed.
2221-2260	1	Comment: As mentioned in the heading and further elaborated in Chapter 6, it is important to consider certain aspects of target animal safety according to the route of administration. One example is the local tolerance that might differ after intramuscular or subcutaneous injection, albeit PK profiles of both routes of administration seem to be similar.	In regard to the studies provided by the MAHs under Step 1, both products OTC1

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		Unfortunately in this example safety profiles were not determined according to the route of administration. Two separate evaluations for intramuscular and subcutaneous administration are warranted to meet the requirements mentioned in Chapter 6, albeit with some overlapping. Furthermore, in accordance with the comments to lines 1600 and 1604, it might be advantageous, if the scheme presented in part 6.3. would be applied in the examples as well. Numbered subheadings would furthermore facilitate a clear presentation of the results. Proposed change: It is proposed to differentiate between subcutaneous and intramuscular administration and evaluate target animal safety profiles for both routes of administration separately. Else, it should be at least explained, why in contrast to the proposed approach in chapter 6, subcutaneous and intramuscular application were evaluated together. Furthermore, it is proposed to restructure this paragraph and include subheadings according to the suggestion already made for amoxicillin and in Chapter 6.	and OTC2 were administered via the intramuscular route. This information is now included in the report. Literature reports were available (CVMP FOIA) where the local tolerance for the SC route of administration was investigated for Liquamycin 200 LA. PK studies showed similar profiles for administration via the SC or IM routes; therefore the route of administration (IM/SC) should not affect the MOS for systemic toxicity. This has now been noted in the introduction (8.5). Step 1a of the method discusses extrapolation of data used to derive the MOS between different routes of administration. Since few studies were available in which the SC route was specifically investigated, a separate report was not produced for the reflection paper The possible impact of route of administration on local tolerance is noted, but does not affect the final conclusion on risk management. Sub-headings have been added.
2226-2227	1	Comment: Considering the provided information on target organs and adverse effects, it is not clear, if those are the conclusions of studies or more general information derived from other sources. For study results it might improve transparency to	This information was derived in a literature review performed by an MAH in an MA submission. This has been deleted

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		give at least a brief overview of the study and provide the reference (see also comment to line 1604). If these are general information derived from textbooks, they should be presented in Step 4. Furthermore, it seems that these data do not refer to the target population, despite the aforementioned requirements for studies used in Step 1. A margin of safety in cattle can hardly be establish based on studies in laboratory animals. It is understood that for these exemplary evaluations of oxytetracyline and amoxicillin several data were missing, however, if that is the case, it should be clearly mentioned that a determination of toxicity profiles was not possible. Proposed change: It is proposed to revise this paragraph and elucidate on the studies used to appraise the target animal safety profile.	from the paper as it was not essential to the conclusions.
2228-2242	1	Comment: The studies summarized in this paragraph were not conducted according to current guidelines, e.g., control animals were treated with a different OTC product in contrast to a placebo. Therefore, it is at least in some parts difficult to draw substantiated conclusions. While those studies were accepted in the past, it should be pointed out that results gained from those studies, may be more prone for bias. Proposed change: It is proposed to critically discuss the deficits of the cited studies in the conclusions.	A statement has been included that studies were not fully compliant with VICH GL 43 due to the absence of a negative control group; however, a detailed critique will not be given in the context of the reflection paper (see general comment, line 1600).
2242	1	Comment: Unfortunately, it is not clear, why conclusions are drawn for individual products. As described in chapter 6 and applied in the example on amoxicillin, results should be presented for product groups according to target species,	

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		pharmaceutical form and route of administration, but not according to product name. Proposed change: It is proposed to reconsider, if conclusions shall be drawn on a product individual level or by product group. The favoured approach, however, should be explained in Chapter 6 and used in both examples without significant variation to prevent confusions.	The conclusions have been deleted from this section as they are essentially repeated elsewhere.
2245	1	Comment: In order to interpret the results, it is necessary to know the injection volume per injection site, or at least the used dosage. Proposed change: Please include the injection volume or at least the dosage in this sentence.	The information has been updated.
2249-2250	1	Comment: The conclusion, to restrict the injection volume is not backed up by the information provided by the authors within the scope of this re-evaluation. According to the provided reference, injection site reactions were seen after injection of 10ml. However, there is no evidence that a restriction of injection volumes would prevent injection site reactions. The reference only indicates that local tolerance is poor. Proposed change: It is proposed to delete "hence there is a rationale to restrict the injection volume." Additionally discrepancies between locale tolerance of product OTC 1 and OTC 2 should be discussed, as a limited injection volume of 10ml per site is proposed for OTC 1, but injection site reactions were found in animals receiving OTC 2 at the same dose.	The conclusion has been deleted as repeated elsewhere. No comparison will be made between the studies for the two products due to differing study conditions.
2256-2257	1	Comment: The last sentence of this paragraph seems not to be related to the studies	Not agreed. It is useful to highlight that since there were IS reactions with several

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		presented before, as excipients are only evaluated in Step 6. Proposed change: It is proposed to delete the last sentence of the paragraph and refer to excipients at Step 6.	different formulations, it is plausible/likely that oxytetracycline itself is irritant; however individual excipient compositions may contribute to the level of reactions seen.
2272	1	Comment: It is not clear, if the cited reference "Prescott & Dowling" is actually "S Giguère, JF Prescott, PM Dowling, Antimicrobial therapy in veterinary medicine, 2013". In order to provide transparency, cited literature should be comprehensibly documented. Furthermore, it might be helpful, if citations are made in the same format/ style throughout the paper (please compare the reference to Plum's Veterinary Drug Handbook in this paragraph to the citation in line 1666 "Prescott, J.F., & Dowling, P.M. (Eds.). (2013). Antimicrobial therapy in veterinary medicine. John Wiley". Proposed change: The authors are kindly asked to check the mentioned reference as a reference "Prescott & Dowling" cannot be found using the standard research methods. Furthermore, it is proposed to apply the same citation style throughout the paper.	Antimicrobial Therapy in Veterinary Medicine. John Wiley & Sons. 5th Edition. Eds. Giguere S, Prescott JF, Dowling P. Chapter 15
2272-2274	1	Comment: In order to improve interpretability of information and as not all references are freely available, it would be beneficial to state, if information refers to humans or animals and in the latter case to which species. Proposed change: The following wording is proposed: "Giguère et al., (2013) state that in animals tetracyclines are irritants and may cause damage at injection sites."	This has been amended, only where stated clearly in the cited references.
2275-2276	1	Comment:	It is noted that the SPC for one product

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		It is not fully clear, how the information about milk:plasma ratios can be used to re-evaluate target animal safety. It might be plausible to add a warning to the SPC that milk from cows treated with OTC cannot be fed to calves. Unfortunately, such a conclusion is missing. Proposed change: The authors are kindly asked to explain the relevance of the aforementioned information.	advises that it can be 'safely administered' to lactating animals. The case study explores the practicability of the methodology and it is useful to highlight issues that might have needed further exploration had a dose increase been necessary.
2290	1	Comment: It is not clear, where the statement on "low general toxicity" originates from. Furthermore, because this is a scientifically based re-evaluation of target animal safety, the word "reputed" is difficult to interpret, as it does not suggest a certain level of evidence and does not indicate the origin of the following information. Proposed change: It is proposed to indicate the origin of the aforementioned statement and rephrase it in order to agree with scientific standards.	This text is summarised from the content of various product SPCs that are publicly available. It can be assumed that the information contained in the authorised SPC is based on reputable evidence, but the origin of the evidence is not in the public domain.
2292-2293	1	Comment: As this sentence refers to Liquamycin, it might be more suitable to shift it to under the heading in line 2294. Proposed change: It is proposed to shift this sentence under the heading for Liquamycin.	Accepted.
2300-2310	1	Comment: The cited study should be evaluated carefully, as Hexasol is a fixed combination including oxitetracycline and flunixin meglumine. That mentioned, flunixin might cover possible adverse effects of oxitetracycline like local swelling or inflammation and even systemic adverse effects. Therefore, results should be	A comment has been added to acknowledge that the safety profile seen in this study may have been affected by the combination with flunixin. Since the 'no effect level' for renal toxicity

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		critically discussed. Proposed change: It is proposed to revise this paragraph and put more emphasise on the differences between the oxytetracycline products that are re-evaluated within the scope of this paper and Hexasol, a fixed combination including OTC and flunixin meglumine. The conclusions should be worded more carefully as well taking this difference into account.	and conclusions on local safety are not dependent on this specific study, and in the interests of brevity for the reflection paper, further discussion is not included.
2308-2310	1	Comment: It is not clear, why there is a conclusion for Hexasol and Tetradure, but not Liquamycin. Proposed change: For a better transparency, it is proposed to revise this paragraph and handle all referenced products in the same way, either by drawing a conclusion for each product separately or just drawing a conclusion at the end for all products together.	The conclusions for Liquamycin were clear in the study summary and it was felt unnecessary to repeat them.
2312-2313	1	Comment: It is not clear, why this references are cited here, as further information on what should be derived from these papers is missing. Proposed change: The authors are kindly asked to explain, why these references are mentioned here and explain their relevance for the re-evaluation of target animal safety.	As part of the purpose of the case studies was to explore the practicability of the methodology, it was considered useful to highlight available references.
2314-2332	1	Comment: The presented studies use the product Oxytet 30, the heading for this paragraph, however, states Tetradure 300mg. It seems likely that a subheading for Oxytet 30 is missing. Proposed change:	This study is included within the FOI summary for Tetradure, but the product used in the cited study is reported as OXYTET 30.

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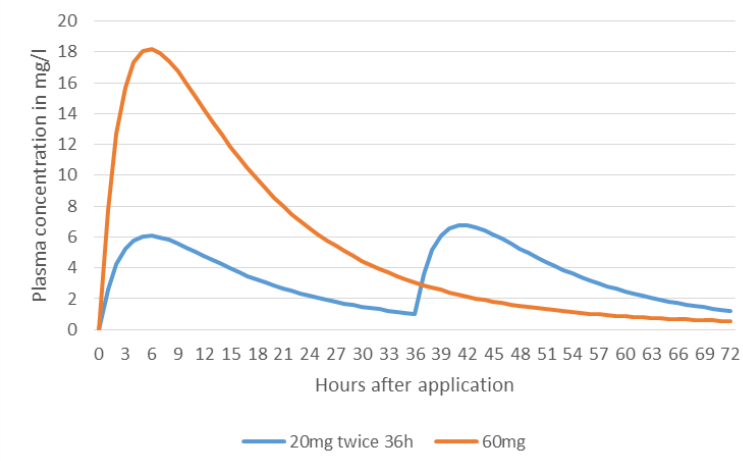
		The authors are asked to add a subheading for Oxytet 30 in order to improve legibility.	
2336-2337	1	Comment: The conclusion about toxicity after i.v. application is not backed up by the studies presented above and it is not clear on what data this conclusion is based. Furthermore, while dosing regimen were improved for intramuscular and subcutaneous application, a conclusion on safety after s.c. administration is missing. This is in disagreement with the general approach proposed in Chapter 6, stating that different routes of administration have to be evaluated separately. Reproductive toxicity was not mentioned to be evaluated at all, most probably due to a lack of available data. Proposed change: It is proposed to revise the conclusion and elucidate, which data were assessed to back up the conclusions on toxicity after i.v. injection. Furthermore, it is proposed to put more emphasis on the 2 different routes of administration (i.e., intramuscular and subcutaneous) and comment on the lack of data for reproductive toxicity.	This information was taken from a literature reference (Lairmore et al, 1984), which was cited in the FOI report for Tetradure 300. It has been deleted as the case study does not investigate the IV route. Comments have been added in sections 8.5.5. and 8.5.7, regarding the lack of reproductive safety studies.
2349-2366	1	Comment: In agreement with the comment on 1698, not only the type of excipients but also their doses need to be considered. Therefore, it is proposed to include the maximum dosage of excipients after dose adjustment in the manuscript in order to improve transparency. Furthermore, as step 6 is indicated for individual products, relevant excipients should be matched with the corresponding products. Finally, some informations on safety of the individual excipients would increase comprehensibility. Proposed change:	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. It is not intended to provide this level of detail for each product in the context of the pilot project and was not possible within the timeframe.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>Please see the comment on line 1689.</td><td></td></tr>
<tr><td>2367-2368</td><td>1</td><td>Comment:
The conclusion that the mentioned excipients only impact on local tolerance, might need to be reconsidered again. At least for the following excipients severe adverse reactions are known.
<table><tr><th></th><th>Hazard (substance as such)</th></tr><tr><td>Benzylalcohol</td><td>considered as (skin) sensitizer</td></tr><tr><td>Dimethylacetamide</td><td>Developmental toxicity (Repr. 1B) (harmonized classification according to Reg. (EC) 1272/2008)
→ PDE set in VICH GL 18R (Impurities Solvents)</td></tr><tr><td>Monoethanolamine</td><td>corrosive
(classified according to Reg. (EC) 1272/2008)
possible skin and respiratory sensitizer (C&L inventory)</td></tr><tr><td>N-methyl-2-pyrrolidone</td><td>Developmental toxicity (Repr. 1B); STOT SE 3, skin and eye irritant
(harmonized classification</td></tr></table></td><td>A full review of all excipients was not possible within the scope of the pilot project. As commented in chapter 6.2, most commonly used excipients have a wide margin of safety and the extensive review proposed is rare even for new MA applications including excipients with well-established use.
In the oxytetracycline case it was proposed to reduce the injection interval leaving the dose administered at each injection site unchanged, therefore local tolerance would be unchanged.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><td></td><td>according to Reg. (EC) 1272/2008) → PDE set in VICH GL 18R (Impurities Solvents)</td></tr><tr><td>Sodium formaldehyde sulphoxylate dihydrate</td><td>possible mutagen (suspected of causing genetic defects; notified classification according to Reg. (EC) 1272/2008; C&L inventory)</td></tr></table> Proposed change: It is proposed to review available data on adverse effects of the mentioned excipients and critically discuss those. Especially mutagenicity and developmental toxicity are important and need to be included in the target animal safety considerations.	
2369-2387	1	Comment: As there have been some concerns pertaining dose linearity between different routes of administration (see comment to line 2049), it is hardly feasible to conclude on the target animal safety of a subcutaneous injection based on data generated with intramuscular injections. As it has been proposed in Chapter 6, the re-evaluation of products has to be based on active substance, route of administration and pharmaceutical form. Therefore, the conclusions for the 20% formulation of OTC should be drawn for i.m. and s.c. application separately. If there is a lack of sufficient data for subcutaneous injections this should be addressed as well.	See comment to line 2049.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: It should be taken into consideration that conclusions on the safety of the improved dose should be drawn based on route of administration.	
2375-2376	1	Comment: Conclusion on renal toxicity after repeated treatment with oxytetracycline can only be drawn, if in addition to the single dosage and the number of treatments, the route of administration and the dosing intervals are known. Assuming that this statement originates from the study NADA 141-143 (Tetraure 300) with 72h between treatments and i.m. administration, the question should be addressed, how this dosing regimen can be compared to the proposed doing regimen of 2 injections 36h apart. The following graph shows plasma levels in relation to time after treatment comparing the injection of 60mg or the injection of 20mg twice 36h apart. Data were generated based on the publication from Meijer et al. (1993) that was previously used for the calculation of withdrawal periods (see Figure 24). Dose linearity was assumed between the administration of 20mg/kg and 60mg/kg, respectively. After 36h animals with 60mg/kg have a plasma concentration of approx. 3 mg/l and of approx. 0.5mg/l after 72h. Animals treated with  	Whether toxicity of oxytetracycline relates to peak plasma levels, overall exposure, or cumulative exposure has not been directly and specifically investigated. However, some 10% formulations are approved for doses up to 20 mg/kg for up to 5 consecutive days (Table 26). This supports the cumulative safety for repeated injection of the 20% formulation at 20 mg/kg on two occasions at 36 h apart. Outside of the pilot project, the TAS data for the 10% products may have been available from MAHs and would have been sought. Conclusions have been updated.

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		20mg with repetition after 36h, however have a plasma concentration of 1 mg/l after 36h, which increases again to 6.8 mg after the second administration. Levels decline to 1.2mg after 72h. Considering these estimations, it can be seen that plasma level in animals with 20mg and a dosing interval of 36h have higher plasma levels between 37h and 72h compared to animals treated with 60mg/kg. As toxicity depends on exposure but also on time of exposure, and the threshold for cumulative toxicity is - so far - not known, it is not valid to draw the conclusion that the overall exposure from the improved dosing regimen is below the threshold for renal toxicity and that the proposed dosing regimen, therefore, is likely to be well tolerated. The higher plasma levels between 37h and 72h should be discussed critically and a carefully worded conclusion might be prudent. Proposed change: It is proposed to revise the conclusion according to the comment above. In particular the authors are asked to elaborate, how target animal safety studies with 72h dosing intervals can safely be extrapolated to 36h dosing intervals.	
2388-2425	1	Comment: 8.6. Overall conclusion on oxytetracycline The comment on lines 1932 – 1934 and 1952 – 1955 apply also to this chapter. Proposed change: Please consider to include respective conclusions also in this chapter with regard to the comments made on lines 1932 – 1934 and 1952 –1955.	See above.
2412-2414	1	Comment: Please see the comment to line 2376. It should be indicated that the available data only cover dosing intervals of 72h and an extrapolation to 36h dosing intervals might be hardly feasible. Proposed change: It is proposed to revise the conclusions and also discuss limitations of this re-	Not agreed. The conclusions have been updated.

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		evaluation of target animal safety data.	
2428-2475	1	Comment: This chapter is roughly reviewing the concept that has been used rather than presenting a critical analysis on the applicability, feasibility and drawbacks of the PPHOVA approach when applied in the case studies. An analysis of the oxytetracycline case study is missing at all. A discussion on the appropriateness of the PDTs that have been used in the case study is likewise missing. It is noted again, that in both case studies the PDTs were derived from in vitro studies that have not been validated/correlated to clinical efficacy. In addition, the PDT used in the amoxicillin case study was determined in calves instead of pigs and considers different target animal pathogens (please refer to more detailed comment on PDTs in the case study sections). Moreover, in the amoxicillin case study it is stated: " … due to the low susceptibility, it was not possible to establish a dose for B. bronchiseptica, and therefore pigs infected by this pathogen should not be treated with amoxicillin via the drinking water". This finding should be discussed and a conclusion/recommendation should result whether this target pathogen can be longer be part of the indications. Proposed change: Please revise the chapter taking into account the comment above.	OK a paragraph added for OTC.
2429-2433	1	Comment: … investigate the differences between different PK/PD indices, … comparison of PK/PD indices will allow review of advantages (such as applicability, feasibility) and drawbacks (such as data requirements, complexity) of each PK/PD index. This conclusion is not agreed to. In the amoxicillin case study the PK/PD index AUC/MIC was used for a first PK/PD integration to define a daily dose. This	The CVMP does not fully agree. The use of two different PDI for the modelling allow a comparison on the applicability, feasibility, complexity etcetera, and the data needed in order to perform the modelling according one or

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approach was subsequently "refined" by use of the PK/PD index T/MIC in a second PK/PD integration approach aiming to investigate dosing intervals. Both approaches made use of different underlying PK data. Thus, it cannot be concluded that differences between different PK/PD indices were investigated or compared. Consequently, the application of the methodology does not allow review of advantages (such as applicability, feasibility) and drawbacks (such as data requirements, complexity) of each PK/PD index. Proposed change: Please revise the paragraph according to the comment made above.	the other PDI.
2434-2447	1	Comment: Information presented here seems to be of general nature (although references were not provided). It would be helpful to have this general information already in chapter 3 for a better understanding of the PPHOVA approach. However, the paragraph would need some clarification with regard to the following: "…AUC/MIC is simple to perform… time to maintain the MIC … cannot be derived from a simple formula and needs to be computed …" Both parameters, AUC/MIC and T>MIC, need reliable concentration-time curves to be calculated. From such curves, both parameters can easily be determined (the first by a trapezoidal integration, the second by the time points where the curve intersects the horizontal line of height MIC). Perhaps it is meant that if only summary PK data (t_{max}, C_{max}, AUC, $t_{1/2}$, ...) are known, it is easier to calculate AUC/MIC (namely simply by division because someone else has already calculated AUC) than T>MIC (for this, the curve has to be determined from the summary PK data by modelling approaches)? This is not clear from the text. In addition, if a dose is changed by a factor, in case of dose proportionality AUC/MIC changes by the same factor. This is generally not true with the parameter T>MIC. Is the text also aiming at this difference between the two	Agreed.

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		parameters? Please clarify. Proposed change: Please revise the paragraph according to the comment made above and move this information on the PPHOVA approach to chapter 3. In addition, the information provided would require references in support.	
2443-2444	1	Comment: …and not dose proportional. The sentence is unclear, particularly the last part. Proposed change: Please clarify.	Agreed.
2459-2469	1	Comment: The publications cited here and results of the amoxicillin case do not unambiguously support that the AUC/MIC is in general a useful PDI for β-lactams. Nielsen *et al.*, 2011 report "…The in silico predictions based on the in vitro PKPD model identified the previously determined PK/PD indices, with fT>MIC being the best predictor of the effect for ß-lactams…" Nielsen & Friberg, 2013 concluded: …" the best PK/PD index shifts towards AUC/MIC as half-life increases while for an AUC/MIC dependent antibiotic a decrease in half-life will lead to a shift into a T>MIC relationship." Nevertheless, they do not challenge in principle that the best PK/PD index for β-lactams is the T>MIC. In the amoxicillin case: "…results revealed that fractionation of the dose increases the probability to attain the target value of the PDI. This is mainly due to the short half-life of the active substances." Proposed change: The suggestion to use the PDI: AUC/MIC as 'a point of departure' for all	Text modified.

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		antibiotic classes should be critically reconsidered unless the approach is supported by sound scientific data.	
2470-2475	1	Comment: Information of the publication of Nielsen et al., 2011 is presented here without direct relation to the case studies. Proposed change: Please explain how this information (quantitative description of the full time course of PK and PD) correlates to the case studies.	It is not directly correlated to the case studies but provided information on how PK/PD approach based on in vitro data can actually be done.
2476-2497	1	Comment: 9.1.2 PK/PD and prevention of resistance The information of this chapter on the concept of the mutant selection window (MSW) including the mutant prevention concentration (MPC) is of general nature. It was neither introduced in chapter 3 (as part of the PPHOVA approach) nor was it considered in one of the case studies. Thus, it is not understood why MSW, MPC concept is included in this chapter on discussions and conclusions. Proposed change: If the MSW, MPC concept should be considered in the PPHOVA approach, it is suggested to move the entire information of 9.1.2 to chapter 3. In addition, it should be outlined in which situations this concept should be applied.	Agreed. However, the concept of MPC is still under investigation. This chapter aims to introduce that the first objective is to optimise efficacy against WT population, but in case the optimisation should also consider prevention of resistance, then the MIC is not the adequate PD indicator.
2498-2565	1	Comment: 9.1.3 Limitations of the modelling approach: A general discussion is missing with regard to the limitations of the approach that may be founded in the underlying data basis (PD, PK, PDI, PDT etc.) necessary to determine an "optimal" dose by use of the PPHOVA approach. In other words the outcome of the PPHOVA can only be as good as the data basis that has been feed in. What data are appropriate and eligible? It is acknowledged that PPHOVA is a pragmatic approach using existing data and	Please note that this is a pilot project on the feasibility of such modelling approach and not a guideline.

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		does not intend to aim guideline status by defining clear data requirements. Nevertheless, at least minimal requirements on the quality and quantity of data should be defined and discussed for each data set (PD, PK, PDI, PDT etc.), separately. Furthermore, it needs to be discussed how the PPHOVA approach can be applied at all in case underlying data are not sufficient, inappropriate or data are not available at all? Proposed change: Please revise chapter 9.1.3 according to the comment made above.	
2505-2516	1	Comment: 9.1.3.1 Use of the MIC as a PD indicator This chapter should include a critical discussion on which MIC data (single MICs e.g. MIC_{90}, whole MIC distributions, WT MIC distributions etc.) are appropriate and eligible with regard to the aim of dose optimisation. Proposed change: Please revise the chapter according to the comment made above.	Please note that this is a pilot project on the feasibility of such modelling approach and not a guideline.
2526-2533	1	Comment: 9.1.3.4. Duration of treatment It has been correctly outlined that one of the main limitations of the PPHOVA is that is does not give any information on the duration of treatment. With regard to the aim of the project to use the dose optimisation in the context of SPC harmonisation prospects should be made/discussed how the duration of treatment can be addressed. Proposed change: Please revise the chapter according to the comment made above.	Agreed.
2541-2543	1	Comment:	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The information of this sentence is not correct. For the PPHOVA the PTA was set at 90%. The limitation of the PPHOVA approach is the potential lack of information on reliable PDIs and corresponding PDTs that have been established in animals for target bacteria. - Proposed change: … lack of information on reliable ~~PDT~~ **PDIs** and corresponding ~~PTA~~ **PDTs** for …	
2543	1	Comment: Mode of administration Proposed change: delete "Mode of administration" in line 2543 and introduce in subsequent line as a subheading: "9.1.3.6 Mode of administration"	Agreed.
2544-2565	1	Comment: Mode of administration The route of administration and corresponding limitations should be discussed in the context of a more detailed chapter on PK data (please see previous comment on lines 2498 – 2565) Proposed change: Please revise the chapter according to the comment made above.	Agreed.
2566-2578	1	Comment: 9.1.4. Data requirements A rough listing of data requirements is presented but a discussion/conclusion on the data requirements is missing at all. Proposed change: Please revise the chapter according to the comment made on lines 2498 – 2565.	Please note that this is a pilot project on the feasibility of such modelling approach and not a guideline.
2581-2584	2	Comment: The approach of dose optimisation neglects the risk of AMR	Agreed.

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		development in the environment. Thus, an optimised dosage can serve the objective to ensure the efficiency of the treatment in the animal, but it is not an appropriate approach to sufficiently prevent the emergence, selection and/or dissemination of resistant micro-organisms in a bacterial population in all compartments. Proposed change (if any): The importance of revising the dosages is based on a need to optimise the doses of older antibiotics because repeated exposure to inappropriate concentrations represents a major risk in terms of antimicrobial resistance in target pathogens. An optimal dosage must be determined to ensure the efficacy of the treatment, but also to prevent the emergence, selection and/or dissemination of resistant micro-organisms in a bacterial population **in the animal.**	
2585-2589	1	Comment: Inter-individual variability has been found to be one of the risk factors and should be taken into account of the PK/PD approach. However, no conclusion has been drawn if and to what extent the PPHOVA approach has considered this aspect. Proposed change: Please clarify according to the comment made above.	Agree. Sentence added
2592-2595	1	Comment: Information provided here relates to prospective PK/PD approaches while the PPHOVA is a retrospective approach. The relevance of this information is not understood. Proposed change: Please clarify with regard to the comment made above.	Agree sentence deleted

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2596-2598	1	Comment: This sentence and its purpose is hard to understand. Proposed change: Please clarify.	OK, Sentence modified
2599-2609	1	Comment: 9.1.5.2. The feasibility of the PK/PD approach A discussion/conclusion is missing whether the case studies are representative to extrapolate the PPHOVA approach to different situations i.e. different substances/classes of antimicrobials, animal species, clinical indications, routes of administrations, pharmaceutical forms. For different situations it is very likely that will be considerable data gaps leading to limitations already mentioned in this chapter (e.g. the need for consolidated data, scientific evidence supporting the setting of PDI and PDT). Thus, a prospect is missing whether the PPHOVA can finally be applied/recommended for future dose optimisation of the broad and diverse field of established antimicrobial VMPs. Proposed change: Please revise the chapter with regard to the comment made above.	It should be noted that the case studies were presented as an illustration of how the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2626-2627	1	Comment: It is acknowledged that the hour-glass approach was used, since for other approaches not all necessary information is available. However, a critical discussion and validation of its impact concerning (tissue) half-lives, dose linearity and ADME would be useful to allow for an assessment of its influence on conclusions of preconditions (e.g. linear kinetics) as well as on results from Equation 2. It should be evaluated whether withdrawal periods for various formulations (e.g. long acting and short acting, irritating and non-irritating, without proven bioequivalence etc.) can be extrapolated based on the same	The purpose of the exercice of case studies (as is high lighted in the CVMP response in the general section) was to give an indication that the non experimental approach could work. Since it is now generally acknowledged that the algorithm is correct, and can be used, the applicability of the method would largely depend on the available data. Further

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		half-lives and when adjustment for differences in relative bioavailability between products would be needed. The limitations of the hour-glass approach should be critically discussed in chapter 4 and the main issues should also be included in chapter 9 (conclusions). Proposed change: Please include a critical discussion as mentioned above.	evaluation, however valuable this might or not might be would go beyond the scope of this RP.
2628-2629	1	Comment: It is noticed that Equation 2 was used for extrapolating WP in the case studies. However, it cannot be checked if the results are reliable as no residue data for the other dosages/dose regimes are available. Therefore, it would be good to have some kind of ideal example(s). This would be data on product(s) with two (recent, GLP-compliant) residue depletion studies for two different dosages available. Also the information on terminal half-lives and dose linearity should be available. Use of the formula could then show that similar WPs would result from extrapolation and from residue studies. Further on, more examples could show further pitfalls and problems to the reader including a scientific discussion on how to deal with these. Proposed change: The case studies analysis should include a critical discussion, which also points out the uncertainties (see comments in the case study sections).	In the general section of the WP algorithm, the example of the residue study in the guideline on harmonisation of WP was used. This was a GLP- study. The effect of different dosing was simulated by multiplying the experimental data. At present there is no need for additional data in the scope of this RP. Please note that the algorithm is considered to be mathematically correct, and is used for several years by FARAD.
2634-2650	1	Comment: Withdrawal periods already set are mostly based on results from residue depletion studies (either published ones, or those only available from MAHs and/or CAs). As these residue depletion data are intended to be used as starting points for the extrapolation of withdrawal periods for higher dosages and as extrapolation adds a certain amount of uncertainty to the results, results from Equation 2 are very likely to be inferior to the "golden standard".	In these cases groups of similar products were used. In other cases a single product could be evaluated, and harmonised across the EU. The unequal relative increase in WP's would indeed be the case, if the WP's

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		Depending on how similar or how different the products taken together in the hour-glass approach are, this would increase variability in data and, therefore, introduce further uncertainty in the results. As far as we understood the hour-glass approach, **one (mean) half-life** will be derived from all available products with the same active substance and used in Equation 2 for each VMP. For products with equal increases in dose, the same difference between old and new withdrawal period would then be added to each of the concerned products, i.e. the same number of days is added to the old WP for each product. As already discussed, this would introduce an unequal relative increase in withdrawal periods. For products with long WP the increase would be much lesser than for products with shorter WP. This might be suitable to "not disturb the market" but it seems questionable whether this sufficiently takes formulation differences into account and would be suitable to ensure consumer safety. In conclusion, it needs to be ensured that only sufficiently similar products (and it needs to be defined what this would be) should be taken together in the hour-glass approach. Proposed change: Please address the points mentioned above in the text.	would differ widely (from very short to very long). We freel that in practice this effect would be minor.
2644-2645	1	Comment: Taking together all shortcomings and preconditions not met (see comments on case studies above), we are of the opinion that it has not been shown that the proposed approach for adjustment of WP is not inferior to the conventional approach to conduct new residue studies. Based on the current level of knowledge, extrapolation of WP may only be used in exceptional cases if no further data are available and should not be presented to the reader as a valid alternative to conducting new residue studies. Therefore, this statement seems to be overconfident.	It is believed that for the case studies the extrapolation of the WP's would ensure consumer safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The conclusions should be revised, mentioning and discussing all pitfalls and preconditions not met in the case studies and possible other limitations. Maybe some kind of abbreviated confirmatory residue depletion studies could be a viable approach to allow for confirmation of extrapolated withdrawal periods.	
2674-2699	1	Comment: It is not clear, why the lack of pivotal study data is discussed critically at 9.4., but was hardly mentioned in the examples. There are furthermore incongruities pertaining, what has to be considered on a product-by-product-basis and which products can be pooled. Proposed change: The authors are kindly asked to ensure that Chapter 6 and the two example on amoxicillin and oxytetracycline are coherent and the requirements implemented in Chapter 6 are followed in the examples. Conclusions and especially critical discussions should match throughout the paper.	Within the case studies, the aim has been to draw concise conclusions from the data available. These are guarded as necessary. Due to the overall length of the reflection paper, some of the critique is reserved for the chapters that consider the overall approach more widely.
2759-2762	2	Comment: In any case, veterinary antibiotics should only be prescribed by a veterinarian after a positive test for a specific pathogen has been carried out. Otherwise, a considerable risk of AMR development is taken. Even if it is presumed as common practice, inadequate handling should not serve as a yardstick for the possibility of adopting measures.	This point is outside the scope of this Reflection Paper.
2773-2774	1	Comment: This point is supported. Proposed change: None.	Noted.
2811-2813	1	Comment: Concluding on several abovementioned comments on the two case studies (e.g. missing data for dose linearity, preconditions not met), these sentences need to	Comment noted. It should be noted that the case studies were presented as an illustration of how

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		be put into question: "It is envisaged that the data that are needed as input for these approaches will be available for the vast majority of the established veterinary antibiotics. Indeed, sufficient data was available to conduct the case studies for amoxicillin and oxytetracycline." It is not clear, why "sufficient data" are confirmed in this paragraph, when the authors themselves underlined that there was a lack of available data in Chapter 9.4. Further case studies would be needed to show reliability of results from the proposed approach. These should include substances from other classes of antimicrobials with several studies on different dosages available, which would allow for comparison of withdrawal periods resulting from linear regression analysis with those derived from use of Equation 2. In addition, it is anticipated that under veterinary conditions for the vast majority of antimicrobial classes reliable PDIs and PDTs will not be available. Available data for the case studies were not sufficient, for re-evaluation of target animal safety. Proposed change: It is proposed to rephrase this sentence and put more emphasis on the fact that sufficient data were not always available. Amendment of the conclusion is deemed necessary and it is suggested to include that further research is needed on this area.	the methodology could work, and were based on a limited dataset. The RP clearly states that the case studies should in no way be regarded as the final answer.
2846-2847	1	Comment: We do not agree with this conclusion based on the comments provided above. Further evaluation of the hour-glass approach would be necessary, including instructions on grouping of VMPs and limitations of the approach. Proposed change: Please modify the wording for recommendation No. 5 accordingly.	See response above.

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2851-2853	1	Comment: Due to the concerns on WP, TAS and efficacy raised in the comments above, recommendation 7 can yet not be agreed with. Proposed change: This recommendation should be critically reconsidered	See response above.
2924	1	Comment: Separate definitions for PK/PD modelling and PK/PD integration should be included in the glossary. It is proposed to use similar explanations to those included in the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) Proposed change: PK/PD modelling: ~~A technique that combines the two classical pharmacologic disciplines of pharmacokinetics and pharmacodynamics. It integrates a pharmacokinetic and a pharmacodynamic model component into one set of mathematical expressions that allows the description of the time course of effect intensity in response to administration of a product dose.~~ ***in silico*** **modelling of PD and PK data generated in the same study** **PK/PD integration: integrating of a PD parameter with one or more PK parameters generated in a separate PK study.**	Done
3182 Annex 3	1	Comment: As this paper is written in English, posologies for products from all countries should be translated to English as well in order to provide transparency (e.g., German and Austrian posologies). Furthermore, it was noticed that at least the information concerning products registered in Germany should be revised as there are several mistakes. In	Comments noted. It should be noted that the case studies were presented as an illustration of how the methodology could work.

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		detail: Aciphen should be either "Aciphen Kompaktat" or "Aciphen AMV". The Aciphen AMV registration, however, has already been withdrawn 2003 and the approved dosage had been 2-20mg powder/20kg bw 2 times daily for 2-5d. Aciphen Kompaktat is still on the market, the dosing, however, is not correct. Aciphen Kompaktat should be administered twice daily with 20mg/kg. The withdrawal period for meat and offal is only 1d. Amoxicillin 2,5 almapharm and Amoxicillin 100% have not been registered in Germany at all. Amoxicillin 10% was registered in Germany only until 2015. Amoxicillin-Trihydrat was meant to be registered in 1992, the MAH, however, withdrew the application in 1994. If this is an incorrect denomination and the veterinary medicinal product Amoxicillin-Trihydrat 100% (ENR 0893825) is meant, the currently proposed dosage is 10mg/kg bw 2 times daily for 3-5d. Amoxicillin-Trihydrat 10% was registered in Germany only until 2001. Amoxicillin C20 GKS is not registered in Germany. The proposed posology, however, refers to Ampicillin C20 GKS, what explains the uncommon dosage of 100mg/kg bw. If this was meant to be Amoxicillin C20 KS, the dosage is 10mg/kg bw 2 times daily for 3-5d and a withdrawal period of 3d for meat and offal. Amoxicillin C20 KS, however, is only registered for in-fed use opposed to use in drinking water. Proposed change: It is proposed to translate all posologies to English. Furthermore, it should be considered to carefully review the list of products. Those products, whose registration was withdrawn should not be included. Posologies should be checked for mistakes, trade names should be written in full and checked for	

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		mistakes as well. The following veterinary medicinal products administered by drinking water are currently registered in Germany for the treatment of respiratory disease in pigs: • Amoxicillin-Trihydrat 100% • Maxyl 500 mg/g Pulver zum Eingeben über das Trinkwasser (only for Pasteurellosis) • Centicillin • STRENZEN 500/125 mg/g, Pulver zum Eingeben über das Trinkwasser für Schweine (Amoxicillin and Clavulanic acide) • AMOXY ACTIVE, 697 mg/g, Pulver zum Eingeben für Schweine und Hühner • Octacillin 800 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine (only for pleuropneumonia caused by Actinobacillus pleuropneumoniae) • Rhemox 500 mg/g (only for infections with Streptococcus suis) • Triamox 100 W • Amoxin • Biocillin 500 mg/g Pulver zum Eingeben über das Trinkwasser (only for Pasteurellosis) • Amoxicillin Trihydrat 11,5% • Aciphen Kompaktat • Amoxanil 1000 W • Amoxanil 200F • Tamox Pulver 100% • Amatib 800 mg/g Pulver zum Eingeben für Schweine und Hühner (not for using in drinking water but in liquid feed) • Amoxicillin C20 KS (only for in-fed use, not in drinking water) • Amoxicillin-Trihydrat 100 (only registered for gastrointestinal infections)	

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Annex 4 Study type	1	Comment: It is recommended to label the study types according to VICH guideline 43. In agreement with the aforementioned guideline, injection site and administration site safety studies are furthermore listed separately from margin of safety studies. Proposed change: It is proposed to substitute Target Animal Safety Studies by "Margin of safety studies" and reproductive TAS studies by "Reproductive safety studies". Additionally another row should be added for "Injection site and administration site safety studies".	Amendments have been made. As the methodology has not been applied to topical products, Administration Site Safety studies are not included.
Annex 4 Study type	1	Comment: It should be "clinical field studies". Proposed change: It is proposed to substitute "Clinical field" by "Clinical field studies"	Accepted.
Annex 4 Study type	1	Comment: If "Safety studies in non-target laboratory animals" refers to "non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals", it might be useful to rephrase the "study type" and include the reference to ICH guideline M3(R2). Proposed change: See comment above.	There is no intention to reference specific study requirements for these studies.
Annex 4 Main objective	1	Comment: "Toxicity syndrome" is no standard term used in the VICH 43 guideline. Proposed change: The following wording is proposed in agreement with VICH 43: "Characterise toxicity target organs, identify the margin of safety (MOS) and	Amendments have been made consistent with VICH 43 and Chapter 6. Characterise the toxicity ~~syndrome~~ profile and target organs Identify the margin of safety (MOS) based

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		adverse effects associated with overdose/ increased duration of administration".	on the occurrence of adverse events.
Annex 4 Main objective	1	Comment: According to VICH 43, the main objective of reproductive safety studies is to identify "adverse effects" and not "safety effects" on male or female reproduction or on offspring viability. Proposed change: The following wording is proposed: "Identify adverse effects on male or female reproduction or on offspring viability"	Accepted.
Annex 4 Design	1	Comment: According to VICH 43, it is recommended to use 8 animals per treatment group for the MOS studies as well as for reproductive safety studies. This recommendation should be added to the table. Proposed change: It is proposed to add the recommendations for group size to the Design column for Margin of safety studies and Reproductive safety studies.	Reference is made to VICH GL 43. It is not intended to include all information in regards to study requirements in this document, and some flexibility may be required for pre-VICH studies.
Annex 4 Design	1	Comment: The VICH guideline 43 states that for target animal safety studies the final market formulation should be used or bridging studies might be necessary. There is no hint that "close" formulations can be accepted. Furthermore, "Clinical observations" is originally "Physical examinations and observations". Proposed change: It is proposed to delete "(or close)" and substitute "clinical observations by "Physical examinations and observations".	TAS are 'preferably' according to VICH 43. Some flexibility may be required. No change required. 'Clinical observations' amended to 'Physical examinations and observations.'
Annex 4	1	Comment:	See above.

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Design		As mentioned above, injection site and administration site safety studies should be mentioned in a separate row. Proposed change: It is proposed to move information on local tolerance to "Injection site and administration site safety studies".	
Annex 4 Design	1	Comment: As "pre-breeding" also refers to all activities designed to identify desirable characteristics and/or genes from non- adapted (exotic or semi-exotic) materials, and transfer these traits into an intermediate set of materials, the term used in VICH "prior to breeding" might be more suitable. Proposed change: It is proposed to substitute "pre-breeding" by "prior to breeding".	Accepted.