09 September 2024
EMA/CHMP/422204/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 Rev. 1)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA - Medicines for Europe - AESGP
2	Krka
3	Galen Pharma GmbH, Germany
4	Aristo Pharma GmbH, Germany
5	Gilead Sciences International
6	Orion Pharma
7	AstraZeneca
8	Pro Generika e.V., Germany
9	Pfizer Inc
10	German Pharmaceutical Industry Association (BPI)
11	Tim Verslycke
12	Fraunhofer IME-AE (Dieter Hennecke)
13	Fraunhofer Institute for Molecular Biology and Applied Ecology (Kerstin Hund-Rinke)
14	Toxicology Knowledge Team Sweden AB
15	Smithers Viscient
16	Technology Catalysts International Corporation
17	Charles River den Bosch, NL
18	Pharmalex GmbH, Germany

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Stakeholder no.	Name of organisation or individual
19	R. Arno Wess, Innovative Environmental Services (IES) Ltd, CH
20	Norwegian Environment Agency
21	ECHA - European Chemicals Agency
22	Swedish Medical Products Agency (MPA)
23	Finnish Medicines Agency, FIMEA
24	Matti Leppänen, Finnish Environment Institute (SYKE)
25	Lauri Äystö, Finnish Environment Institute (SYKE)
26	Jukka Mehtonen, Finnish Environment Institute (SYKE)
27	National Institute for Public Health and the Environment (RIVM), NL
28	AGES - Austrian Agency for Health and Food Safety
29	UBA (German Environment Agency)
30	Finnish Safety and Chemicals Agency (TUKES)
31	Marlene Ågerstrand, Stockholm University
32	Tiziana Di Lorenzo, Research Institute on Terrestrial Ecosystems Italy
33	Michael S. McLachlan, Department of Environmental Science and Analytical Chemistry, Stockholm University
34	Kathrin Fenner, Juliane Hollender, Carolin Seller, Nicolas Creusot, University of Zürich, department of environmental chemistry
35	Klaus Kümmerer, Leuphana University Lüneburg, Germany
36	University of Helsinki, Faculty of Pharmacy, Tiina Sikanen
37	Health Care Without Harm (HCWH) Europe
38	International Society of Doctors for the Environment (ISDE) – Germany
39	The Water Management Association in North Rhine-Westphalia
40	Pharmaceutical Group of the European Union (PGEU)
41	Thomas Backhaus, Dep. of Biological and Environmental Sciences, University of Gothenburg
42	Saijariina Toivikko, Finnish Water Utilities Association
43	Alfons Uijtewaal, Stichting Huize Aarde, Netherlands & Member of Management team INTERREG-VA MEDUWA-Vecht(e)-project
44	Emma Grange, Cruelty Free International
45	Stockholm region, Sweden
46	Klaus Guenter Steinhäuser
47	Tom Wikberg, FIMEA
48	Chemical Assessment Unit, Environment Agency, UK

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**Introduction** EFPIA, Medicines for Europe and AESGP would like to thank the EMA for opportunity to comment on the draft "guideline on the environmental risk assessment of medicinal products for human use" (15 November 2018). We are pleased to see that many of the comments that we provided in response to the ERA Concept Paper consultation have been taken into consideration within this revised draft guidance and that the guideline explicitly states that the environmental impact should not constitute a criterion for refusal of a marketing authorisation. The current guideline has been in place for a period of 13 years during which time the ERA outcomes clearly indicate that most human medicinal products pose low or insignificant risk to the environment through patient use (Gunnarsson et al., 2019; Kuster & Adler, 2014; Roos, Gunnarsson, Fick, Larsson, & Ruden, 2012); even in many cases with worst case environmental exposure assessments. We are committed to providing environmental risk assessments of human medicinal products using sound, science-driven approaches that focus on risk. We are pleased to see that the draft guideline has focused on maximising the use of data collected within the ERA; we did have concerns that some data e.g. the OECD 308 and OECD 305 studies have limited use in the current ERA guideline; these concerns have in part been addressed in the updated draft. We also welcome the increased guideline on tailored ERAs for antibacterial and endocrine active substances (EAS); the continued application of a total residue approach; bringing forward the sediment assessment for all products in scope; and an improved definition of naturally	All general comments noted.

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	occurring substances. We also recognise the draft guidelines ambition to include guidance from, and create greater harmonisation with, REACH and the veterinary medicines environmental risk assessment guideline. We have proposed some areas where greater harmonisation with the veterinary medicine's guideline should be sought e.g. the triggers for a terrestrial assessment and fish bioconcentration studies. **Scientific Justification and Transparency** As a stakeholder most directly affected by implementing the draft Guideline, we are concerned that the proposed changes are provided with no publicly available performance analysis of the existing Guideline supporting these proposed changes. At times, the draft Guideline has strayed from the principle of science-based policy and realistic risks, and instead appears to rely on judgement without enough substantiation or a clear scientific basis. This includes changes to the groundwater risk assessment, secondary poisoning assessment and the revised triggers for conducting a terrestrial risk assessment. We elaborate on these points in our comments below. The EMA has also missed an opportunity for transparency, it would have helped if the EMA had explained specifically how and why the proposed changes are putting ERAs on a better scientific footing for risk assessment and risk management. We suggest the EMA provide a scientific report or scientific opinion detailing the evidence base for the decisions behind the changes, and the basis for sticking with existing triggers e.g. what is the justification for maintaining the current PEC Action limit of 10 ng/l for surface waters. A number of comments captured below on the draft guideline are seeking clarification and justification of proposed changes or maintenance of particular triggers. These requests for clarification may have been negated with greater transparency of the scientific basis behind the decision-making process. As an	Justification and/or scientific background of changes in the GL is given in response to the specific comments. In addition, supporting literature is cited in the revised guideline.

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	example, the European Food Safety Authority often produces a detailed scientific opinion on the state of the science shortly prior to or alongside releasing a draft guideline update. This process enables stakeholders to understand the basis of the guideline updates and an opportunity for those stakeholders in possession of data to provide data which may help in guidance revisions or filling data gaps (e.g. Scientific Opinion of the PPR Panel on the Science behind the Guidance Document on Risk Assessment for Birds and Mammals (The EFSA Journal (2008) 734: 1-181 [https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2008.734]). The value of this public transparency cannot be underestimated. **Use of Publicly Available Data** Given the large amount of data EMA has accumulated since the first draft of the Guideline nearly 13 years ago, one would expect that an analysis would have been prepared as a companion or supplemental document to guide internal deliberations on any proposed changes. This analysis would have at least qualitatively evaluated the scientific evidence supporting the proposed changes. Publication of such an analysis would instil stakeholder confidence in the scientific credibility of the proposed changes to the Guideline and the decision trees. To support the underlying scientific basis for the proposed guideline we also encourage that the EMA evaluate the environmental monitoring data for pharmaceuticals in different environmental media for two purposes. Firstly, such data could be used to evaluate the validity of its existing and proposed criteria and trigger values. We have concerns that the conservative approach to environmental exposure assessment is over-estimating environmental risk in 95% of cases (fundamental consequence of	Please see response above and also responses to specific comments.

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	how the fPen of 1% was determined) and this is resulting in unnecessary risk refinement and risk labelling. Secondly, as a public educational outreach tool graphical depiction of the safety margin between PNEC values and real-world measured concentrations may help address concerns regarding the presence of trace levels of some pharmaceuticals in environmental media; and support the development of a more refined, data-driven, integrated testing strategy (ITS) for pharmaceuticals and support scientifically and ecologically relevant prioritisation efforts under the Water Framework Directive. The EMA, NCAs and industry have an equal role to play in reassuring society that the environmental risks and human medicinal products are being effectively managed. **Data Accessibility, Study Repetition and Ethical Considerations** The draft guideline states that "In order to avoid unnecessary repetition of studies, and in particular animal studies, applicants are encouraged to share their data. If the current applicant has access to an ERA that was performed earlier by another marketing authorisation holder, this ERA (including study reports) may be submitted, including a letter of access." We welcome the draft guidelines ambition to reduce repetition of testing and looking to review all available reliable and relevant data. However, to realise this ambition, it is critical that the EC and EMA work in partnership with industry to develop a centralised ERA database to facilitate data transparency and accessibility. The transparency of the data, especially for products registered through national or decentralised procedures, is still an issue that needs to be addressed. Data that are available in European Public Assessment Reports (EPARs) are also presented in an inconsistent manner and have to be accessed on a product-by-product basis. Unless improvements to data transparency and data accessibility are addressed urgently, the	The proposed availability of a centralised ERA database is supported and is anticipated in the PREMIER project. In addition, EMA would also support a monograph system to assess possible environmental risk at the level of the API. However, this is beyond the scope of the guideline revision. The outcome of the ERA in a marketing authorisation is summarised and publicly available in the EPAR, for which there is 1 common template/table for ERA results.

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	proposed guideline have the potential to increase the repetition of data generation, particularly for established products that have lost exclusivity where generic applicants may not have visibility to existing datasets and where those data exist. Agreement of a common ERA reporting template for the EPARs to ensure data availability and accessibility is presented in a consistent manner would be the first stage to improve consistency and transparency of ERA data. The EPAR data also needs to be presented in a more consolidated and searchable manner. Increased transparency may allow ERAs to be prioritised and updates to be provided for only those products losing exclusivity that contain active pharmaceutical ingredient (APIs) where the margin of safety is low (e.g. margin of safety <10). This would reduce the burden on industry and authorities, without compromising environmental protection. Resources could then be effectively targeted towards APIs that lack data or pose greater concern. The availability of a central EMA ERA database containing the available physico-chemical property/ecotoxicity data for market authorised drugs could spur data exploration and development of (quantitative) structure-activity relationship (Q)SAR models for physicochemical, environmental fate and ecotoxicity endpoints for APIs. Others have taken steps to advance the science, and we encourage EMA to support these endeavours (Grisoni et al., 2018, 2019; Thomas et al., 2019; Valsecchi et al.,2019; Vestel et al., 2016; Gunnarsson et al. 2019). The development of such validated models, especially if they were publicly available, could reduce unnecessary expenses for testing and use of animals consistent with the 3R principle whilst also assisting industry in screening early development candidates for more environmentally benign APIs, just as intelligent solvent selection has been a component of green chemistry for organic syntheses used to produce APIs.	It is agreed that there is a need to further explore methods to derive (Q)SAR models and a need for data to do so.

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	Filling of Data Gaps The generic industry recognises its responsibility for generating environmental data for APIs that have insufficient data to conclude on environmental risk. However, the proposed guideline is in danger of placing the regulatory testing burden in a disproportionate manner for established generic products that have data gaps i.e. the testing burden will fall on those companies making marketing applications and it may not reflect all those industries with an interest in that product/ API; this could be perceived as anti-competitive. The guideline has no coherent approach to gathering data on established products/ APIs where significant data gaps exist. This will result in the unnecessary generation of repetitive testing data and likely conflicting ERAs, especially through national and decentralised procedures. The current approach of filling data gaps is considered neither efficient nor effective and it does not share the testing effort proportionately across relevant companies. The draft guideline is in danger of driving more repetition of testing creating potentially more conflicting ERA data if issues around data transparency are not urgently addressed. We propose that the EMA postpones data gathering for established products until the second IMI pharmaceuticals in the environment project, funded by the European Commission and Efpia member companies, has delivered a list of priority APIs that has been agreed upon with relevant stakeholders. This will enable regulatory authorities and industry to gather data for APIs of potential concern in an intelligent, coordinated, resource and bioethically efficient manner that involves relevant companies sharing the costs equitability. Gunnarsson et al (2019) recently conducted EU-wide consumption-based ERAs, assuming worst-case exposure, for the aquatic environment on >100 APIs. This study demonstrated that most APIs had low or insignificant risk before any refinements to	The concept of increased transparency is supported, and anticipated in the PREMIER project, however, this is beyond the scope of the guideline revision. The special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision. Possibilities for data sharing by pharmaceutical industry is encouraged. In this respect, fulfilling 3Rs principles should also play an important role.

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	environmental exposure and risk. Those which did highlight a potential environmental risk were restricted to only EAS's which require a tailored ERA within the current and draft guideline irrespective of exposure. This illustrates the need to effectively prioritise any data gap filling. **Legislative Framework** The draft guideline states: "According to Directive 2001/83/EC, applicants are required to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA. However, cross reference to the ERA dossier of the originator is permitted with consent from the originator." The draft guideline later states that "For APIs that are already marketed, information may be available in the public domain. To prevent repetition of (animal) studies and allow identification of signals emerging from environmental monitoring and research, the Applicant should provide a complete literature review (See section 6.1 on data search). When other marketing authorisation holders have already performed relevant studies, they are encouraged to share data with the Applicant, in order to minimise the number of tests having to be re-performed. Public Assessment Reports (PARs) and EPARs and reviews or summary data from other regulatory frameworks cannot be used in the ERA dossier without the underlying study reports." Clarification is required about the level of detail required in the ERA dossier for cross-referencing. If a letter of access or use of an ERA dossier is granted by the market authorisation holder for regulatory data that has been subject to regulatory review and is available in the EPAR, why is there a need for the new applicant to provide the underlying study reports? There are also no obligations for MAHs to make data accessible. No models for doing so are described or referred to within the draft	

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	guideline. The innovator places a new product on the market for which a complete evaluation of efficacy and human/environmental safety has to be performed. After obtaining the marketing authorization a data/market exclusivity period of 10 years is granted for the innovator. A generic product (Article 10 (1)) is allowed to refer to the innovator data by demonstrating essential similarity with the innovator product thus confirming equal efficacy as well as safety. As the ERA studies are performed with API not the finished product, the ERA performed by each MAH should come to similar conclusions on environment fate, behaviour and effects. Where differences in environmental risk occur, this can only result if increased exposure is anticipated. It is therefore reasonable that the generic products marketing authorization dossier should be able to refer to the efficacy and human/environmental safety data of the innovator product and all other publicly available data (scientific literature, PAR, EPARs) without necessarily repeating efficacy and human/ environmental safety studies. According to Article 10 of Directive 2001/83/EC the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if they can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. Although the ERA is not part of the risk-benefit assessment it constitutes pre-clinical data and is part of pre-clinical assessment of the dossier. If ERA studies are considered as pre-clinical data, then it raises the question of whether or not they should be requested for generic applications. Clarity is requested on the regulatory and/or legal basis upon which ERA studies are exempted from this rule and why ERA data cannot be cross-referenced.	Only study reports reflect the individual data which are needed for the regulatory assessment and detection of possible data gaps. Some historic ERAs may not have been performed to the standard required and may not conform with the updates and revisions to the guideline.

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	Where data exist, we also challenge the need for all new generic applicants to conduct an ERA where there is a large safety margin and the generic product is replacing the marketed reference product or other generics as pointed out in the document "Overview of comments received on 'Guideline on the environmental risk assessment of medicinal products for human use'(EMA/CHMP/SWP/44609/2010 Rev 1*)". If the marketing authorization of a new generic product does not lead to a significant increase in the environmental exposure of a particular API, and there is a sufficient margin of safety within the existing ERA (e.g. margin of safety >10), it would not be expected to have an adverse effect upon the environment. The guideline should cover and implement a mechanism for Regulatory bodies to waive ERA studies for compounds where studies have already demonstrated a lack of environmental risk (even with potential increased use). Would it be possible for the EMA to identify APIs where no generic applicant ERA updates would be required based on existing data generated under the current ERA guideline for APIs with a low risk/ high margin of safety?	Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision.
	Eco-Pharmaco-Stewardship As part of a wider Eco-Pharmaco-Stewardship (EPS) initiative, Industry has developed an extended environmental risk assessment (eERA) framework that addresses environmental risks based on total substance use and not on product specific use. Within this eERA framework we propose that innovator companies update their ERAs prior to loss of exclusivity and making these data publicly available. This removes the need for generic companies to update an ERA and places the burden on the innovator company. This opposes the current draft ERA guideline; the emphasis in the draft guideline is on the new generic applicant to review and update the ERA. This will duplicate effort across the industry as there could be	EMA welcomes and encourages data sharing initiatives between innovator and generic companies such as the eERA framework. However, this is a voluntary scheme. Data sharing in general is encouraged in the guideline.

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	several generic companies coming to market and it could also lead to greater inconsistencies in the updated ERA requiring greater regulatory oversight. If through working with the EC and EMA we can realise this eERA approach with the required transparency and regulatory oversight this could reduce the requirement for having additional and potentially conflicting ERAs conducted for generic medicines. Transparency and access to data, or an ability to cross-reference needs to be provided in a timeframe that allows generic companies to update the ERA if required. Failure to provide an adequate timeframe may result in the need to provide a window for post-authorisation commitments (e.g. 2 years) to ensure that the generic companies have access to the updated ERA either via public domain or via EMA/competent authority. **Implementation of Guideline** Member States and National Competent Authorities (NCAs) also need to recognise that some ERA testing has been commissioned prior to this proposed revision. Consequently, it is sometimes difficult to follow the latest guideline unless repeat studies are commissioned even though the ERA studies were in compliance at the time they were conducted. Industry requests a period of time for compliance with the draft ERA guideline rather than enforcement of the new guideline overnight. There also needs to be some recognition that innovative medicinal products being tested now will be providing environmental data for generic applicants coming to market in 10+years' time; again, some of these studies may not be providing some of the endpoints requested in the draft guideline (e.g. the shift towards an EC10 over a NOEC). Duplicate studies should not be requested in these instances. **Conflicting Regulations**	More than 5 years elapsed between the public consultation phase and the guideline revision coming into force. Additionally, no major changes were introduced compared to the draft submitted for public consultation. Hence, a transition phase of 6 months was considered sufficient between publication and implementation. For generic applications submitted post-implementation of the revision for which a reference ERA was performed according to the first version of the ERA guideline, no duplicate testing will be required but missing ERA data according to the guideline revision will have to be provided by the generic applicant.

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	Industry is concerned about conflicting and duplicative ERAs being conducted under the Water Framework Directive (WFD) and other regulatory frameworks. This can lead to dual regulation where the patient and societal benefits are being excluded. Patient welfare including unimpaired access to innovative medicine should be of the utmost importance. We would like to see more ownership from EMA and NCAs (e.g. via CMDh) of the environmental risks posed by medicinal products throughout their life cycle and not just at the point of authorisation. In particular, we would like the EMA & NCAs to assume responsibility for the human medicinal product prioritisation for the WFD. This could fall within the remit of a dedicated EMA-HMA (or CMDh) Task Force composed of EMA and Member States ERA experts, potentially supported by a Scientific Advisory Group to EMA/CMDh. **Further consultation period** Finally, given the nature of the comments and challenges posed by this draft guideline, and the lack of transparency behind some of the decisions made within this draft guideline, we strongly recommend that the EMA conduct a further consultation period of 3 months for stakeholders to review the next version of technical guideline and the scientific opinion we have requested to be published as a companion document.	Outline of study types to be performed to evaluate a possible environmental risk of a human medicinal product is only given in the ERA guideline. In this respect there is no overlap with the WFD. Prioritisation for the WFD is not in the remit of the ERA Guideline. No major changes were included for finalisation of the revision after the public consultation period. Therefore, no further consultation period is deemed necessary.
2	**Cross reference to originator ERA** The innovator product places a new product on the market for which a complete evaluation of efficacy and human/environmental safety has to be performed. After obtaining the marketing authorization a data/market exclusivity period of 10 years allows the innovator product to make the profits which also covers the expenses for the R&D of the product. A generic product (Article 10 (1)) is therefore allowed to refer to the innovator data by demonstrated essential	All general comments noted.

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	similarity with the innovator product thus confirming equal efficacy as well as safety for the user and environment. There are no reasonable arguments why ERA studies are exempted from this rule. Because the ERA studies are performed with active compound (API) not the finished product, the ERA performed by each MAH coming to similar conclusions means unnecessary repetition of the studies. What is more this would prolong and enlarge costs of generic product development which could hamper availability of affordable generic products in the market. It is therefore reasonable that the generic products Marketing authorization dossier refers to the efficacy and human/environmental safety of the innovator product and all other public available data (scientific literature, PAR, Assessment reports/monographs) without necessary repetition of efficacy and human/ environmental safety studies. In this respect it should be noted that ERA data is not considered confidential. According to HMA/EMA Guidance document on the CCI (1) ‘’In general, information on ERA in the human medicines fields is not confidential and all of the section 1.6 can be released. Information encompassing non-clinical and clinical development of the medicinal product and the subsequent assessment by Competent Authorities is not *per se* commercially confidential. This includes information related to environmental risk assessments and risk management plans.’’ In addition, to be consistent with the innovator’s SmPC generic products should be allowed to directly refer to the ERA performed by the originator. Namely, according to all valid guidelines, especially EMA/627621/2011 rev.1 from 18 June 2018: ‘’content of the generic’s SmPC should be *in all relevant aspects consistent with that of the reference medicinal product*, except for indications or dosage	Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision. The confidentiality of ERA data is a legal issue. GMO products are not included in the scope of this ERA guideline.

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	forms still covered by patent law.'' Because Directive 2001/83/EC states that ''ERA information presented in the dossier should also include a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars *which need to appear in the Summary of Product Characteristics, labelling and package leaflet*'', this consequently means that generic SmPC should be the same also in risk mitigation measures resulting from the innovator's ERA. This further supports the claim that innovator's ERA data should be for generic applications treated in the same way as other (non)clinical data.	
	According to Article 10 of directive Directive 2001/83/EC the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. Although ERA is not part of the risk-benefit assessment it constitues non-clinical data and is part of non-clinical assessment of the dossier. ERA guidelines are part of non-clinical guidelines according to EMA (2), Ecotoxicity/ERA are during the registration procedur evaluted within the non-clinical assesment (3, 4). Considering ERA studies non-clinical data, ERA study results should not be requested for generic applications. Although ERA study reports are currently included in Module 1.6, they could alternatively be included in Toxicology section of Module 4 in Chapter 4.2.3.7 Other Toxicity Studies.	Article 10 makes reference to the derogation of the requirement for non-clinical and clinical data laid down in 8(3) (i), but not 8(3) (ca) which lays down the requirement for ERA. Therefore, currently reference to the ERA of the originator product for applications according to Article 10 is not possible.

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2	**Waiver of generic ERA studies** As already pointed out in the document (1) "Overview of comments received on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev 1*): "*generic products are replacing the marketed reference product or other generics*." The marketing authorization of a new generic product will therefore not lead to a significant increase in the environmental exposure of a particular API and would thus not be expected to have an adverse effect upon the environment. Additionally, the guideline Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use states (2): "*Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the introduction of a new generic medicinal product in a member state where the reference product is not marketed*." In the proposed guideline (3) no explanations or exceptions for generics are present, even though previous documents (1,2) are confirming that no increased impact for the environment exist for generic products. Therefore, for generic products ERA will typically include justification for not submitting ERA studies based on the claim that increase in the environmental exposure is not expected. Proposed change (if any): The proposed guideline should include an explanation in line with the previous documents, where the generics are exempt from conducting an ERA phase II, because they are not in general	All general comments noted. Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision. According to Directive 2001/83/EC an ERA has to be performed regardless of the legal basis. The Phase I decision tree which is followed to identify the products that require a Phase II risk assessment is also applicable for generic products. Additionally, for some generics there is no relevant ERA available, therefore an absence of increased environmental exposure does not provide any information on the environmental risk *per se* of the product.

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	increasing the impact on the environment. The special cases where generics do increase the impact on the environment should be specified (MDD increase, added indication, additional pharmaceutical form)	
2	**Past experiences** <u>Case report 1: Public available ERA data for API is not complete:</u> DCP registration procedure (well established use - Article 10a) for product widely used and available on EU markets over 50 years. The Applicant provided a justification that the proposed product does not increase the risk for the environment since API is present on the markets for several decades as an originator's or generic's product. It needs to be emphasized that in the recent registration procedures for several generic products containing the same API an omission of ERA was accepted by the Regulatory authorities based on the justification that the product was a generic substitution of the reference product. Despite the well-established use of API, documented efficacy and an acceptable safety, the Applicant was asked by CMS to demonstrate the consumption data for the past four years. If a decrease can't be demonstrated, ERA phase II was required due to its specific use of action. The Applicant presented the consumption data where a slight increase of API consumption was demonstrated for 9 out of 13 countries included in the registration procedure. The actual consumption data resulted in a PECsw < 0.01 µg/L for all countries included in the registration procedure. Nevertheless, the Applicant performed an ERA phase II based on the available literature data which confirmed that API does not present a risk for the	All general comments and case reports noted. However, the legal restriction related to the current version of Directive 2001/83/EC cannot be solved by the guideline revision.

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	environment (RQ < 1). The applicant claimed that conducting its own physical-chemical, environmental fate or environmental effect studies is thus not considered necessary. Although the published literature demonstrated no bioaccumulation potential (logKow = 1.72-2.12), low adsorption potential (logKoc = 1.57-2.46) and no persistency potential (> 65% degradation in 14 days incubation with sewage water, > 7 degradation products formed) for API, the Applicant was asked by the Regulatory authorities to perform its own Kow, Koc and sediment degradation study. No additional benefit for the risk assessment was gained from the studies performed by the Applicant, since the risk assessment is always based on the PEC/PNEC correlation which was already established from the publicly available data (RQ < 1).It was therefore expected that a requirement for a specific ERA study would be the result of an identified risk, and not only to fulfil the guideline´s study list. The applicant would like to emphasize that in situations where no environmental/ecotox data are available for API which might represent a potential risk for the environment, the obligation for the additional studies should be binding for all MAH present on the markets, since the outcome of the studies is compound specific and should be applied to all products containing the same API. <u>Case report 2: API ERA data are not available:</u> CP registration procedure (10(1) generic application) for API started on May 2018. The Applicant provided a justification that the proposed product does not increase the risk for the environment	

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	since API is present on the markets for several years in form of an originator or generic products. EMA asked to present any data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected e.g. consumption data or PEC determination. Additionally, an experimentally determined Kow value was requested. The applicant emphasized that in a recent registration procedure a generic products containing the same API an omission of ERA was accepted by the Regulatory authorities based on the justification that the product was a generic substitution of the reference product. Additionally, in the years 2017 and 2018 no adoption, revision or questions & answers to the current Guideline on the environmental risk assessment of medicinal products for human use (Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 1*) were published, therefore it is reasonable to expect that there were no changes to the criteria for the ERA on the EU level. However, the Regulatory authorities still required from the applicant to perform the studies necessary for the ERA phase II, nevertheless a product of the same composition, proposed for the same indication with the same therapeutic regimen obtained the marketing authorization in an equal registration procedure (CP registration procedure (10(1) generic application) without performing ERA phase II. The applicant would like to emphasize again that in situations where no environmental/ecotox data are available for an API for which a potential risk for the environment is identified, this should be a burden for all MAH present on the markets not just for a particular	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	applicant. The outcome of the studies performed is compound specific and should be applied to all products containing the same API. Additionally, the applicant expects that equal ERA criteria/requirements within the EU level are applied to all applicants present on the market. Proposed change (if any): In the case where no ERA data exist, e.g. innovator product registered before 2006, all interested MAHs should be invited to jointly perform the necessary studies for ERA, the costs should be equally divided between the MAHs. The principle of data sharing or study performing between the MAHs should be in line with ECHA mechanism supervised by ECHA or EMA. An unified ERA report (all MAHs included) should be provided to the Regulatory authorities. The same principle should be applied for all MAHs in cases where a new risk for a particular API is identified for the environment (endocrine disruption potential, PBT potential) even though ERA phase II data already exist. A MAH introducing a new product with properties different form the already registered products (new indications, new patient group, increased maximum daily dose, new route of administration or new pharmaceutical form) has to perform a new ERA evaluating the risk for the environment based on publicly available literature (scientific literature, PAR, Assessment reports/monographs). Mechanism for such data/costs sharing procedure should be established. **A common database of ERA studies** run by an appointed authority is proposed to most efficiently ensure data sharing and its public availability (in a similar way as proposed for	Possibilities of data sharing should be explored by the pharmaceutical industry and are encouraged by EMA. In this respect, fulfilling 3Rs principles should also play an important role. EMA would support a monograph system with regard to the assessment of a possible environmental risk of an API. However, this is beyond the scope of the current guideline revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	veterinary products - EU Commission should deal with how to establish a monography system by 2021).	
	In the last version of Q&A Guideline for human pharmaceuticals (1) the applicant was allowed to justify the absence of the complete ERA by demonstrating no significant increase in consumption data for the past 4 years. There is no explanation why this ERA phase I justification possibility was withdrawn from the proposed draft guideline. Proposed change (if any): Justifying the absence of the complete ERA by demonstrating no significant increase (≤ 10%) in API consumption data for the past 4 years should be possible also in the new draft guidance. Possibility of product specific PECsw refinement in phase I should be possible based on consumption data and market forecast data. Prevalence data for a specific indication may be additionally refined based on amount of population actually treated with a specific API.	The term "significant increase" was omitted due to a missing definition leading to reduced harmonisation in regulatory assessment. A new approach in the revised guideline is outlined in the decision tree.
3	Regarding generic products, e.g. page 4/91 The situation for generics or generally for medicinal products containing an active pharmaceutical substance that is already marketed remains unsatisfactory. The current guideline (EMEA/CHMP/SWP/4447/00 corr 2) states "There may be cases in which the absence of ERA studies could be justified (e.g. marketing authorisation applications for generic medicinal products or type II variations). In these cases, the expert should provide a rationale for the absence of ERA studies, **taking into consideration a possible significant increase** of environmental exposure to the drug substance."	All general comments noted. Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision. The term "significant increase" was omitted due to a missing definition leading to reduced harmonisation in

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Further explanation is provided in the current Question & Answers paper (EMA/CHMP/SWP/44609/2010 Rev. 1): • "In case of a generic application, however, the applicant can also provide other convincing arguments that the **introduction** of their product to the market will not lead to an increase of an environmental exposure." • "Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the **introduction of a new generic medicinal product in a member state where the reference product is not marketed**." In summary, according to the current guideline it is acknowledged that the introduction of a generic does not lead to an increase of a drug substance to the environment since the number of patients does not change. Thus, the provision of results of Phase II studies was not intended for generics as unambiguously evident from the statement in the current Q&A "a generic does not generally lead to an increase of the treated population" and the following example "introduction of a new generic medicinal product in a member state where the reference product is not marketed". Although it is acknowledged that the presence of pharmaceuticals in the environment is a serious cause for concern, it is incomprehensible that the fact that the introduction of a generic does usually not affect the overall introduction of the active component in the environment has not been considered and that the respective exemption has been deleted. It should be considered that release of the draft guideline with its current content would result in dramatic consequences for the whole health sector since manufacturers of generics expecting an annual	regulatory assessment. A new approach in the revised guideline is outlined in the decision tree.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	turnover of 1 million Euro for their product are not able to cover the costs of Phase II ERA studies. As the result, market access for generics would be substantially hampered and bottlenecks in the security of supply and economic consequences for the health insurances can be anticipated. In this context, it should be considered that also according to the draft guideline the results of Phase II ERA studies have no effect on the authorisation of a new drug product. Considering these arguments, it is recommended to maintain the exemption for not providing Phase II study results for generic products	
4	In general, the revised guideline provides many new and useful advice for the preparation of an ERA, e.g. the more detailed description of the single steps that need to be performed. Especially, the introduction of flow charts guiding through the process of the ERA are extremely valuable. On the other hand, especially for generic companies, the possibility to waive an ERA in justified cases is strongly limited in the revised guideline. In the present guideline (EMEA/CHMP/SWP/4447/00 corr 2) it is mentioned that "There may be cases in which the absence of ERA studies could be justified (e.g. marketing authorisation applications for generic medicinal products or type II variations). In these cases, the expert should provide a rationale for the absence of ERA studies, taking into consideration a possible significant increase of environmental exposure to the drug substance." In addition, in the Question & Answers paper (EMA/CHMP/SWP/44609/2010 Rev. 1) it is stated:	All general comments noted. Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• "In case of a generic application, however, the applicant can also provide other convincing arguments that the introduction of their product to the market will not lead to an increase of an environmental exposure." • "Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the introduction of a new generic medicinal product in a member state where the reference product is not marketed." Therefore, one can conclude that according to the current guideline it is well accepted that the introduction of a generic product does not necessarily lead to an increase of a drug substance to the environment since the overall consumption does not change. Investigations of surface water performed in the last decades revealed alarming concentrations of individual drug substances demonstrating that pharmaceuticals are a real thread for the environment. However, the presence of drugs in the environment is not caused by the availability of generics but rather on the consumption and prescription behaviour of patients and medical doctors. Thus, it is not comprehensible why this fact has not been considered and why the exemption discussed above has been deleted in the revised guideline. Additionally, the possibility to use PARs/EPARs is now explicitly excluded. Indeed, the possibility to cross-reference to the	The term "significant increase" was omitted due to a missing definition leading to reduced harmonisation in regulatory assessment. A new approach in the revised guideline is outlined in the decision tree.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	originators ERA dossiers is mentioned as a legit option but only in case of the permission of the originator. Even though the originators/MA holders are "encouraged to share their data", there is no real motivation given why the originator/MA holder should do so. Therefore, this option can be regarded as a rather hypothetical one. By not providing access to the ERA dossier the originator/MA holder can further impede the possibility of generic competition. A better solution would be the integration of defined criteria that allow the applicant to waive ERA studies in case of generic marketing authorization applications if certain conditions are fulfilled. Otherwise, this will lead to the unnecessary repetition of ERA studies often including animal studies since every applicant has to provide their own data. This will make development of generic medicinal products extremely unattractive, is generating no additional benefit for either the nature or the patient and in case of repeated animal tests seems to be ethically at least very questionable. In addition, we like to focus on the fact that implementation of the draft guideline without respective changes would drastically affect the whole health sector. This conclusion is based on the circumstance that the average annual turnover of a generic is usually lower than the costs of Phase II ERA studies. Moreover, the additional development time of up to two years make the development non-profitable. Consequently, potential business opportunities for generics and related investments will be diminished. Since, a major part of the daily need of medicinal products is covered by generic products (in Germany, for example, about 78 %) this could lead to increased supply shortages and an	Only study reports reflect the individual data which are needed for the regulatory assessment and detection of possible data gaps. According to Directive 2001/83/EC an ERA has to be performed irrespective of the legal basis. The Phase I decision tree which is followed to identify the products that require a Phase II risk assessment is also applicable for generic products.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	increase in prices in the future. Affordable medicines for the patients and sustainability of healthcare systems in the EU seem to be under threat.	
	Generic marketing authorizations are allowed to refer to the originator product in terms of efficacy and safety studies. Since the originator does not have this chance, the originator is compensated for these costs by granting market exclusivity after approval. The possibility of reference to the originator's dossier particularly makes sense if one considers the general efforts to minimize unnecessary human and animal studies. Therefore, the question arises why this shall not be possible for ERA studies. In cases where the originator did not submit an ERA, because the corresponding law was not in force at the time it is questionable to make the following generic developers responsible to catch up on this matter. There will be no compensation of such costs in terms of market exclusivity or grant of any other compensation.	Article 10 makes reference to the derogation of the requirement for non-clinical and clinical data laid down in 8(3) (i), but not 8(3) (ca) which lays down the requirement for ERA. Therefore, currently reference to the ERA of the originator product for applications according to Article 10 is not possible.
	Based on these facts, it is of high importance to maintain the possibility for not providing ERA studies for generic products or even establish more defined criteria and possibilities to waive unnecessary ERA studies. As an alternative and especially for cases where a full ERA study is inevitable, a data base for already implemented ERA studies which can publicly accessed should be established. There can also be a reasonable fee in case of pharmaceutical companies accessing and cross-referencing to the data base which could be used to generate a real benefit for the environment by for example supporting scientific studies for effective wastewater treatment aiming at the	This is out of the scope of the ERA guideline.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	establishment of new technologies for removal of pharmaceutics in sewage treatment plants.	
6	Orion endorses the comments given on this guideline by industry associations and recognise the importance of this topic. We would like to point out a particular group of established generic products for which ERA regulatory testing burden is huge because of existing data gaps. On European Union market we have currently generic medicines which have been granted marketing authorization before the current legislation, so called legacy products. It is not fully clear in these cases, which product is the originator, and in some cases the originator products might already been withdrawn from markets. Many of these legacy products may still have important role in patient's treatment regimens on a national level. The draft guideline later states that "For active substances that are already marketed, information may be available in the public domain", however this may not always be the case or if available in the scientific literature, the endpoints may differ and the level of detail in reporting rarely meet the criteria for studies to be used in risk assessment. Therefor strict implementation of the proposed requirements can potentially result problem of availability of these products. This also highlights the need to use science-driven approaches that focus on risk-based approach and careful consideration on implementation deadline of requirements. We proposed that for RUPs ERA would not be required and there would be exemption possible for type II variation as well as described Agency's pre-authorisation guidance, Q&A No 3.4.2. . This would allow the member states an option to consider the approval of such a product without ERA also in future	All general comments noted. RUP does not constitute a reason for exemption to include an ERA in Module 1.6. Refer to the decision tree.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
7	The opportunity to comment on this guidance update is greatly appreciated. The majority of AstraZeneca comments have been submitted as part of the wider trade association comments. The comments below are mostly those which were identified subsequent to the trade association comments being finalised. The submission of separate comments from AstraZeneca does not indicate any lack of alignment with the Efpia, Medicines for Europe and AESGP response. **3Rs** The acknowledgement of the 3Rs in several places within the guidance is appreciated. Particularly the emphasis on lack of fish testing for antibiotics. AstraZeneca is fully committed to principles of the 3Rs and having a positive impact on the amount and quality of animal work we conduct. There are a number of areas in the guidance where the 3Rs message may be lost, however, and repeat testing or inappropriate and unnecessary animal usage may result. Some of these have been highlighted in the comments below and within the Efpia, MfE and AESGP comments. Of particular note are: • The requests for repeat testing in ALL cases of a particular situation (e.g. validity criteria not being met or unbounded NOECs) • NOECs) • The firm rejection of alternatives such as QSAR and minimised BCF design • The lack of discussion on *in vitro* options within a tailored ERA for endocrine active substances	All general comments noted. In addition to a general statement to follow the 3Rs principles wherever possible, QSARS, read across and the development of alternative in vitro tests are also mentioned in the guideline. Additionally, the newly introduced tailored testing strategy for active substances with a specific mode of action supports the reduction of in vivo studies.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• The assumption of risk at all trophic levels when a single RQ >1 This final point is raised in many sections of the guidance and so specific comment is included below: **Compartmental Risk** ***"When the PEC/PNEC ratio is ≥ 1, a risk to the entire XXXX compartment (not a particular sensitive group of species) is indicated."*** This statement is not a logical one in all cases. Where a particular trophic level or species has highlighted a risk, it is important to recognise such. If other trophic levels or species show a clear lack of risk, then this should not be ignored. This is the principle which has, in some respect, lead to the removal of fish testing for antibiotics. There are several well-established risk refinement options available for effects assessments, which are specific to the species or trophic level which is shown to be sensitive (e.g. SSDs). It is considered that this statement could lead to these valuable risk characterisation methodologies becoming redundant, and/or the introduction of additional unnecessary testing in species which are not highlighting a risk. We suggest that this statement is subtlety changed to reflect the above: ***"When the PEC/PNEC ratio is ≥ 1, the risk to all tested species in the XXXX compartment should be examined; any subsequent refinements should account for the sensitivity of the entire XXXX compartment (not only a particular sensitive group of species)"***	Risk assessment is aimed at the whole compartment, assuming that the three trophic levels reflect the whole ecosystem, with an assessment factor for interspecies extrapolation. Approach does not apply here, application for a specific mode of action only.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Referencing and historic traceability The scientific referencing and justification in this document is notably absent in many cases; even where significant changes have taken place (e.g. terrestrial assessment riggers). This should be clarified in order that applicants can best understand the science behind the aspects of the guidance and design ERAs which best assess the perceived risk. But this does not only apply to the aspects which have changed, in this update. In the previous version of the guideline all parameters of the calculations were referenced. Many of these parameter default values have remained unchanged however the references have been removed. Due to the infrequent nature of these updates, the references are important to enable traceability and justification of the values moving forwards. Further, many of these defaults were taken from other associated guidance (e.g. REACh) which may have subsequently been updated and therefore up to date referencing will be even more important.	References are included.
8	Pro Generika e.V. thanks EMA for the opportunity to comment on the Draft Guideline on the environmental risk assessment of medicinal products for human use. The revised guideline provides many new and useful advice for the preparation of an ERA, e.g. the more detailed description of the single steps that need to be performed. The introduction of flow charts guiding through the process of the ERA is very valuable. The current guideline has been in place for 13 years and the ERA-outcomes clearly indicate that most human medicinal products pose low or insignificant risk to the environment through patient use – even in many cases with worst case environmental exposure assessments. The generic industry recognises its responsibility for	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	generating environmental data for APIs that have insufficient data to conclude on environmental risk. However, the proposed guidance seems to place the regulatory testing burden in a disproportionate manner for established generic products that have data gaps while not reflecting all those industries with an interest in that product; this could be perceived as anti-competitive. The guidance has no intelligent approach to gathering data on established APIs with significant data gaps. This will result in repetition of data and likely conflicting ERAs, especially through national and decentralised procedures. The current approach to fill data gaps is considered inefficient and does not share the testing effort proportionately across relevant companies.	Special situation for generics recognised, however this is a legal restriction related to the current version of Directive 2001/83, which cannot be solved by the guideline revision. EMA welcomes and encourages data sharing initiatives between innovator and generic companies such as the eERA framework. However, this is a voluntary scheme. Data sharing in general is encouraged in the guideline. Please see also responses to general comments above.
	We propose that the EMA postpones data gathering for established products until the second IMI pharmaceuticals in the environment project, funded by the European Commission and Efpia member companies, has delivered a list of priority active substances that has been agreed with relevant stakeholders. This will enable regulatory authorities and industry to gather data for APIs of potential concern in an intelligent, coordinated and resource efficient manner that involves relevant companies sharing the costs equally. *Gunnarsson et al (2019)* recently conducted EU-wide consumption-based ERAs, assuming worst-case exposure for the aquatic environment on >100 APIs and demonstrated that most APIs had low or insignificant risk to environment. This illustrates the need to effectively prioritise any data gap filling.	Comment noted.
	Another significant burden for generic companies is the strong limitation of the possibility to waive an ERA in justified cases. The commonly accepted opinion that generic marketing authorizations do not lead to an increase of exposure to the environment is not	According to Directive 2001/83/EC an ERA has to be performed irrespective of the legal basis. The Phase I decision tree which is followed to identify the products that

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	taken into account. The possibility to argue based on market data as considered before in Question 1 of the "Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010 Rev. 1) as an option to waive an ERA is not considered anymore. Additionally, the possibility to use PARs/EPARs is now explicitly excluded. The guideline should implement a mechanism for regulatory bodies to waive ERA studies for compounds where studies have already demonstrated a lack of environmental risk (low risk/ high margin of safety) - even with potential increased use. The possibility to cross-reference to the originators ERA dossiers is mentioned, but only in case of the permission of the originator. Even though the originators/MA holders are "encouraged to share their data", there is no real motivation given why the originator/MA holder should do so. Therefore, this option can be regarded as a rather hypothetical one. As a result, this will lead to the repetition of ERA studies often including animal studies since every applicant has to provide their own data. This will make development of generic medicinal products extremely unattractive as the ERA costs of easily up to one million Euros or more and the additional development time of up to two years make the development non-profitable. Consequently, potential business opportunities for generics and related investments will be diminished. In the draft guideline there are no models described or referred to for making data of the MA holder mandatorily accessible. The innovator places a new product on the market for which a complete evaluation of efficacy and human/environmental safety has to be	require a Phase II risk assessment is also applicable for generic products. Only study reports reflect the individual data which are needed for the regulatory assessment and detection of possible data gaps.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	performed. After obtaining the MA a data/market exclusivity period of 10 years is granted. A generic product is allowed to refer to the innovator data by demonstrating essential similarity with the innovator product thus confirming equal efficacy and safety. As the ERA studies are performed with API - not the finished product - the ERA performed by each MA holder should come to similar conclusions on environmental fate, behaviour and effects. Where differences in environmental risk occur, this can only result if increased exposure is anticipated. It is therefore reasonable that the generic product marketing authorization dossier should be able to refer to the efficacy and human/environmental safety data of the innovator product and all other publicly available data (scientific literature, PAR, EPARs) without necessarily repeating efficacy and human/ environmental safety studies. Since, a major part of the daily need of medicinal products is covered by generic products (in Germany, for example, about 78 %) the issues described above could lead to increased supply shortages and an increase in prices in the future. Affordable medicines for the patients and sustainability of healthcare systems in the EU seem to be under threat.	
10	General remarks to the concept of the environmental risk assessment: Independently from the guideline on environmental risk assessment, we want to encourage considering the concept of the environmental risk assessment generally. To provide an environmental risk assessment with each single marketing authorisation application for a medicinal product result to the fact that for the same API multiple environmental risk assessments	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	based on identical or at least similar studies are performed. This represents a high burden for industry and for competent authorities as well, because they have to assess the same data many times. BPI wants to suggest an API-based approach regarding the environmental risk assessment, filing all generated studies in a master file. The applicants should have the possibility to refer to these data based on a cost-sharing model and to adapt these to product-specific exposures. The European Agencies should publish a list on APIs, where no environmental risk assessment exists across the EU and only focus on missing information. This approach avoids the repetition of tests and supports the reduction of unnecessary (animal) studies and the use of chemicals for the analytical testing. Furthermore, we want to suggest including the environmental risk assessment to the generic concept in the next Revision of the Directive 2001/83/EC. General remarks to the Guideline on the environmental risk assessment: It should be made clear that the conduct of clinical trials falls outside the scope of this guideline.	The proposal is appreciated but would need to be based on an industry initiative, it is beyond the scope of the GL revision. Comment is supported. The scope of the GL is outlined in section 2 of the GL text.
11	The draft revised guideline is much more detailed, incorporating recent Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) guidance and information provided in questions and answers documents on the current guideline, published by the European Medicines Agency (EMA in 2011	All general comments noted.

	(EMA/CHMP/SWP/44609/2010) and 2016 (EMA/CHMP/SWP/44609/2010, Rev. 1). This is to be applauded, and the draft revised guideline is a significant improvement on the existing guideline. However, the revised guideline would benefit from a summary (or an accompanying document) that clearly identifies the differences between the revised and the current guideline, specifically with respect to changes in test requirements or changes in the use or interpretation of test results in the environmental risk assessment. It is my opinion that this would be of significant benefit to users of the revised guideline. For example, the following appear to be changes from the current guideline: • **Dissociation in Water:** Dissociation data are often generated during the drug discovery or pre-clinical stages or can be estimated using QSAR or read-across approaches. Dissociation data from a GLP-compliant OECD 112 study are unlikely to be available. This is a new test requirement, and the generated data appear to be required primarily to interpret results from other environmental fate and exposure studies. • **Water Solubility:** While water solubility data are often generated during the drug discovery or pre-clinical stages, water solubility data from a Good Laboratory Practice (GLP)-compliant Organisation for Economic Co-operation and Development Test Guideline 105 (OECD 105) study at three different pH levels are unlikely to be available. Water solubility can also be estimated using quantitative structure-activity relationship (QSAR) or read-across approaches. The requirement for conducting an OECD 105 study at three different pH levels is new and the generated data appear to be required primarily to interpret results from other environmental fate and exposure studies.	First compilation of changes published in Rhys Whomsley et al., Environmental Sciences Europe 31, Article number: 17 (2019) (DOI: https://doi.org/10.1186/s12302-019-0198-9) Dissociation constant and water solubility are usually already part of the dossier and a prerequisite to perform OECD toxicity studies. Please see responses to related specific comments for details.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• **Adsorption/Desorption Using a Batch Equilibrium Method**: Under the existing guideline, a sludge adsorption coefficient (K_{OC}), determined using the United States Environmental Protection Agency (US EPA) Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Guideline 835.1110 and using one or two sludge types, was typically adequate to complete the environmental risk assessment. The sludge K_{OC} is used in Phase IIA to determine whether a Phase IIB assessment for soil or groundwater is triggered (*i.e.*, when sludge K_{OC} > 10,000 L/kg, a Phase IIB soil assessment is triggered and a groundwater assessment is not required). The draft revised guideline appears to require testing of three soils and two sludges for all drugs as part of Phase IIA using OECD 106. For water-soluble drugs with a low propensity to bind to organic carbon, determining the soil K_{OC} may have limited value, because a Phase IIB soil risk assessment would not be expected for such drugs. It also appears that the soil K_{OC} is now required in Phase IIA to calculate the predicted environmental concentration in sediment (PEC_{SED}), whereas calculation of the PEC_{SED} was previously only required when the OECD 308 test indicated that greater than 10% of the drug at any point on or after 14 days was detected in sediment. The requirement to test three soils and two sludges for all drugs in Phase IIA is a new test requirement. The reliance on the soil K_{OC} in Phase IIA to calculate the PEC_{SED} is a change from the existing guideline. • **Aerobic Transformation in Aquatic Sediment Systems:** Under the existing guideline, this test is required if the drug is not readily biodegradable. Given the cost and length of this test (including the need for ^{14}C-labelled compound) and its primary use to evaluate whether a much shorter and less	Sediment evaluation was already requested in the current ERA guideline. Please see also responses to related specific comments to section 4.2.4. Sediment evaluation was already requested in the first version of the ERA guideline version. Please see also responses to related specific comments section 4.2.4.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	costly sediment toxicity test is triggered, it makes sense that it is no longer a mandated test in Phase IIA. However, it appears to still be required when a Phase IIB groundwater assessment is triggered. Furthermore, it appears that an OECD 308 study may still be required as part of the persistence, bioaccumulation, and toxicity (PBT) assessment when a drug is not readily biodegradable. Because few drugs are readily biodegradable, it would seem that the OECD 308 test will still be required for most drugs. The draft revised guidance indicates that an OECD 307 (soil simulation) or OECD 309 (surface water simulation) study may be performed instead, although it is not entirely clear from the guidance which test is preferred. It appears that an OECD 309 study is preferred for drugs not requiring a Phase II assessment and an OECD 307 is required if a terrestrial risk assessment is triggered. More importantly, it is unclear whether the revised guideline would allow waiving of the simulation test (*i.e.*, assume the drug is persistent based on the results of the ready biodegradability test) as part of the persistence assessment by directly moving to the bioaccumulation criterion and conducting a fish bioaccumulation study (OECD 305). If the fish bioaccumulation study demonstrates that the drug is not bioaccumulative (which is the case for most drugs), then simulation testing would not be needed to complete a PBT assessment. • **Earthworm Test:** The draft revised guideline mandates an enchytraeid reproduction test (OECD 220) or an earthworm reproduction test (OECD 222), whereas the existing guideline lists an acute earthworm toxicity test (OECD 207) as part of the recommended tests for conducting a terrestrial risk assessment.	Due to the mode of action of antibacterials a tailored testing strategy is appropriate to dispense the fish tests

	• Anti-infectives**:** The draft revised guideline mandates a Phase II assessment for the aquatic compartment. It requires testing with four different aquatic species (two cyanobacteria species and one green algae using OECD 201, and a daphnid reproduction test using OECD 211); however, fish testing is not required. The previous guideline requested that testing be conducted with fish (OECD 210), daphnid (OECD 211), and a species of cyanobacterium (OECD 201) for anti-infectives. • **Endocrine Active Substances (EASs):** The draft revised guideline mandates a tailored assessment for all EASs, independent of the PEC action limit and independent of evidence (*e.g.*, from the scientific literature) demonstrating that endocrine effects are not expected at or below the PEC. Information on the target and potential non-target endocrine activity of drugs is expected to be available from *in vitro* and/or *in vivo* testing done as part of drug discovery or pre-clinical testing. For drugs with a well-known mode of action (*e.g.*, hormone-receptor mediated), no known non-target effects (*e.g.*, based on *in vitro* and/or *in vivo* data), and strong *in vivo* evidence that effects are not expected at or below the PEC (*e.g.*, the drug is a weak estrogen or progestin), mandating additional in vivo vertebrate testing seems unnecessary and counter to the principles of the "3 Rs" (replacement, reduction, and refinement). In such cases, a weight-of-evidence argument should be allowed. It is not clear from the draft revised guideline whether this would be allowed. • **Secondary Poisoning:** Consistent with the existing guideline, a log $K_{OW} \geq 3$ triggers the requirement for a fish bioaccumulation test (OECD 305) in the draft revised guideline. The draft revised guideline now also mandates a secondary poisoning assessment when the bioconcentration	and to focus on the other groups of organisms; please see also Schwarz et al., 2021 (Environ Sci Eur 33:68). Comment noted. Considerations of 3R principles and "weight of evidence" approach are mentioned in sections 3.1.3, 3.1.4 and 4.3.2.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	factor in fish (BCF_{FISH}) exceeds 100 L kg-1. In this case, the draft revised guideline does not mandate additional mammalian toxicity testing, rather it allows for reliance on existing mammalian toxicity data or waiving of further assessment when mammalian toxicity data are not available.	
13	Besides conventional pharmaceuticals also pharmaceuticals containing one or more nano-components as active ingredient or as coating / formulation / carrier are on the market and under development. Organic and inorganic substances are used. Currently, information on fate and behaviour of these forms compared to the conventional forms is very limited. It is well known that nanoforms of conventional chemicals can behave differently compared to the bulk form. Therefore, pharmaceuticals containing nano, either as active ingredient or as additional component, should be considered and treated separately from conventional pharmaceuticals, addressing specific features. It should be known, in which form the individual components are excreted and via which pathway they are released into the environment (depending on their sorption behaviour via effluent or via sewage sludge). Furthermore, fate and effect in the affected compartment should be considered. The total residue approach (section 3.2.1) may not be suitable for nano-pharmaceuticals as specific features can be achieved which can change significantly if the pharmaceutical is excreted and separated in the individual components or transformed / degraded in wastewater treatment plants or in the environment.	All general comments noted. Nano-components as active ingredient are difficult to assess with regard to nano-specific mode of actions leading to a nano-related hazard in the environment. Currently, no test systems are available specifically and exclusively evaluating the environmental risk of a nano-scaled API of human medicinal products, only OECD test guideline 23 for "difficult compounds" might be considered. Therefore, it was regarded as premature for this guideline revision to take up specific testing recommendations for nano-scaled APIs.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	In order to decide on the need for a tailored risk assessment (tailored or phase II) for nano pharmaceuticals the following procedure could be considered. For nano pharmaceuticals the questions Q1 – Q3 in Figure 2 could be replaced or complemented by following questions: Q1: Is the nano-portion of a nano-pharmaceutical excreted? no → decision tree according to Figure 2 yes → Q2: Action value exceeded? (action value regarding the percentage of the excreted portion for further testing still has to be defined.) no → decision tree according to Figure 2 yes → Q3: Is degradation in sewage treatment plants expected? no → Is a specific toxic profile of **the nano-portion** expected? ➔ Yes → tailored risk assessment; no → risk assessment phase II yes → Is a specific toxic profile of the **degradation product** expected? ➔ yes → tailored risk assessment; no → risk assessment phase II Tables 1, 10, 11-14 have to be adapted to the parameters relevant for nanomaterials; additionally, to the determination in water, the PC-parameters have to be determined in test media. The test guidelines adapted or already developed for the testing of nanomaterials and the recommendations on alternative endpoints should be considered. A differentiation in organic and inorganic substances seems to be advisable.	
16	Pharmaceutical companies should be transparent with their environmental data, increasingly people are concerned with the environmental impact of the product that they consume and	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	purchase. Companies such as AstraZeneca have made their complete Environmental Risk Assessment reports public, allowing people to understand the environmental impacts of the medicines that they are taking. This should not be an unconventional standing, but an industry standard. https://www.astrazeneca.com/content/dam/az/PDF/2017/Environmental_risk_data_relating_to_our_medicines.pdf	
18	The revised guideline is much clearer, better organised and easier to understand than the initial version. Many previously indistinct aspects have been defined and are now presented in a coherent way; the flowcharts provide a very useful overview of the process. It is especially appreciated that the definition of compounds for which an action limit does not apply, or which have to undergo a tailored risk assessment has been clarified. Further, the defined proceeding for tailored risk assessment makes the ERA data set much more plannable. It is also appreciated that e.g. OECD 308, which was an integral component of Phase II Tier A, is now only demanded when a trigger value indicating a relevant risk to groundwater is exceeded. # generics, e.g. page 4/91 The situation for generics or more generally speaking for medicinal products containing an active substance that is already marketed remains unsatisfactory.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	As the proposed draft guideline precludes most realistic options of referring to data included in dossiers of already authorised products, all pharmaceutical companies are forced to repeat the same studies although the outcome is already known. In our opinion, this proceeding is a waste of time, resources and efforts, as the repetition of already conducted studies will not yield any additional insight in the environmental behaviour of that active substance. Especially for animal studies, this process does not appear to be ethically justified. Although the guideline states that marketing authorisation (MA) holders are encouraged to share their data, there is no incentive for them to do so. Medicinal products containing active substances that were approved for the first time in the EU after the guideline came into effect were required to submit an ERA, and the ERA forms part of the marketing authorisation of those products. As such, the same rules concerning periods of data exclusivity and market protection should apply for ERAs as for all other documentation on nonclinical test and clinical trials submitted with the initial authorisation in the EU. Therefore, reference to this part of the dossier should be possible in the same way as it is for the nonclinical and clinical data package. We agree that also for active substances contained in medicinal products authorised before the guideline came into force, it is of public interest to gain further knowledge about their environmental risk. It is encouraged to enforce competent EU agencies, e.g. ECHA supported by EMA, to identify marketed active substances carrying	Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83/EC, which cannot be solved by the guideline revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	a potential environmental risk for which no satisfactory body of information on environmental fate and effects is available. The competent EU agencies, e.g. EMA, shall be entitled to request holders of valid MAs for medicinal products containing those active substances to provide publicly available or own environmental data, e.g. in a similar procedure as commonly used in Art. 31 referrals triggered following concerns relating to quality, safety or efficacy issues. In case the competent EU agency, e.g. ECHA, concludes that essential data on environmental risk are missing, it should be entitled to initiate those environmental studies and charge a fee from all holders of valid MAs in the EU containing that active substance. Part of the fee may be utilized for research on wastewater treatment to actively reduce the environmental load of medicinal products. MA holders that submitted own data about the environmental risk in the initial request for information by the competent EU agency shall receive fee exemption as an incentive for their contribution. # metabolism (e.g. page 20/532) It is generally assumed that most environmentally critical effects of pharmaceuticals relate to their therapeutic activity, e.g. engagement of specific receptors that are also present in non-target organisms. One may therefore deduce that metabolites lacking therapeutic efficacy according to pharmacodynamic endpoints are rather unlikely to have relevant effects on environmental organisms in the relatively small quantities of human pharmaceuticals and their metabolites typically observed in the environment (compared e.g. to herbicides or industry chemicals). Relevant effects by metabolites are therefore not likely to occur if the metabolites have been	This is out of scope for the guideline.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	demonstrated in nonclinical tests to be significantly less active than the parent active substance. For these reasons, it is not clear why 1) metabolism may only be considered in Tier B and not already in Tier A when the initial PEC_{SW} is calculated and 2) why metabolites should be subjected to extensive Phase II testing during PEC_{SW} refinement in Tier B based on the excreted quantity without consideration of their therapeutic activity. A full Phase II risk assessment for potentially several metabolites (those constituting ≥ 10% of the administered dose according to the guideline) is not a realistic option considering the associated costs. In light of the fact that relevant effects not already found for the parent compound are unlikely observable for inactive/less active metabolites, it is questionable that this approach yields relevant insights. It is proposed that metabolites for which low or absent efficacy based on the primary pharmacodynamic endpoints has been demonstrated during nonclinical testing should be exempted from Phase II testing during PEC_{SW} refinement in Tier B. Also, environmental entry of metabolites is hardly controllable with the risk mitigation measures currently proposed in the guideline (warnings in the label), which have no impact on excretion of metabolites by the patient. Therefore, any potential risks associated with metabolites cannot be properly addressed.	Please see responses to related specific comments regarding the total residue approach.
19	Seemingly the draft guideline is intended to contain all points of the Q&A document from 2015, but this is not clearly stated. Proposed change: Insert a short statement, that the new guideline makes the Q&A document obsolete.	All general comments noted. It will be marked on the website accordingly.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	However, PNEC will be derived in the ERA, no EQS according to the WFD has to be proposed. Proposed change: The applicants may propose and EQS according to the WFD within the ERA.	No change to the guideline. Rationale: Applicants may use an EQS in the ERA if it is already formally established under WFD and covers the required scope and endpoints of GL. New EQS proposals are out of scope of this GL.
21	We were wondering why metabolites of active ingredients in drugs are not assessed specifically since this is a common assessment for e.g. biocides and plant protection products. Is it a general understanding and proven fact that metabolites of active ingredients in drugs are less toxic to the environment than the parent?	All general comments noted. Please see responses to related special comments section regarding the total residue approach.
22	This revised and improved guideline is highly welcomed! It is noted that antimicrobial resistance is not covered or mentioned at all, not even in the paragraph dealing specifically with antibiotics. The assessment of the impact of antimicrobial resistance arising from antibiotics released to the environment through manufacturing, use and disposal is of high importance. It is however recognised that it will take time to produce relevant guidance covering antimicrobial resistance and it is not useful to delay the finalisation of this guideline for that purpose. Instead, it is proposed to start working on an additional guidance document dealing with antimicrobial resistance. It would be of value if the ERA report was accompanied with the data in a format that would facilitate constructing a database at the EMA for availability and easy access of environmental information. It is suggested that such work is initiated.	All general comments noted. This is out of scope for the current guideline revision. In general EMA is in favour of an ERA database, however this is out of scope for the current GL revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The overall structure and readability could be improved by moving some technical descriptions and equations into an Appendix. Furthermore, there is some repetition throughout the document, which should preferably be avoided to enhance readability. Throughout the document, the language used contains a lot of strong expressions as 'mandatory', 'requested' etc. Such language should not be used in a guideline – and should be replaced by other wording. It does not change the strength of the recommendations provided throughout the guideline, and specific studies can always be requested for a specific product. Nevertheless, this document is not law, but a guideline. Figure labels should be placed under the figure. Consider labelling the tables with descriptions for the parameters used in equations as tables. There are some abbreviations which need spelling out – e.g. line 63 HMP The decision tree (Figure 2) is appreciated!	Effort has been made to address these aspects in the GL revision. Effort has been made to address these aspects in the GL revision where appropriate. Effort has been made to address these aspects in the GL revision where appropriate. Comment noted.
23	Thank you for the opportunity to comment the Guideline on the environmental risk assessment of medicines for human use. The effect of pharmaceuticals on the environment is a highly important topic. We applaud the well-structured and detailed guideline which	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	will help the developers of new medicines to carry out the proper risk assessment. Our concern focuses on the request to provide the complete ERA by the marketing authorization holders of generic medicines (Question 2a, lines 230-234). The mechanism to provide this document is suggested to be shared by the originator to the generic manufacturer(s) (Question 2b, lines 235-241). In practice this would rarely happen unless the generic producer would commit to a substantial financial agreement with the originator, and not even then due to the commercial competition. In all EU countries one is already facing severe availability problems of generic products because many markets are not anymore commercially attractive to generic manufacturers due to the very low prices. Putting the demand to develop and/or purchase a complete ERA document would put an extra burden on these manufactures and might again lead to further availability problems of these medicines. The suggestion of having to redo the rather comprehensive ERA studies is against the very principle of 3R, and also ethically questionable. It would be important to understand the background of such a request for generic products. Typically, generic manufacturers can refer to the data of the originator, and it is hard to understand why generic manufacturers could not be allowed to refer also to the ERA of the originator. One possibility is also to make the ERA developed by the originator public, as it is of interest for many parties, not only for the stakeholders working at the pharmaceutical field.	Special situation for generics is recognised, however this is a legal restriction related to the current version of Directive 2001/83/EC, which cannot be solved by the guideline revision.
25	The document is a significant improvement to the 2006 ERA-guideline. While the subject matter has not changed all that much, in the document is much more unambiguous. However, there are	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	some things that should be revised or stated more clearly (more specific comments in section 2). Pharmaceutical industry should be encouraged to publish their ERA-documents, or their significant findings. This would be in line with the EU Strategic Approach on Pharmaceuticals (EC Communication 2019, 128). Currently there are several points where instructions are given as "should" (e.g. rows 354, 387, 420, …). To make the text more unambiguous, these should be stated in a more binding form. Are "action limit" and "trigger value" basically the same thing? If so, it might be appropriate to use similar terms for similar things throughout the document.	No change to the guideline. Rationale: "should" is used to indicate obligation and is not considered ambiguous.
26	In general, draft document is a significant improvement to the 2006 ERA-guideline. However, there are some things that should be revised or stated more clearly (more specific comments in section 2). Pharmaceutical industry should be encouraged to publish their ERA-documents, or their significant findings. This would be in line with the EU Strategic Approach on Pharmaceuticals (EC Communication 2019, 128). Currently there are several points where instructions are given as "should" (e.g. rows 354, 387, 420, …). To make the text more unambiguous, these should be stated in a more binding form.	All general comments noted. No change to the guideline. Rationale:

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		"should" is used to indicate obligation and is not considered ambiguous.
27	All references to 'Water Framework Directive EQS (European Communities, 2011)' should be updated as this document is superseded by the following document: European Commission. 2018. Technical Guidance for Deriving Environmental Quality Standards. Guidance Document No. 27. Updated version 2018. 207 p. https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/ba6810cd-e611-4f72-9902-f0d8867a2a6b/details or guidance document nr. 27 from this page: http://ec.europa.eu/environment/water/water-framework/facts_figures/guidance_docs_en.htm. Substance and compound are used in the document. This should be harmonised into one. Please adhere to the worldwide convention of displaying physical/scientific parameters. Consult the IUPAC rules on using italic and roman fonts for symbols in scientific texts. The well-known acid dissociation constant (a textbook example) should be typographed as pKa. Italic, capital font is used for variables, subscripts in normal font (non-italic) is used for label (here: acid) Kow and Dow have a different meaning than Kow Dow. Proposed change (if any): pKa into pK_a	All general comments noted. Not agreed. Rationale: Substance and compound are widely understood terms. They have been used interchangeably in the GL text aligned with commonly used terminology e.g. 'active substance', 'dissociating compound'.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Kow into K_{ow} Dow into D_{ow} Kd into K_d Koc into K_{oc} In addition, we have commented that the section on secondary poisoning be revised as it is not in line with the current WFD guidance document for the derivation of Environmental Quality Standards, where this was the intention. We provide a revised text that could serve as a replacement for section 4.8.2 for the drafting group to consider. Our proposal is submitted both as a Word document with track changes and a clean version (pdf).	Proposal has been taken into account and text has been revised.
28	The current draft guideline does not specifically cover an environmental risk assessment of metal-containing medicinal products, e.g. such as contrast agents or metal complexes. As these compounds have different physicochemical characteristics than pure organic medicinal substances, and as some of these products (specifically their metal component) are emergent environmental contaminants (e.g. Gd in contrast agents), the specificities of metal containing medicinal products for environmental risk assessments should be adequately covered in the new guideline. This especially becomes relevant for the proposed PBT screening method of medical products: A definitive PBT assessment of a medicinal product is only required when the investigated substance has a Kow > 4.5. Since metal containing medicinal compounds will likely have a lower Kow, definitive PBT assessments would consequently not be required, incorrectly suggesting that they are degradable. This is problematic as the metal part of such medicinal products is	All general comments noted. Contrast agents and metals fall within the scope of the guideline. No specific guidance for these compounds is given in the guideline. For more detailed information on PBT/vPvB assessment of organometals and metal complexes the stakeholder is referred to the REACH Chapter R.11 on PBT/vPvB assessment.

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	of course non-degradable and therefore persistent in the environment.	
29	The draft guideline on the environmental risk assessment of human pharmaceutical products is highly appreciated by UBA. The high relevance of knowledge about pharmaceuticals in the environment and their possible risks was recently highlighted in the Global Environment Outlook (GEO 6, UN Environment) and the EU Strategic Approach to Pharmaceuticals in the Environment (COM(2019) 128 final). The prospective assessment of environmental risk of pharmaceuticals is one of the most important elements to acquire this knowledge. The new structure is very clear. For each environmental compartment the Tier B assessment is described and possibilities of refinement were given. This is much more comprehensible and more detailed than in the current guideline. Applicants have the possibility to follow step by step the described assessment for the different environmental compartments, if required. We as environment agency expect that the new guideline will minimize uncertainties and discussions. Furthermore, UBA appreciates that the guideline now includes all relevant information for the performance of an ERA and reference to other guidelines is not required anymore. This poses a great facilitation for applicants and assessors. The new approach for generic applications (in accordance with article 10 of 2001/83/EG) is one of the major improvements of the new guideline. It is scientifically sound, considers the current legislation given by the Directive 2001/83/EG and recommends data sharing by the applicants. The 'EU Strategic Approach to Pharmaceuticals in the Environment' goes in the same direction by	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	addressing knowledge gaps for pharmaceuticals authorised before 2006. The technical part on how to conduct an ERA in Phase II reflects the current state of knowledge and the guideline is in line with other guidelines dealing with environmental risk assessments of substances with similar exposure routes e. g. biocides, veterinary pharmaceuticals. The detailed advice on a tailored risk assessment of antibiotics and endocrine active substances and the revised soil trigger, the groundwater risk assessment and risk for secondary poisoning are very welcome. This provides a consistent approach for products with those substances and gives a higher certainty for applicants and assessors on what to do.	
	Comment: Fate assessment The application for a marketing authorisation of a medicinal product is the best time point for receiving detailed information needed for a prospective risk and hazard assessment. A prospective ERA consists of an effect and a fate & behaviour part. In other chemical regulations (Plant Protection Products, Biocides) one or more simulation test(s) of transformation in aquatic systems are mandatory if the substance is not readily biodegradable and will enter the aquatic environment. By omitting the OECD 308 from the base data set, only very scarce information on the transformation are available. In the 'EU strategic approach to pharmaceuticals in the Environment' of the EU Commission (COM, 2019, 128 final), it is noted that the issue of pharmaceutical residues cannot be ignored.	Please see response to comments on section 4.2.1.2.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Concerns about known risks and the increasing presence of pharmaceuticals in the environment should be considered. In the recently published Global Environment Outlook (GEO 6, UN Environment) pharmaceuticals are considered as emerging pollutants as well. The presence of pharmaceuticals in surface water and groundwater is one of the issues of concern worldwide. In our point of view this draft version of the guideline does not considers sufficiently this point about presence in the environment. A better knowledge is required about the fate & behaviour of the active ingredients to conclude on possible hazards, such as a high concern for extremely persistent substances (Cousins et al., 2019: Why is high persistence alone a major cause of concern? Environ. Sci.: Processes Impacts, 2019, 21, 781). Waiving data on fate & behaviour in the environment because there is no direct use in the Phase II risk assessment at present, is not in line with the state of scientific knowledge. ERA DG is asked to discuss how to fill this data gap.	
	Nanomaterials: It is unanimously acknowledged that nanomaterials are special forms of chemical substances entering the environment and may posing a risk to environmental organisms. However, nanomaterials feature specific challenges with regard to the assessment of their environmental fate & behaviour and effects [UN, 2019; UBA, 2016; RIVM, 2015; OECD, 2014; Danish EPA, 2011*]. Due to their specific properties distinguishing them from other chemicals, adaptations of the different regulations are needed for an appropriate risk assessment. To account for this need, specific provisions for nanomaterials were already included in the biocidal product regulation (EU 528/2012) as well in the REACH Regulation (EU	All general comments noted. Nano-components as active ingredient are difficult to assess with regard to nano-specific mode of actions leading to a nano-related hazard in the environment. Currently, no test systems are available specifically and exclusively evaluating the environmental risk of a nano-scaled API of human medicinal products, only OECD test guideline 23 for "difficult compounds" might be considered. Therefore, it is

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	1907/2006, coming into force 01.01.2020). In these regulations nanomaterials are legally defined as proposed by the EU Commission (2011/696/EU). In addition, also other regulations give specific provisions for nanomaterials, e.g. the regulation on cosmetic products (EC 1223/2009), on novel foods (EU 1169/2011), on plastic materials and articles intended to come into contact with food (EU 10/2011), on the provision of food information to consumers (EU 1169/2011). The amendments of these regulations in terms of nanomaterials are accompanied by specific guidance on information requirements, e.g. for REACH by ECHA. Furthermore, EFSA is giving guidance on risk assessment of nanomaterials in food and feed chain. There, EFSA currently develops also a guidance for assessing environmental risk of nanomaterials (EFSA 2017). A number of specific standardised test guidelines, guidance documents and guidance (e.g. by OECD) are available for nanomaterials or underway. Thus, the relevance of advice for a specific risk assessment for nanomaterials in a regulatory context is obvious and available. Thus, it is important to note that an ERA of medicinal products should also cover nanoscale active substances. However, the current guideline does not address nanomaterials. The proposed ERA in the guideline includes a number of approaches and tests which do not provide appropriate data for a valid ERA for nanoscale active substances. Hence, there is urgent need to give advice on the needed adaptation to account for the peculiarities of nanomaterial testing. Proposed change:	regarded as premature for this guideline revision to take up specific testing recommendation for nano-scaled APIs.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	It is proposed to add "active substance that falls under the definition of nanomaterials", e.g. referencing to the EU COM recommendation* for a nanomaterial, line 108, in addition to EAS and antibiotics. The EU COM recommendation could be reference e.g. by a footnote under 3.1). Alternatively, the EMA working definition on nanomedicines might be referable as well. Additionally, we propose to include a tailored risk assessment for nanomedicine in chapter 4. This should include endpoints relevant for nanomaterials (e.g. dispersion stability, dissolutions rate and transformation in relevant environmental media) which inform about the fate & behaviour and can serve as triggers for a nanospecific testing strategy, too.	
30	In comparison with the previous GL, this GL is much improved with clearness and a more detailed advice. However, the same approach as in previous GL is kept: dividing the guidance in two Phases, where the Phase I relies on the exposure only (except for PBT assessment, which is a good improvement). The whole GL seems to rely on specific triggers, whose intention is to avoid a complete testing of the active substance. This contradicts with the plant protection products ERA where a whole data set with fate and effects of the active substance (and partly for formulation, too) is required. Furthermore, a "Monograph" system on environmental fate and effects data on active pharmaceutical substances would be an excellent instrument to provide an up-to-date data set for the	All general comments noted. For marketing authorisation of a human pharmaceutical a complete dossier should be submitted at the time of application, containing a full data package with regard to quality, non-clinical and clinical assessment of the active ingredient.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	environmental risk assessment of medicinal products. There is a lot of good experience within other chemical frameworks such as biocides, plant protection products and REACH with a monograph approach. This would help to evaluate studies and to agree on the endpoints to be used for ERAs of medicinal products. There is an increasing request on publicly available environmental data from different stakeholders such as water authorities, water boards, the public, etc. Pharmaceutical substances are biologically highly active substances, and they are unintentionally, but regularly released in the environment. Hence, there is a huge public concern regarding the occurrence of pharmaceutical substances in environment. Due to the fact, that environmental information is vital for any kind of risk management, these data should be adequately available. A publicly available database on validated data on fate and effects of active pharmaceutical substances in the environment is therefore urgently needed. This would be possible by publishing the endpoints from the environmental studies from the monographs (like the Review Report with the LoEP published by EFSA from ppp-substances).	EMA would support a monograph system with regard to the assessment of a possible environmental risk of an API. However, this is beyond the scope of the guideline revision. In general EMA is in favour of an ERA database, however this is out of scope for the current GL revision.
31	The use of a wider definition of EDCs is appreciated. However, it is not clear which exact definition that is used. Considering the conflicts in this policy area, a clarification is warranted. This is also importance for coherence between regulations. The more substance specific adjustments are appreciated, e.g. shift from fish tests to algae tests for antibiotics, and the increased	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	coherence with other regulatory frameworks (potential for secondary poisoning). The increased guidance on "Search and evaluation of data" is appreciated. To be preventive and learn from other regulatory fields (e.g. REACH) it is recommended that a detailed reporting format for evaluations and study summaries are used to promote transparency and structure of assessments. For scientific studies on this see: 1. Ingre-Khans E, Ågerstrand M, Beronius A, Rudén C. 2019. Toxicity studies used in REACH - How accurately are they reported? Integrated Environmental Assessment and Management 2. Ingre-Khans E, Ågerstrand M, Beronius A, Rudén C. 2018. Reliability and relevance evaluations of REACH data. Toxicology Research. DOI: 10.1039/c8tx00216a 3. Inge-Khans E, Ågerstrand M, Beronius A, Rudén C. 2018. Improving structure and transparency in reliability evaluations of data under REACH – suggestions for a systematic method. Human and Ecological Risk Assessment 4. Inge-Khans E, Ågerstrand M, Beronius A, Rudén C. 2016. Transparency of chemical risk assessment data under REACH. Environmental Science: Processes & Impacts 18(12):1508-1518. Considering the strong focus on the 3R principle the following text "If of acceptable quality, data from published literature on the active substance may be employed in the ERA" should be changed to "If of	Additional text included: "*The applicant is requested to show how the literature search was performed, e.g. by stating the search engine and search terms used."* Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	acceptable quality, data from published literature on the active substance **should** be employed in the ERA". Several major deficiencies remain in the draft: It only apply to new market authorizations. To update of the assessment is needed. Mixture assessment is not considered. The ERA is not used in any decision-making process. Two major environmental and health problems are not considered: emissions from production and antibiotic resistance. And please improve the reporting in the EPAR and make it possible to search for the data per substance.	Proposals are beyond the scope of the guideline revision
34	**Lack of data to assess P:** Due to changed requirements for risk assessment, far less OECD 308 studies will be carried out at Phase II Tier A (i.e., no degradation information required at the level of Phase II Tier A as detailed in Table 1). At the same time, PBT assessment is a two-tiered process with an initial screening for substances with log Kow > 4.5. Only for those substances, P testing and assessment will be required. Effectively, the suggested changes will lead to a complete lack of information on the extent of degradation in the environment for >60% of APIs (see "Retrospective ERA for human pharmaceuticals based on new proposed guidance", Daphne de Roode, Charles River Laboratories, iPiE Final Conference, York, 25. June 2019). Results from OECD 301 are not a good substitute for this since these tests are carried out under conditions that are not representative of environmental conditions (Kowalczyk et al., 2015, Ecotox. Environ. Safe., 111, 9-22), and it is well known that hardly any active pharmaceutical substance passes the ready biodegradability cut-off. Yet, P assessment should be a requirement for any chemical on the market, based on the following arguments:	All general comments noted. Persistence can be assessed in the PBT/vPvB assessment and Risk Assessment. For PBT/vPvB, screening the need for assessing persistence with the log Kow/Dow trigger is in line with REACH and is considered sufficient. In the Phase II Risk assessment, risks are based on the ratio between PEC/PNEC. Information on degradation can be used in higher tier assessments to refine the PEC and is used in the PBT assessment to assess it as hazardous property. Also, metabolites are assessed when abandoning the total residue approach. Therefore, current requests for data are considered sufficient.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	- First, persistence has been shown and widely acknowledged to be a problematic property per se (Cousins et al., 2019, ESPI, 21, 781-792). This is demonstrated by the fact that compounds that are persistent and either nonpolar, bioaccumulative (i.e., POP-type compounds) or, in contrast, highly polar (i.e., PMT-type compounds) are perceived as posing significant threats to the environment. A pre-screening based on log Kow completely neglects the possibility that compounds might be of concern due to persistence in combination with high mobility. - Second, log Kow is not an appropriate criterion to assess bioaccumulation, particularly for ionizing substances, which is the case for many pharmaceuticals. For instance, bioaccumulation of amine-containing compounds (approx. 60% of all active substances) in higher microorganisms has been demonstrated (Gulde et al., 2018, ES&T, 52, 52-60). - Third, the suggested procedure is not in line with REACh guidance. REACh guidance clearly states that "The PBT/vPvB assessment must cover a consideration of each property persistence, bioaccumulation and toxicity against each respective criterion (P or vP, B or vB, and T) …" (R11.4.1). REACh thus requests that data for all three endpoints must be available before any PBT assessment can be conducted. This is not the situation if the suggested EMA guideline is followed. - Finally, the fact that OECD test guidelines such as OECD 308 and 309 still raise some issues in terms of reproducibility, stringency and data interpretation (e.g., Honti et al., 2016, ES&T, 50, 6865-6872; Shrestha et al., 2016, ES&T, 50,	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	6856-6864) should not be used as a reason to do without them. Rather, knowledge on biotransformation and factors influencing biotransformation should be improved and the guidelines should be revised to deliver as accurate and representative biotransformation information as possible. We strongly advise that initial screening for log Kow > 4.5 should be removed from the PBT assessment scheme. Rather, test data to assess all three endpoints (P, B and T) should be required for all APIs.	
34	**Use of different simulation studies for P assessment**: If an active substance enters definitive P assessment, different OECD guidelines might be used for P assessment, including OECD 307, 308 and 309. There are two points of concern here that might need to be addressed or at least commented on in the guidelines: - First, each of these OECD guidelines covers different environments (surface water, sediment, soil) and each environment comes with an own P criterion (Table 16). However, there is no direct intercomparability between these environment-specific P criteria, since the environment-specific criteria have never been derived on a fundamental understanding of how biodegradation might differ between these environments. Therefore, using different test guidelines and different P criteria effectively means that different active substances are measured against different "triggers", or, in simpler words, that apples and oranges are compared. We, however, acknowledge the practicality aspects of the suggested procedure and therefore do not suggest that this should be changed, but at least commented on in the guideline.	All general comments noted. The guideline gives some guidance on testing strategies to provide sufficient information to assess persistence (P), further detailed information on testing strategies is given in REACH R.11 on PBT/vPvB assessment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	- Second, according to lines 1127-1130, which describe the procedure to select one of the possible OECD studies for P assessment, it is very likely that OECD 309 will be heavily defaulted to. Yet, according to lines 1144-1146, the most appropriate half-lives for P assessment are total system or sediment degradation half-lives. This seems inconsistent with the preference for OECD 309 since OECD 309 tests are mostly carried out as pelagic tests (i.e., without any sediment added) and hence (i) typically give rise to very little or no degradation (and would thus lead to P classification in almost all cases), and (ii) cannot give any information on degradation in contact with sediment. Therefore, we suggest that usage of OECD 309 should be further specified in the guideline in the sense that OECD 309 studies should be carried out with the addition of sediment, which is allowed according to the guideline up to concentrations of 1 g sediment/L. It needs to be understood though that there is hardly any experience with this type of OEC 309 studies, which makes it questionable whether this should be the test guideline that is heavily defaulted to or promoted in the guidance. In contrast, there is a lot of experience (also from different regulatory contexts) with the OECD 308 guideline and it is clearly relevant to assess biodegradation in contact with sediment. While we acknowledge that there are some issues with the interpretation of OECD 308 studies, these can be solved with the appropriate modelling algorithms and tools (Honti et al., ES&T, 2015, 49, 5879−5886). We therefore suggest that OECD 308 should be more emphasized as "default" test	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	for P assessment, and that OECD 309 should rather be considered as a 2nd test option, which will also help improve interpretability of OECD 308.	
34	**Assessment of endocrine disrupting effects:** We were surprised that only estrogenic, androgenic and thyroidic activities were considered. In fact, several recent publications have highlighted that glucocorticoids and progestagens are prescribed and released in higher amount than estrogenic or androgenic or even thyroidic drugs [Runnals et al. 2010, Hum. Ecol. Risk Assess.; Besse and Garric, 2009, Environ Pollut.]. This is not only reported in Europe but also in Asia and North America [Chang et al. 2017, Environ. Sci. Technol., Daniels et al. 2018, Chemosphere]. This environmental occurrence should be considered in the selection of the assays. For instance, detection of chemicals with thyroidic activity is scarce. Thus, even though the HPG axis is of particular concern, other endocrine pathways involved in crucial physiological processed should also be considered. Also, since some drugs can modulate the clearance rate of endogenous hormones (and so homeostasis) by increasing/decreasing gene expression of detoxification enzyme activity (PXR, CYP3A4) through activation of specific nuclear receptors, such targets should also be investigated. Therefore, it is surprising that the guideline specifically mentions that this should not be considered as a mechanism that would warrant evaluation as an endocrine active substance (L1022-1023).	All general comments noted. Selection of endocrine features to be addressed in the guideline revision was based on a thorough scientific discussion considering data available for identification of EAS. Glucocorticoids and progestins are includes in the EAS approach (see also specific comments on EAS).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
35	I would like to see that a monograph system will be implemented (see veterinary pharmaceuticals) too to make available information on active compounds easier and have it more structured. That is a big issue not only in research but even more important in regulatory affairs. In the document I found: "For some substances with specific classifications (e.g. endocrine active substances (EAS), antibiotic substances), a tailored risk assessment is necessary. The PBT assessment concerns the intrinsic properties of a specific group of active 109 substances, which are potentially harmful to the environment regardless of the levels of exposure." I would advice to add also cytoxics/antineoplastics in case of direct interaction with DNA (see: Antineoplastic compounds in the environment—substances of special concern Klaus Kuemmerer et al. Environmental science and pollution research, Antineoplastic compounds in the environment—substances of special concern. 2016, DOI:10.1007/s11356-014-3902-8 Often pharmaceuticals are not completely mineralised resulting in the formation of new products which have been shown in some cases to be even more persistent and more toxic (e.g. mutagenic, gentotoxic, ecotoxic) than the parent compounds. That happens in the environment and also often in effluent treatment and potable water treatment. Therefore, these products of incomplete mineralisation should be included into the testing scheme and risk assessment (e.g.	All general comments noted. EMA would support a monograph system with regard to the assessment of a possible environmental risk of an API. However, this is beyond the scope of the current guideline revision. It is not deemed necessary to specifically address genotoxic compounds since trigger values will apply also for them. In risk assessment the total residue approach can be followed, which assumes that metabolites have similar or lower toxicity of the parent substance. Including data on metabolites is possible when abandoning the total residue approach, and in some higher tier studies data is generated.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	if incomplete degradation has been found). Not including these products of the active ingredients will result in an underestimation of risks in many cases. Furthermore OECD 308 should be included into the base data set to allow for fate assessment at this stage already (i.e., no data for metabolites and transformation products will be available as for the issues addressed by this test (water -sediment). In addition, what I mentioned above as for transformation products (i.e. products of incomplete mineralisation (btw. I would recommend using this expression throughout the document to address the issue of possibly incomplete degradation) such data are of utmost importance for water works e.g. for monitoring purposes (see for example the example of NDMA). An exhaustive and reliable risk assessment has to address this by at least providing knowledge and data for other domains of legislation. It is neither green nor sustainable to keep the different domains separate by not generating data needed and helpful. Why "QSARs (Quantitative 181 Structure-Activity Relationships) and read-across cannot replace the studies requested in this 182 guideline"? There are quality criteria available and such methods are applicable under REACH and within assessment of pollutants in drinking water e.g. according to German regulation (GWO concept)	Currently available QSARs are not yet qualified to replace chronic toxicity tests.
36	The revised ERA Guideline includes many significant improvements to the existing guideline. For example, Figures 1 and 2 excellently simplify the relatively complex matrix of test requirements and their stepwise execution, and generally, the rationale behind the test requirements has been successfully clarified.	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	However, there are a few points that could benefit of further refinement and/or deserve additional attention. These are itemized below. Ideally, all possible efforts should also be made to extend the ERA assessment to apply to all renewals of marketing authorizations (Type II), also of those active substances that have been authorized prior to 2006. Similarly, all possible efforts should be made to foster the publishing/public availability of the ERA documentation (on top of the current recommendation of such practice).	The renewal procedure is currently performed 5 years after marketing authorisation. The environmental risk evaluated at the time point of marketing authorisation is considered to be the same, if no new ERA data are available. If new ERA data of the API become evident, the marketing authorisation holder should submit them via a variation procedure (Type IB C.I.z) to adapt the ERA of the marketing authorisation. As a rule, Marketing authorisation for products authorised before 2006 will not undergo a renewal procedure anymore.
37	Health Care Without Harm (HCWH) Europe welcomes the opportunity to comment on the draft revision of the 'Guideline on the environmental risk assessment of medicinal products for human use'. We understand the need to revise the guideline that came into force in 2006 to address implementation issues, take into account scientific developments, and reflect the experience gained with the current guideline. We recognise that the revised guideline introduces significant structural and substantive changes to provide a more consistent	All general comments noted. It is not in the remit of the European Medicines Agency to introduce legally binding changes in Directives etc. This task lies in the sole responsibility of the European Commission. A guideline is not legally binding, therefore legal changes are out of the scope of such a guideline.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	approach to environmental risk assessment for human medicinal products. We recommend, however, that the European Medicines Agency considers more fundamental revisions to the ERA guideline, notably in view of the development and spread of antimicrobial resistance (AMR), even if this requires legislative changes. We therefore call on the European Medicines Agency to address the following shortcomings in its current revision process: 1. The revised guidelines should include Environmental Risk Assessments in the Risk-Benefit Analysis Environmental Risk Assessments should become a criterion for refusal of market authorisation. The intention here is not to prevent new products from entering the market, but to emphasise the importance of Environmental Risk Assessments that aren't currently prioritised by pharmaceutical companies as there is no penalty for noncompliance. 2. The revised guidelines should include requirements to assess the risk of AMR development in the environment The revised guideline should require impact assessments of antimicrobials for human use on the prevalence of AMR in the environment. Pharmaceutical pollution is a driver of antimicrobial resistance that kills an estimated 700,000 people a year worldwide.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	By 2050, antimicrobial resistance could kill up to 10 million people annually, making it a major cause of death globally. 3. The revised guidelines should also apply to human medicinal products authorised on the market before 2006 Many pharmaceuticals detected in the environment were authorised before 2006 when the guideline came into force and therefore did not undergo an Environmental Risk Assessment. It is doubtful whether the current industry-led iPiE project will manage to fulfil its mandate to perform a prioritisation exercise of legacy pharmaceuticals. 4. The revised guidelines should consider data from APIs manufacturing production and formulation The current process doesn't consider discharges to the environment throughout the life cycles of pharmaceuticals as it does not look at the production and formulation stages. To limit potential adverse effects of pharmaceuticals on the environment, Environmental Risk Assessments should address the risks associated with API discharges from manufacturing sites, also outside the EU. 5. The revised guidelines should provide a centralised database for Environmental Risk Assessments open to the general public ERA dossiers are not currently available to the public. Creating a publicly available centralised database would make external comparison and evaluation possible to identify possible shortages.	The scope of the ERA guideline is to outline the testing strategies for environmental hazard and subsequent risk assessment. Manufacturing considerations are out of scope of this GL.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Such a database would also benefit the research community and avoid unnecessary and repetitive testing.	The generation of such a data base is supported, however, it is out of the scope of the ERA GL to create such a data base.
38	As a Physicians Society we're wondering that Nanomedicine is not mentioned in the draft. Nanomedicine is an emerging field of innovations and for example, every nano-pharmaceutical is passing through the human body, underlying metabolism and is at last entering the environment. And what happens with nanocarriers after they have delivered their drugs? There are so many unanswered questions yet, that we see the urgent need for the EMA to recognize, that nanomedicine with its broad range of products should play an important role in the revised guidelines. For example, we see the need for separate environmental risk assessments for nano-pharmaceuticals. Therefore, manufacturers have to provide specific information about nano-scale ingredients.	All general comments noted. Nano-components as active ingredient are difficult to assess with regard to nano-specific mode of actions leading to a nano-related hazard in the environment. Currently, no test systems are available specifically and exclusively evaluating the environmental risk of a nano-scaled API of human medicinal products, only OECD test guideline 23 for "difficult compounds" might be considered. Therefore, it is regarded as premature for this guideline revision to take up specific testing recommendation for nano-scaled APIs.
39	The link between "substance based law", such as an European medicine law and media-related environmental law, such as the Water Framework Directive, is missing. Therefore, from our point of view the interaction in this field could be improved. Against the background of monitoring obligations, our members are reliant on data on metabolites and transformation products of medicinal products. The findings on potentially environmentally hazardous substances and environmental risks, which are obtained in the context of product approval of medicinal products, represent a valuable record here.	All general comments noted. The legal basis for this guideline is Directive 2001/83/EC, as amended, which relates to those risks to the environment arising from the use, storage and disposal of medicinal products and not to risks arising from the synthesis or manufacture of medicinal products. This guideline is focused on environmental risks associated with the use of HMPs. Alignment with other legislative frameworks is out of scope of the guideline revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The degradation study in the water-sediment system (OECD 308: Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) in the basic dataset was abandoned in the draft. The use of OECD 308 allows conclusions about the fate of substances. By not using the study, the basic dataset will in the future neither contain information on half-lives nor on metabolites and transformation products. Based on these statements, we would like to ask you to reconsider this decision. From our point of view the guideline draft does not take into account the topics of antibiotic resistance in the environment and mixture toxicity.	Current data requirements are considered sufficient to evaluate potential risks to the environment arising from the use of medicinal products
41	The guideline draft is a major step forward, and certainly aligns the environmental risk assessment of pharmaceuticals better with other pieces of chemical regulation, such as the Regulation on plant protection products, or biocides. In particular the dedicated PBT assessment is a substantial step forward. However, not too many human pharmaceuticals are expected to be bioaccumulative to an extent that would trigger the "B" or even the "vB" criterion. Compounds that are only "P" and "T" might still warrant specific consideration during the risk assessment for the aquatic compartment, if the compounds are sufficiently mobile. In the context of assessing their risks for the aquatic environment, pharmaceuticals should therefore also be assessed whether they are	All general comments noted. Due to overlapping timelines of the current guideline revision, the regulation of the new hazard classes PMT/vPvM under CLP and the revision of the pharmaceutical legislation, the guideline does not address the assessment of PMT/vPvM.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	PMOC (persistent and mobile organic contaminants), also termed compounds with PMT (persistent, mobile and toxic) properties. See e.g. Reemtsma, T. et al. 2016. Mind the Gap: Persistent and Mobile Organic Compounds - Water Contaminants That Slip Through', Environmental Science and Technology, 50(19), 10308 This would be straightforward to implement, given that only the "M" criterion needs to be quantified in addition to the "P" and "T", which are already recorded in the context of the PBT assessment. The "M" criterion can be simply estimated using the available phys-chem data, following the approach published by Kalberlah a couple of years ago (water solubility at pH 6–8 and 12 °C equals or exceeds 150 µg/L, and the log Koc at pH 6–8 and 12 °C is at or below 4.5., see Neumann et al. 2017 Protecting the sources of our drinking water: a revised proposal for implementing criteria and an assessment procedure to identify Persistent, Mobile and Toxic (PMT) and very Persistent, very Mobile (vPvM) substances registered under REACH. UBA position statement, ISSN 2363-8273	
42	Since environmental information is vital for any kind of risk management, all ERA-document should be adequately available. A publicly available database on validated data on fate and effects of active pharmaceutical substances in the environment is very much needed.	All general comments noted. Comment supported
43	a. Because insights are advancing, an ERA should also apply to substances that are already in the market. b. It is known that during the use of medicines, multi-resistance occurs in microorganisms to which the substance is intended. These	All general comments noted. Cannot be solved by the ERA guideline, would need legal changes in the responsibility of the European Commission.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	multi-resistant microorganisms and their genes in the case of bacteria are then released into the environment. They can return to humans via the environment. In addition, resistance formation by microorganisms can also occur at low environmental concentrations of these substances (e.g. Gullberg E. et al. 2014). The risk of formation, strengthening, spread and return of antimicrobial resistance, of which the humanitarian and economic costs are already known (AMR Review, 2016), should not be missing from a risk assessment.	Comment supported; however, this is out of the scope of this GL revision.
44	Cruelty Free International warmly welcome the opportunity to comment on the test guideline. We suggest that the scope of the ERA should be further defined in the beginning of the document (e.g. the "1. Introduction (background)" section or "2. Scope and legal basis" section) to explain: • that the required assessment only addresses releases to the environment via human consumption i.e. other pathways (such as releases during manufacturing, for example) are not within the scope of the assessment. • That the risk assessment applied to all types of medicines and all types of chemistries, i.e. inorganic as well as organic, mono-constituent as well as UVCB type, active drug substances as well as pro-drugs.	All general comments noted. Editorial changes have been made to section 2 to enhance clarity. The scope is clearly outlined in section 2. The ERA is conducted for the environmentally relevant substance. In case of a pro-drug, it's the metabolite that's tested
44	It is apparent that the field of animal-free methods, including *in vitro* assays, *in silico* approaches, as well as structured read-across and Weight of Evidence arguments, for the generation of key	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	information for the purposes of chemical safety assessment is rapidly evolving. In fact, there are an increasing number of animal-free OECD test guidelines becoming available that may be relevant for generating the data required for ERAs. In the context of minimising the use of vertebrate animals in experiments, we ask that this test guideline is updated so that the use of non-animal methods is maximally exploited and that *in vivo* tests on vertebrates are replaced wherever possible. The estimation of bioconcentration, for example, may be very well suited to the application of animal-free methods such as *in silico* QSAR estimations. It seems that all bullet points throughout the document are blue instead of black (this may not have been intentional).	3Rs aspects are taken up in the guideline revision reflecting the current state of the art. This is the EMA standard layout.
45	Region Stockholm is very positive about the extension of the environmental risk assessment (ERA) including a tailored risk assessment for substances with specific classifications (e.g., endocrine active substances (EAS), antibiotic substances) and further tests e.g. the estimation of the exposure of predators to pharmaceuticals through the food chain ('secondary poisoning'), as well as directly through the environment. The Drug and Therapeutics Committee in Region Stockholm, as well as other Drug and Therapeutics committees in Sweden, take environmental aspects into consideration when selecting pharmaceuticals that are to be recommended. For that work, Region Stockholm has a database, Environment and Pharmaceuticals, at	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Janusinfo.se. The database uses information from ERAs published in European Public Assessment Reports (EPAR). It is necessary that trigger values for different parameters, e.g. persistence, bioaccumulation, toxicity and risk, are clearly stated, preferably in a table, in the guideline. This would increase transparency and would also make it easier for healthcare providers and other actors to use the information. Please also see specific comments below. It is important that the environmental information for individual pharmaceutical substances is updated at regular intervals, so the information is kept up-to-date. A change in use can alter the calculated risk, and new knowledge could affect the conclusions in a previously performed ERA. For other legislation and regulations such as BPR (Biocidal Products Regulation), data is evaluated at regular intervals, as for BDR upon renewing approval of an active substance. It is necessary that the environmental information, including underlying studies, are made publicly available for increased transparency. EMA's conclusions about how results have been interpreted also need to be clearly stated. For example, in the assessment report for Betmiga 18 October 2012 EMA/706651/2012/corr there are no remarks on how the result of OECD 308 for mirabegron has been interpreted. Another example is for lurasidone. The following information is in the assessment report for Latuda (23 January 2014, EMA/113836/2014): "In conclusion, lurasidone is not a PBT substance and is not expected to pose a risk	Revisions to the EPAR table are out of scope for the GL revision. These aspects are address in the revised GL text.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	to the environment." To increase transparency, the underlying data for the interpretation that the substance does not "pose a risk to the environment" should also be published. It is important that environmental data for individual pharmaceutical substances are published on the EMA's website, to be searchable and easily accessible with the latest available information. At present, documentation in EPARs for all products containing the same active substance must be reviewed to be able to get the latest information. Sometimes, the Swedish Medical Products Agency must also be contacted to ask if information that has been requested by the CHMP in assessment reports has been received, or whether they can provide underlying data for reported values. Three examples: 1. requested data from CMHP for bupropion (assessment report Mysimba, 18 December 2014, EMA/805547/2015: "The Applicant is requested to perform all the planned studies for the environmental risk assessment for bupropion [e.g. OECD 106, 210 and 211] and naltrexone [OECD 106, 201, 209, 210, 211 and 301] as well as OECD 308 for both compounds, should the results from the respective OECD 301 studies deem this necessary."). 2. underlying toxicity data was not found for the reported PNEC for posaconazole (assessment report for Noxafil 20 February 2014 EMA/159150/2014). 3. requested data from CMHP for nilotinib (several tests are requested as follow-up measures (FUM) in the assessment report för Tasigna (nilotinib) 20 December 2010, EMA/CHMP/678167/2010).	ERA study data submitted by applicants currently cannot be publicly shared due to the confidentiality of these submissions to EMA. However, the outcome of the ERA with regard to specific endpoints in a marketing authorisation is summarised and publicly available in the EPAR. Building a database is also anticipated from the PREMIER project but is not within the scope of the current guideline revision.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The answer from the Swedish Medical Products Agency was that no new data were received from the pharmaceutical companies for bupropion or nilotinib. For posaconazole, toxicity data was received. It would be desirable that pharmaceutical companies submit at joint ERA for a pharmaceutical substance instead of submitting one per company. This is possible for other regulations, e.g. Reach: "All companies registering the same substance need to agree on the data for their joint REACH registration. This is a collective responsibility which applies equally to all co-registrants." This would have a positive impact on reducing the number of tests performed.	Comment supported. However, action in this respect should be taken by industry, it is not in the scope of the guideline revision. Legally binding changes are the responsibility of the EC.
46	The revision of the guideline on the environmental risk assessment of human medicines is well drafted and very much appreciated. Particularly the inclusion of a section on secondary poisoning which is an important path endangering humans as well as ecosystems is very welcomed. Becoming more and more complete the ERA for human medicinal products (HMP) is still a targeted procedure focussing on HMPs which exceed an exposure limit (called action limit). However, there is still an important gap which should be filled. Several active ingredients of human medicines as well as carrier and drug delivery systems in human drugs are nanomedicines which require a differing approach. Nanomaterials - as defined by the EU Commission (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011H0696&from=EN) - exhibit their characteristics not only because of their chemical constituents. Their effects and behaviour in organisms and in environment depend also upon several physicochemical parameters like particle size distribution, shape, zeta potential, surface characteristics like	All general comments noted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	coating etc. A comprehensive characterisation of the nanomaterials is therefore required. This is why nanomaterials are considered in a different fashion in several other parts of EU legislation like Biocidal Products and REACH where for the latter one recently the Commission Regulation 2018/1881 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R1881&from=EN) explains how the annexes of REACH should be applied regarding nanomaterials. With respect to food legislation EFSA developed a guidance document how risk assessment should be conducted with nanomaterials (https://www.efsa.europa.eu/en/efsajournal/pub/5327). OECD is busy to provide adaptions of test guidelines and develop new test guidelines and guidance documents (OECD (2014) Ecotoxicology and environmental fate of manufactured nanomaterials, Test Guidelines in: Series on the Safety of Manufactured Nanomaterials, OECD; Paris, see also: http://www.oecd.org/chemicalsafety/testing/TGP%20work%20plan_September%202018.pdf) giving information how to carry out valid tests with nanomaterials. Several recently adopted test guidelines already address nanomaterials. The necessity of a different approach for assessment of environmental risks of nanomaterials is also depicted in scientific literature (e.g. Berkner et al (2016): Nanopharmaceuticals: Tiny challenges for the environmental risk assessment of pharmaceuticals, Environ. Tox. Chem. 35,780-787 and Steinhäuser K.G. and Sayre P.G. (2017), Reliability of methods and data for regulatory assessment of nanomaterial risks, NanoImpact 7, 66-74). Therefore it is strongly recommended to add a special section on nanomedicines in Chapter 4, in particular in 4.2.	Nanomaterials incl. e.g. particle sizes and distribution have to be completely characterised in the quality module 3 of a marketing authorisation application. Pivotal preclinical testing as well as ADME studies have to be performed with the formulation used for the patients including the nano-distribution. Food ingredient evaluation as well as evaluation of chemicals according to REACH cannot be compared in this respect.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	For example, biodegradation tests are in most cases irrelevant for nanomaterials whereas other fate tests gain importance.	
47	The new version of the guideline is a good compilation of the ERA part needed for a MA dossier and expected to be more useful for the applicants than the former outdated one. Especially the decision trees serve to clarify the different steps of the assessments. However, some of the steps and criteria described in the text are missing in the decision trees. Some clarifications and amendments to the decision trees and the text would further serve to clarify the procedures. Some suggestions for such improvements are listed as specific comments below.	All general comments noted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
58	1	Please include "for patient use" when referring to human medicinal products. As per EFPIA: "As our scientific understanding improves, we will find new ways of detecting the trace amounts of pharmaceuticals in the environment and understand their impact. We, the industry, are striving to improve our processes and develop new ways of creating treatments that not only save lives, but that are also mindful of the environment. We remain committed to continuing to address environmental concerns through the Eco-Pharmaco-Stewardship initiative whilst responding to	Change implemented - wording as per previous version of the guideline, title of this version and relevant legislation (Directive 2001/83/EC). Revised line 58 as follows: "The purpose of this guideline is to describe the assessment of the potential environmental risks and hazards of human medicinal products **for human use** (HMP)."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patient needs and ensuring access to medicines, the paramount objective of our industry." Proposed change (if any): The purpose of this guideline is to describe the assessment of the potential environmental risks and hazards of human medicinal products (HMP) for patient use.	
Throughout e.g. lines 61, 626, 697, 1210	22	The expression 'cannot be excluded' is unfortunate to use particularly in a guidance document. Nothing can be excluded, and is as such not possible to adequately handle. Please change throughout the document to e.g. 'is a reasonable possibility', etc.	No change to the guideline Rationale: In the context of the guideline, a risk is excluded when the outcome of the Environmental risk and PBT assessment is 'No risk', as outlined in Figure 1. For all other outcomes, the risk "cannot be excluded".
63-64	1	The text currently reads that it is mandatory for the dossier for the marketing authorisation of HMP to include an environmental risk assessment (ERA). Given the reduced development time for some precision medicines, and the obligation to meet unmet patient needs, an option for mandated post-authorisation commitments to complete an ERA should be afforded to a marketing authorisation applicant. Proposed change (if any): We request clarification that only C.1.6.a Type II variations or a line extension require an ERA or justification if an increase in environmental exposure is expected Given the unresolved issues with data transparency and data accessibility for generic marketing applications, and	**Regarding the option for post-authorisation submission of ERA**: No change to the guideline Rationale: The requirement for an evaluation of the potential environmental risks posed by the medicinal product to accompany the application for marketing authorisation for a HMP is outlined in the legislation (Article 8(3) of Directive 2001/83/EC, as amended). It is beyond the scope of this guideline revision to amend the legislation. *Article 83. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I: (ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that environmental concerns should not result in the refusal for a marketing authorisation there should be opportunities for an ERA to be accepted as a post-authorisation commitment, in particular for well-known APIs (e.g. generic, well-established use applications). This is also in agreement with EMA pre-authorisation procedural advice for users of the centralised procedure (EMA/821278/2015) which states that 'In the exceptional case that ERA study results are provided stand-alone, they should be submitted as a type IB C.1.z' (Q&A No. 3.4.2). Proposed change (if any): Following the sentence in lines 63-64 'It is mandatory for the dossier for the marketing authorisation of HMP to include an environmental risk assessment (ERA).' please include a sentence that allow ERA study results to be submitted in a post-registration phase based on the commitment agreed during the registration procedure.'	**Regarding the requested clarification regarding type II variations**: Agree - clarification required The guideline clearly outlines under Section 2 Scope and Legal basis, the ERA dossier should be updated for type II variations and extension applications if there is an anticipated increase in the environmental exposure e.g. a new indication which results in an increase in the extent of the use.
63-64	2	As eventual environmental impact should not constitute a criterion for refusal of a marketing authorisation (lines 77-78), the ERA submission should be accepted also as a post-registration commitment, in particular for well-known active substances (e.g. generic, well-established use applications). This is also in agreement with EMA pre-authorisation procedural advice for users of the centralised procedure (EMA/821278/2015) which states that *'In the exceptional case that ERA study results are provided stand-alone, they should be submitted as a type IB C.1.z'* (Q&A No. 3.4.2).	No change to the guideline. Rationale: The requirement for an evaluation of the potential environmental risks posed by the medicinal product to accompany the application for marketing authorisation for a HMP is outlined in the legislation (Article 8(3) of Directive 2001/83/EC, as amended). It is beyond the scope of this guideline revision to amend the legislation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Following the sentence in lines 63-64 *'It is mandatory for the dossier for the marketing authorisation of HMP to include an environmental risk assessment (ERA).'* please add sentence *'For well-known substances (e.g. generic and well-established use medicinal products) ERA study results can be submitted in a post-registration phase based on the commitment agreed during the registration procedure.'*	
63-72 (+ document as a whole)	26	According to the introduction, the guideline gives instructions on how to assess risks not only to aquatic environments, but also to terrestrial environments and groundwater. However, the methods described rely only on the PEC_{sw} exceeding the action limit (10 ng/l). Proposed change (if any): Whether or not the PEC_{sw} exceeds the semi-arbitrary action limit tells very little about potential risks e.g. to the soil environment. Therefore determining if a soil risk assessment is required should not depend on the outcome of PEC_{sw} comparison, but the soil compartment should be taken into consideration already at Phase I.	No change to the guideline. Rationale: The PECsw, as it is calculated in Phase I, reflects the total emission into the environment. This is a pragmatic first criterion, as no experimental studies are necessary yet, for entering a Phase II assessment. In Phase II, distribution to other environmental compartments is taken into consideration, based on experimental physico-chemical data.
63	48	Please consider including in the introduction the circumstances under which the ERA of pharmaceutical metabolites will be performed/triggered	No change to the guideline. Rationale: Section 3.1.2 outlines the Total Residue Approach upon which the ERA is based. Metabolism of the active substance may be taken into account in Phase II, this is outlined in section 4.2.3.2.

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64	22	The use of the product is in most cases not established at the time of MAA and assessment of the ERA, therefore the word predicted could be added. Proposed change (if any): This ERA is based on the predicted use of the product…	No change to the guideline. Rationale: The use of a product will be based on the indication applied for, which is established at the time of MAA.
64-65	26	The ERA considers emissions to occur only during the use-stage of the substance. To ensure sufficient level of environmental protection, it should also take the production phase into consideration, even if it pose some difficulties to do it.	Not agreed - but explanatory wording included Rationale: Risks arising from the synthesis or manufacture of HMP are under the remits of the national competent authorities and outside the scope of this guideline revision. The following text from the first version of the guideline has been added to section 2 Scope and legal basis: "*Directive 2001/83/EC, as amended, relates to those risks to the environment arising from the use, storage and disposal of medicinal products and not to risks arising from the synthesis or manufacture of medicinal products. This guideline is focused on environmental risks associated with the use of medicinal products*".
65-68	25, 36, 42	According to the introduction, the guideline gives instructions on how to assess risks not only to aquatic environments, but also to terrestrial environments and groundwater. However, the methods given in later text are rough and still rely on the PEC_{sw} exceeding the action limit (10 ng/l). Proposed change (if any): Whether or not the PEC_{sw} exceeds the semi-arbitrary action limit tells very little about potential risks e.g. to the soil	No change to the guideline. Rationale: The PECsw, as it is calculated in Phase I, reflects the total emission into the environment. This is a pragmatic first criterion, as no experimental studies are necessary yet, for entering a Phase II assessment. In Phase II, distribution to other environmental compartments is taken into consideration, based on experimental physico-chemical data. The current action limit is triggered if the DOSEas is higher than 2 mg. Based on the exposure scenario via sewage treatment plant the DOSEas (for $Elocal_{WATER}$) is an input value for the PECsoil

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		environment. Therefore, determining if a soil risk assessment is required should not depend on the outcome of PEC_{sw} comparison, but the soil compartment should be taken into consideration already at Phase I.	calculation. There is a linear correlation between $PEC_{surfacewater}$ and PEC values for all the other environmental compartments. Therefore, in Phase I there is an indirect action limit for all other compartments like soil or groundwater.
65-68	47	The sentence could be read: …. the aim of protecting aquatic and terrestrial ecosystems including... and secondary poisoning (i.e. the aim would be **to protect secondary poisoning)** Proposed change (if any): The suggestion is to add the words "targets of" before "secondary poisoning". The sentence would thus read: This guideline describes how to perform this ERA and how to evaluate potential risks to the environment arising from the use of the medicinal product, with the aim of protecting aquatic and terrestrial ecosystems including surface water, groundwater, soil and targets of secondary poisoning - and the microbial community in sewage treatment plants.	Text edited Revised text as follows: "product, with the aim of protecting aquatic and terrestrial ecosystems including surface water, groundwater, soil ~~and~~ **species at risk of** secondary poisoning, [– *delete*] and the microbial community in sewage treatment plants."
69	44	For clarity, suggest rewording this sentence as follows: "Furthermore, the **evaluation of the PBT (Persistent, Bioaccumulation, Toxic) and vPvB (very Persistent, very Bioaccumulative)** hazards of the active substance of a medicinal product is described." Reason for suggested change: to differentiate between the hazard identification process that would typically precede the risk assessment and the PBT (Persistent, Bioaccumulation, Toxic) hazard evaluation which may be separately performed separately to the risk assessment.	Not agreed Rationale: Risk assessment does not precede hazard identification. These are done in parallel.

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79-80	1	The guideline states that "An ERA is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure." Consequently, this draft guideline captures an ERA for all authorisation procedures. However, it should be noted that the availability of Public Assessment Reports (PARs) issued by NCAs – either in the context of EU procedures (DCP & MRP) or after completion of pure national procedures – seems to occur in a less transparent manner compared to the availability of a European Public Assessment Report (EPAR) issued by EMA in the context of CPs. This could hinder the draft guidelines ambitions to reduce data duplication. The EC and EMA should work in partnership with industry to develop a centralised ERA database to facilitate data transparency and accessibility	No change proposed by stakeholder. This issue cannot be solved in the guideline revision. The EC is working on this within the PiE strategy and Pharmaceutical strategy.
79-80	10	It should be made clear that for drugs with high unmet medical need (e. g. PRIME, conditional approval) there might be exemptions from the requirement to submit an ERA at initial MA application; instead it should be possible to commit that the ERA is submitted later in accordance with an agreed time schedule mutually agreed with the CAs.	No change to the guideline. Rationale: The requirement for an evaluation of the potential environmental risks posed by the medicinal product to accompany the application for marketing authorisation for a HMP is outlined in the legislation (Article 8(3) of Directive 2001/83/EC, as amended). It is beyond the scope of this guideline revision to amend the legislation.
79-82	47	a word like "submitted" seems to be missing in the sentence. The centralised, mutual recognititon and decentralised procedures are well defined and known whereas the national procedures can be different in the member states. The below wording would be preferred:	Text edited in line with comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): An ERA is required for all new marketing authorisation applications for a medicinal product submitted through the centralised, mutual recognition, decentralised or a (or any) national procedure.	
81-82	1	It would be helpful if the Agency could clarify what constitutes a significant increase that would justify an update of the ERA dossier in case of an "increase in the environmental exposure". We would suggest alignment with the EMA Q&A on the 'Guideline on the environmental risk assessment of medicinal products for human use' which mentions in its response to question 2 that 'There is no unique value of what constitutes a significant increase. This will be assessed on a case-by-case basis'.	No change to the guideline Rationale: The first version of the guideline stated, "*For type II variations, the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use*." The revised guideline states "*For type II variations, the ERA dossier should be updated if there is an anticipated increase in the environmental exposure, e.g. a new indication which results in an increase in the extent of the use.*" The word 'significant' has not been included in the revised guideline. If there is an anticipated increase in the environmental exposure, submission of an updated ERA dossier is always required, irrespective of the outcome of the updated ERA assessment.
81	22	It is not clear how to proceed with a type II variation. Should an ERA always be submitted? Or only if the "ERA dossier" is updated when a new indication is applied for? Or submit a justification on why the ERA update is not required?	Agree clarification required. Text added to section 2.
81	44	It is not clear what the different variations are (e.g. "type II variations", "Type 1A/1B variations" *etc.*); please could additional text be added to define all terms, and/or provide a reference to where further information can be found.	No change to the guideline. Rationale: Variations are defined in EU legislation, see Commission Regulation (EC) No 1234/2008 ('the Variations Regulation').

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		An update to this (and the next paragraph, starting on line 88) to give a clearer description of the various types of risk assessment (such as a type II variation, an extension application, renewals of marketing authorisations, type IA/IB variations, or any other type of variation) along with a brief description of the requirements triggered for each, would be very helpful. In particular, a clear indication of where previously submitted data can be used again is desirable.	For further information see the Official Journal of the EU 2013/C 223/01, Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.
81-82	45	Other changes than just regulatory ones which may affect the use, e.g. changes in pharmaceutical recommendations may entail changes in use and thus in environmental risk. It is important that such changes are considered as well. New scientific findings can also be published that could affect the conclusions in a previously performed ERA.	No change to the guideline. Rationale: Environmental risk assessment is based on predicted environmental concentration (PEC) and the available scientific knowledge at the time of application. The PEC is calculated using the maximum daily dose of the active substance and Fpen. For either of these factors to change, a line extension or a type II variation application must be submitted, for which an updated ERA is required.
88-89	1, 2, 6	Please add Repeat Use Procedures (RUP) as one of possible exemptions for ERA. Proposed change (if any): 'An ERA is not required for renewals of marketing authorisations, repeat use procedures or Type IA/IB variations.'	No change to the guideline. Rationale: Repeat use procedures are a type of mutual recognition procedure for which an ERA is required, as clearly stated in Section 2 Scope and legal basis.
88	18	An ERA is not required for renewals of marketing authorisations or Type IA/IB variations.	Correct- No change proposed by stakeholder
88	29	In cases an ERA is provided as post-authorisation measure, the application is a Type IB variation. Therefore, the sentence is not fully true.	Text edited for clarity

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		Proposal: An ERA is not required for renewals of marketing authorisations or Type IA/IB variations (unless ERA studies are provided with this variation).	
88-89	45	It is important that ERAs for individual active substances are updated at regular intervals, i.e. is kept up-to-date, including if the use has changed significantly (for the risk calculation).	No change to the guideline. Rationale: Environmental risk assessment is based on predicted environmental concentration (PEC) and the available scientific knowledge at the time of application. The PEC is calculated using the maximum daily dose of the active substance and Fpen. For either of these factors to change, a line extension or a type II variation application must be submitted, for which an updated ERA is required.
89	22	If the Q&A document referred to is updated the reference to a specific section might not be valid.	No change proposed by stakeholder Reference is correct at time of publication.
90-91	1	The guideline states that "According to Directive 2001/83/EC, applicants are required to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA. However, cross reference to the ERA dossier of the originator is permitted with consent from the originator." It should be noted that there is no obligation for originators to provide access to data and the guideline provides no indication on how this can be managed. The guideline does not make it clear what exactly is expected and how it should be organized. From section 3.2.3. it seems that although reference is made to the PAR/EPAR, the full study reports should be submitted as well. As the underlying data in the PAR/ EPAR have already been subject to regulatory	No change to the guideline. Rationale: Proposal is outside of scope of GL revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		review is the need for the full study reports justified with a letter of access in place? Proposed change (if any): In order to facilitate proper data sharing in scope of the ERA, additional clarification should be given either in the guideline or through supporting text on the mechanisms and models (cost sharing and otherwise) to do this. Further dialogue is required between industry and regulatory authorities on this issue.	
90-92 and 230-234	10	For generic medicinal products, a reference to the originator's ERA after expiration of the data protection period should be possible without the prior consent of the originator (comparable to clinical / preclinical data); i.e. in this case there should be no need to actual submit the ERA (including study reports) of the other MA holder together with a letter of access. Instead, a justification that there is no increased environmental exposure should be sufficient. In a next step, it should be considered to include the use of data on environmental risk assessment to the generic concept.	Article 10 of Directive 2001/83/EC makes reference to the derogation of the requirement for non-clinical and clinical data laid down in 8(3) (i), but not 8(3) (ca) which lays down the requirement for ERA. Therefore, currently reference to the ERA of the originator product for applications according to Article 10 is not possible.
91-92	4	The possibility to cross-reference to the ERA dossier of an originator represents in general a good option to prevent repetition of animal studies. However, the required consent of the originator limits this option. By not providing access to the ERA dossier the originator/MA holder can further impede the possibility of generic competition. This could be circumvented by creating an obligation to publish the results of the ERA studies after the marketing authorization was granted. A benefit for the public is	No change to the guideline. Rationale: Creating an obligation to publish the results of ERA studies after marketing authorization is granted is beyond the scope of this guideline revision.

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		generated and it is in the interest of animal welfare since it prevents the repetition of animal tests.	
91-92	16	In Reviewing the EPARs of centrally approved new originator products in the EU, we noticed that many granted marketing authorisations (MAs) from the originator do not have ERAs or they have incomplete ERAs, therefore there is nothing to cross. reference. These MAs also have no justification as specified in 4.1 and 5.1. Proposed change (if any): If there is no ERA available from the originator (Reference ERA) and no justification is given for non-submission of ERA, the generic medicinal product is exempted from submission of the ERA, until the originator provides the missing studies and/or updates the ERA and is required to share this data. The data for the ERA should be accessible to the public to reference in a full and completed report. The public ERA reports must also follow the ERA guideline, fully meet CHMP standards and requirements for approvals.	No change to the guideline. Rationale: The requirements for generics are outlined in the Phase I decision tree.
91	44	Please could additional information be added to this paragraph to address what the applicant is required to do in case cross-reference to the ERA dossier of the originator is not granted consent by the originator, or in case of any other data-sharing and Letter of Access dispute. Additionally, please provide details of any processes by which data-sharing or dossier access may be facilitated by a third party or authority.	Agreed. Clarification included under Question 2b.
92	1	The guideline states that cross reference to the ERA dossier is permitted with consent from the originator. We urgently	No change to the guideline.

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		recommend that the EC and EMA develop a transparent process that leverages available data without burdening either company. Proposed change (if any): An agreed mechanism for data transparency and accessibility is established before this guideline comes into force that places minimum burden on industries losing exclusivity of a product and generic/ biosimilar companies entering the market. Industry is prepared to partner with the regulatory agencies to help develop and implement the most effective mechanisms to realise this ambition.	Rationale: Development of a mechanism for data transparency and accessibility is beyond the scope of the guideline revision.
97	44	The meaning of this paragraph is ambiguous. For clarity, suggest rewording as follows. Either: "For marketing authorisation applications for radio-pharmaceutical precursors**, [i.e. with comma]** for radio-labelling**, [i.e. with a second comma]** and **for** radio-pharmaceuticals, additional requirements on emission standards for radiation set by …" Or "For marketing authorisation applications for ~~radio-pharmaceutical~~ [delete] precursors for **radio-labelled pharmaceuticals** and **for** radio-pharmaceuticals, additional requirements on emission standards for radiation set by …"	Text edited for clarity

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100-101	1	The guideline states that "Excipients do not generally require an ERA unless there is a specific toxicological effect to suggest an environmental risk under the product's conditions of use." The text is vague and should be more explicit as excipients with toxic effects are avoided based on patient safety grounds (e.g., proscription or prohibition of benzyl alcohol use in formulations intended for neonates). Proposed change (if any): If further clarification is not provided excipients should fall outside the remit of this guideline. The phrase "under the products conditions of use" needs to be defined more clearly.	Text revised for clarity, excipients are out of scope of the GL. See also response below
100-101	22	How should absence/presence of such specific toxicological effect be shown? There is a risk of different interpretations and different level of data requirements from different assessors. Proposed change (if any): Delete the entire paragraph.	Text revised for clarity, excipients are out of scope of the GL.
100	46	In contrast to plant protection and biocidal products excipients are generally exempted from ERA. In most cases there will be no need to perform an ERA for excipients because it is assumed that they won't pose an environmental risk. However, this may not always be the case. Proposal: Exclude readily biodegradable excipients but screen others.	Text revised for clarity, excipients are out of scope of the GL. ERA is required on a product specific basis, therefore an evaluation of the potential environmental risk associated with an excipient could be requested if there is a specific toxicological effect to suggest an environmental concern following the products recommended use in patients.
104	30	It is stated that for each medicinal product a risk assessment is required. This is actually not true. Risk	No change proposed.

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		assessment involves the combined evaluation of ecotoxicity and exposure which is done only in Phase II and this assessment is not needed for each medicinal product. Phase I cannot be called "risk assessment", it is only evaluation of the environmental exposure.	While it is true that for some medicinal products the risk assessment and PBT assessment may stop in Phase I/ screening phase respectively, Section 3.1 is intended to provide a general overview of the ERA, clarifying that it includes both risk and PBT assessments. Figure 1 is considered sufficiently clear regarding the need for Ecotoxicity data.
104	44	Please add vPvB (very Persistent, very Bioaccumulative) in the description of the evaluation required (noting that this is mentioned later in the guideline).	Agreed. Text edited.
105-110	47	the following amendments are suggested Proposed change (if any): The risk assessment reflects the possibility of an effect occurring and is an evaluation of both exposure of organisms in the environment to the active substance and its ecotoxicity. For some substances with specific classifications (*e.g.* endocrine active substances (EAS), antibiotic substances), a tailored risk assessment is necessary. The PBT assessment concerns the intrinsic properties of active substances, which are potentially harmful to the environment regardless of the levels of exposure…	Agreed, text edited for clarity
107-109	25, 26	Endocrine active substances and antibiotic substances have been rightly given as substances requiring a tailored ERA. However, it is not sufficiently clear which other types of substances fall into the "substances with specific classifications".	Agreed, text edited for clarity

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		Proposed change (if any): - Please specify more clearly which substances are considered to fall into "specific classifications". - If the previous specification is not possible, please indicate who is responsible for identifying substances that fall into the "specific classifications", that would subsequently require a tailored ERA (i.e. is it the producer's responsibility, or someone else's?).	
107	27	the word "classification" has a specific meaning and is not proper here. Proposed change: classification can be changed into "properties"?	Text edited for clarity.
107-109	30	We appreciate that at least for endocrine active substances and antibiotic substances a requirement of a tailored ERA is provided. However, it is not sufficiently clear which other types of substances fall into the "substances with specific classifications". Proposed change (if any): Please specify more clearly which other substances are considered to fall into class "substances with specific classifications".	Text edited for clarity. See also additional text and table in section 3.2.1.
108	46	It is worrying which substances are subjected to a tailored risk assessment. Apparently, it is needed for endocrine active substances. Furthermore, in some parts of the text antibiotics are designated (line 108, line 341 and section 4.3.1). However, according to line 128 and 341	Text edited and table added to section 3.2.1 for better guidance. It is now stated: "*This guideline provides guidance on specific assessment strategies only for EAS antibacterials and antiparasitics (See Table*

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		antiparasitics (in line 341 called parasiticides) should be subject to the tailored risk assessment. They are missing in chapter 4.3. This is inconsistent! Both groups – antibiotics and antiparasitics - have characteristics and a particular property that are relevant for environment justifying a tailored assessment. Moreover, a tailored risk assessment should be considered for cytostatic drugs and antifungals. Cytostatic drugs are in many cases mutagenic and may influence the genetic diversity of ecosystems. Antifungals may have specific effects on environmental species (cf. high concentration of clotrimazole according to Richmond E.K. et al (2018) A diverse suite of pharmaceuticals contaminates stream and riparian food webs, Nature Communications, DOI: 10.1038/s41467-018-06822-w).	*1 above). However, if the applicant considers there might be other substances for which a specific assessment strategy is relevant due to their specific toxicity profile or mode of action (MoA), they are encouraged to seek scientific advice from the relevant Competent Authority."* A specific assessment strategy could mean that the action limit does not apply (e.g. antiparasitics; Figure 2, Q4). It could also mean that the action limit applies but that a tailored testing strategy is needed upon entering Phase II (e.g. antibiotics; Figure 2, Q7). The currently available information on antineoplastic substances does not show that they have effects below the action limit (see Schwarz et al., 2021 (Environ Sci Eur 33:68)). Thus, for these substances the action limit applies.
109	44	For clarity, suggested rewording: "The PBT assessment concerns the intrinsic properties of **any substance which could render it** harmful to the environment regardless of the levels of exposure**, meaning a hazard evaluation rather than a risk assessment is required."** Reason for suggested amendment: the chemistry (and function) of PBT substances is diverse. i.e. there is no 'specific group' of active substances as such; of, if by "specific group" the sentence means those substances	Text edited for clarity.

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		deemed to have PBT concern then this sentence is tautological.	
111	29	The substances <u>are</u> degraded in the environment and do not degrade for itself. We propose to rewrite this sentence. Proposed changes: The sentence 'Active substances, that do not degrade well in the environment...' should be replaced by "Active substances poorly degraded in the environment…" or ‚Active substances poorly degradable in the environment…'	Agreed, text edited. "Active substances ~~that do not~~ **poorly** degrade**d** ~~well~~ in the environment".
114	44	Please further define the scenario whereby "not submitting ERA studies" may be possible. For example, the amended text may read: "The ERA may consist of a justification for not submitting **some or all of the specified** ERA studies **(meaning either the full study reports or cross-reference to previously submitted studies) and/or not submitting a risk or PBT/vPvB hazard evaluation**". Reason for suggested amendment: any opportunity to submit a new or updated ERA without the need to generate new *in vivo* toxicity data should be made very clear throughout the guideline. Here, it may be that no new study data /access to study data is required but that a new/updated risk assessment is required, or it could be that no new data is required because no new /updated risk assessment is required.	Partially agreed, text edited. "The ERA may consist of a justification for not submitting **some or all** ERA studies. However, this only applies to certain cases which are specified in section 4.1 and 5.1." PBT screening is required for all active substances, so this aspect of the proposed text was not included.

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115	22	The reference to 5.1 does not seem to be necessary since it refers to 4.1. Proposed change (if any): Delete 5.1.	No change to the guideline. Rationale: Section 4.1 describes the Phase I risk assessment and section 5.1 describes the PBT screening. As outlined in Figure 1, for each medicinal product both are required.
116-117 and 1001	2	Further explanation is required regarding the use of 3R principles (replacement, reduction and refinement). This draft guideline stats that the principles of 3R should be implemented whenever possible, but does not explain where this could be possible or give examples on what studies should be omitted. In the "*Reflection paper providing an overview of the current regulatory testing requirements for medicinal product for human use and opportunities for implementation of the 3Rs*" (1) which was adopted in October 2018, an example is made on what studies could benefit from the 3R principle: Fish Early Life Stage Toxicity test (OECD 210) and Fish bioaccumulation (OECD 305). No comment is made in this new draft guideline on how these two studies will implement the 3R principles, therefore further explanation is requested on how to avoid animal testing in these studies. A further explanation is required regarding the use of 3R principles in the scope of PBT assessment. The proposed guideline states that when log Kow is ≥ 3.0 a bioconcentration factor (BCF) should be determined experimentally according to OECD 305 to evaluate secondary poisoning of API. The guideline also states that when the log Kow is above 4.5 the definitive PBT	Text edited. A decision tree has been included to clarify the PBT assessment.

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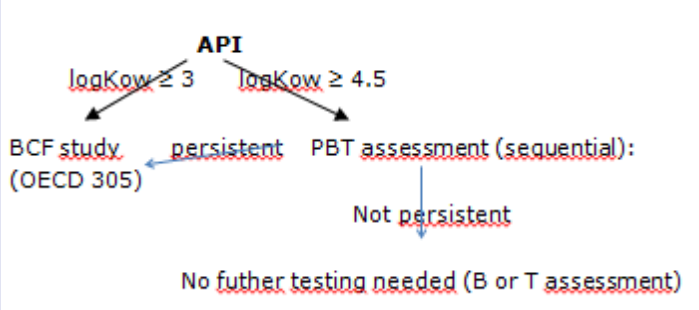
		assessment should be made, consisting of sequentially testing and evaluating first persistence, then bioaccumulation, than toxicity in order to avoid unnecessary animal testing. The current PBT principle is understood that when a substance has a log Kow above 4.5 and it is shown that it is NOT persistent in the environment the PBT assessment STOPs without further testing (no determination of B and T criteria is needed):  On the other hand the guideline clearly states when log Kow is above 3.0 testing for BCF (according to OECD 305) is triggered. This means that when a substance has a log Kow above 4.5, it should be assessed using PBT criterion and secondary poisoning criterion. This means that screening for P and B criterion are automatically requested for all substances which have a log Kow above 4.5. The stated criteria are therefore in conflict with each other. Proposed change (if any):	No change to the guideline. Rationale: PBT is not the only trigger for a BCF study, as a BCF study could still be needed for the secondary poisoning assessment.

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		Summarising the currently proposed approach, by demonstrating no persistency of the API, no further requirement for performing the BCF study exists irrespective of logKow ≥ 3. A clear statement is requested what "*definitive PBT assessment"* means, how the 3R principles (in the scope of PBT assessment) can be implemented and under what criteria BCF or environmental effect studies can be avoided.	
116	44	Suggest amending the wording as follows: "In the interest of animal **protection,** the principles of 3Rs (Replacement, Reduction and Refinement) in accordance with Directive 2010/63/EU **must** be implemented whenever possible." Noting that Directive 2010/63/EU is entitled "on the protection of animals used for scientific purposes".	No change to the guideline. Rationale; "should" considered sufficiently clear.
118 (Figure 1)	1	The figure and supporting text could be clearer with regard to the hazard assessment. Can the guideline clarify that if a compound meets the criteria for a PBT assessment and is determined to be either a PBT or vPvB compound, with no mode of action concerns and falls below the PEC action limit, then no further assessment via risk characterization is required. Proposed change (if any): Clarify the document text and Figure to indicate that a full ERA is not needed in such circumstances. We recommend that the decision trees in all of the Figures be made more intelligible by explicitly listing the criteria and triggers in	***Text related to PBT/vPvB assessment edited.*** *The PBT/vPvB assessment is performed separately from the risk assessment. That is why there are two separate routes in the figure. The figure has been revised for clarity.*

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		each box so as to lead the reader through the decision logic, testing requirements, and outcomes.	
118-121 (Fig 1)	17	The figure is somewhat confusing, as the determination of the logPow is specifically mentioned in Phase II now, which is triggered by the PEC_{SW}, while its results are needed in Phase I (for PBT assessment). Proposed change (if any): Include logPow testing in Phase I	*The PBT/vPvB screening is a separate route than the Phase I risk assessment. Log KOW results are not used in Phase I risk assessment. In the risk assessment they are used in phase II, as part of the physico-chemical properties. However, the log KOW is then already available because it is generated for the PBT/vPvB screening* *Text has been revised.* *Table 1 has been renamed.*
118	20	Time consuming to find the precise criteria for transition to Phase II PBT assessment. Proposed change (if any): Include the criteria in the figure.	To keep the figure easy to read, no criteria are added.
118 (Figure 1)	27	The text in the boxes with 'No risk' should be changed to 'Acceptable risk' or similar. Proposed change: Change 'No risk' boxes into Acceptable risk	Text added: NO RISK is defined as PEC/PNEC < 1.
118-121	47	Comment: Figure 1 and Figure 2 could be improved to encompass all the questions and rules given for the need of an ERA. Simultaneously it could be simplified, making the text easier to follow.	Figure 1 and 2 have been revised for clarity. Colours were added to more explicitly show the difference between risk assessment and PBT/vPvB assessment.

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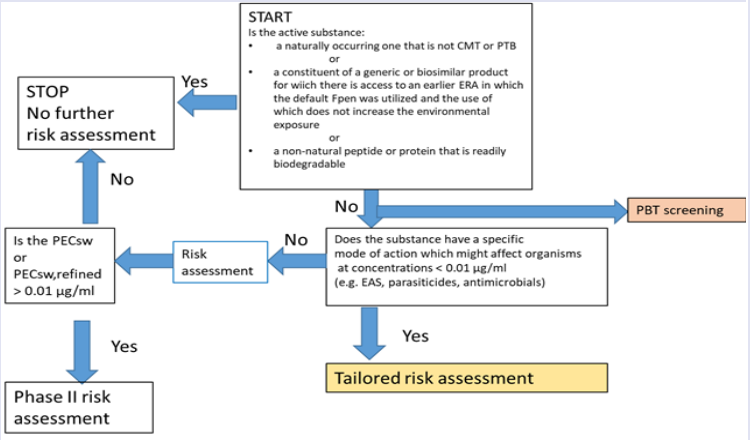
		Proposed change (if any): Figure 1 and Figure 2 could be improved to encompass all the questions and rules given in the text for the need of an ERA. Figure 1 and Figure 2 could be made more informative (especially for new readers) by amending Phase I of the decision trees with a more comprehensive one, like that suggested in the picture below. The different assessment processes would also become clearer to the reader if the boxes for PBT screening and tailored risk analysis would be given other colours than the steps of the standard risk assessment. Alternatively different fonts could be used if colours are not possible to use in a guideline. This would make it easier for the non-expert reader to distinguish the special cases from the "normal" risk assessment.  	

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118	48	Figure 1 – Could you please indicate whether the PBT evaluation in Phase II is performed without an exposure assessment?	Yes, the PBT/vPvB evaluation is performed without an exposure assessment. Text is included at the end of paragraph 3.2.2: Please note that the outcome of the PBT assessment does not influence the risk assessment. The PBT assessment is performed without an exposure assessment. Thus, the risk assessment phase I always needs to be performed, also when the compound is not PBT/vPvB. If a compound is PBT/vPvB but does not meet the trigger value for Phase II risk assessment, no Phase II assessment is necessary.
126-127	1	When this PEC is ≥ the action limit of 0.01 µg/L (10 ng/l), a Phase II assessment (section 4.2) should be performed. The current guideline (EMA, 2006) states in footnote 3 that "The present action limit is based mainly on acute toxicity data and may therefore be revised in future versions of the guideline when a sufficient amount of chronic data is available". The current PEC Action limit for surface waters of 0.01 µg/L was based on data for 800 drugs (out of the 2700 drugs marketed in Germany at the time) and included a mixture of chronic and acute data and mode of action classes including EAS that were captured within a tailored ERA. The PECsw Action Limit should not be based on the data of one country. Moreover, the PECsw trigger value should be re-evaluated including by mechanism of action and data from the chronic data available to date as antibiotics and EASs have a requirement for a tailored ERA these classes should be excluded from the analysis. Furthermore, the basis for the	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.

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		calculation should be published and transparent to all stakeholders. Proposed change (if any): Can the EMA please provide the scientific basis for maintaining the current action limit? This analysis of chronic data should exclude antibiotics and EASs as these have a tailored ERA irrespective of exposure. See Vestel et al. (2016) and Gunnarsson et al (2019). The analysis by Gunnarsson et al (2019) of Phase II Tier A ecotoxicity data clearly demonstrates that the currently PEC Action limit can be raised to 100 ng/l (0.1 µg/L) for non-EAS and antibiotic drugs (see Appendix A). The EMA should publicly disclose the full scientific basis for maintaining the PEC action limit of 10 ng/l as identified in footnote 3 of the existing guideline.	
126, 282	2	The stakeholder requests the CHMP conducts a thorough re-evaluation of the default phase I PECsw of 0.01 µg/L since the value is based on a flawed and potentially biased calculation and is therefore not reflective of the actual situation in the environment nor presents a value which is intended to safeguard the environment from pharmaceutical pollution. This is supported by arguments published in (1): "*… the threshold surface water concentration of 0.01 µg/L that triggered the need for environmental testing was not scientifically based…*" and "*There is no transparency (and potential bias) over the selection of the 800 drugs (out of the*	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson

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		2700 drugs marketed in Germany at the time) used in the calculation" (1) Indeed, as the author states, the intention of the standard PEC calculation seems "*more targeted towards 'capturing' as many drugs as possible for subsequent Phase IIA evaluation in order to build up a database on effect assessment rather than attempting to provide the best estimate of environmental exposure*" (1) It is the opinion of this stakeholder that the PECsw should not be based only on the partial data of one country; Germany, which cannot be reflective (representative) of the rest of European countries. Therefore, the PECsw trigger value should be re-evaluated including data from most (if not all) European countries. Furthermore, the calculation should be publicly available / published to allow for comments in order to provide a non-biased and scientifically based derivation of the PECsw action limit. The second concern of this stakeholder regarding the PECsw value of 0.01 µg/L is the fact that there is no data on which pharmaceuticals were taken for the derivation of the action limit (that is among the 800 drugs taken for the calculation). Indeed, the initial Scientific Committee on Toxicity, Ecotoxicity and The Environment (CSTEE) (2) expressed concerns regarding PECsw trigger value of 0.01 µg/L in that it was not scientifically validated; "*The action limit proposed by the CPMP may be underprotective for some highly*	et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.

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		ecotoxic pharmaceuticals in the case of pseudoestrogens or genotoxic products or be very overprotective for pharmaceuticals which are harmless to the environment. Therefore, it is neither efficient not effective" (2). This new draft guideline addresses the issue of endocrine active substances, for which an ERA Phase II assessment is required regardless of the PECsw calculation. This is clearly stated "…*This concerns compounds for which the action limit does not apply, such as endocrine active substances…* " and "*If there is evidence that the active substance can exert an effect on development or reproduction by directly interacting or interfering with receptors, hormone levels or activities of oestrogens, androgens or other steroid hormones, that active substance should be assessed in Phase II regardless of the predicted environmental concentration*" The problem it seems is solved in a way that no longer connects the PECsw action limit and endocrine disruptors. Therefore, it is only reasonable to assume, the calculation of the initial PECsw action limit of 0.01 µg/L should not include these (hormone disruptors) pharmaceuticals in its dataset. The stakeholder therefore proposes that the PECsw action limit should be re-calculated in a way that it no longer includes known endocrine active substances in its dataset (exclude endocrine disruptors from the 800 pharmaceuticals used to derive the initial PECsw of 0.01 µg/L). The same arguments apply for antiparasitics, which are in the new draft guideline also exempt from PECsw evaluation	

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		– they are required to be assessed in Phase II, regardless of PECsw: "…*Some substances (e.g. endocrine active substances and antiparasitics) should enter Phase II regardless of their PEC value…*". Therefore, the same proposal as above is presented for antiparasitics: the PECsw action limit should be re-calculated in a way that it no longer includes known antiparasitics in its dataset (exclude antiparasitics from the 800 pharmaceuticals used to derive the initial PECsw of 0.01 µg/L). The tailored assessment – entering the phase II ERA independent of the PECsw values is reasonable for endocrine disruptors (effect seen at ng/L range) and antibiotics (due antimicrobial resistance) but does not make sense for antiparasiticides. Prescription of antiparasiticides to EU population is much lower compared to the endocrine disrupting compounds (hormones or corticosteroids) or antibiotics. Additionally, the antiparasiticides used for human prescription are not expected to pose effects to non-target organisms (algae, daphnid or fish) below the trigger value of 0.01 mg/L (3, 4). Proposed change (if any): The PECsw action limit of 0.01 µg/L should be re-calculated using data from most European countries and not only Germany. Present the draft calculation publicly for potential stakeholders to comment.	

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		Data on which the action limit is based on, should not include endocrine active substances and antibiotics because it is not applicable to them, they have to be evaluated in ERA Phase II regardless of the PECsw calculation. Antiparasiticides should be excluded from the tailored assessment approach.	
126	21, 24, 25, 26	For PEC surface water an action limit of 0.01 µg/L is defined. What is the basis for this action limit? Proposed change (if any): Add an explanation or reference on how the action limit was defined/derived. If these justifications are not available, please consider removing this phase, or decreasing the action limit well below e.g. the PNECs of the APIs on the current WFD Watch list, ranging from 0,035 – 200 ng/l (Loos et al 2018).	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.
126	27	textual clarification Proposed change (if any): change 'When this PEC is' into 'When PEC_{SW} is'	Text edited

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126	30	The same action limit 0.01 µg/L as in previous version of the GD is retained without any explanation. In the previous version the following footnote was included: "The present action limit is based mainly on acute toxicity data and may be revised in future versions of GD when a sufficient data is available". Has the new data been available while drafting the updated GD? If not, the same criticism as already stated during the commenting round of the previous GD exists: 1) The scientific validity of the action limit should be justified (which data have been used and how the data was evaluated) 2) Is the data behind the trigger also now based only on (old) acute aquatic endpoints? If yes, the trigger is not science based, since it is well known fact that there is extremely low correlation between acute and long-term effects for pharmaceuticals. Also, in the Introduction, it is said that the aim of the GD is to protect terrestrial environment. How is PECsw trigger reflecting the ecotoxicity of pharmaceuticals to terrestrial organisms? 3) The concept of trigger value in ERA contrasts with ERAs of biocides and plant protection products, which some of them have even the same active ingredients as in medicinal products. 4) In summary: is the trigger value safe enough and why should it be kept in this GL? Furthermore: Phase I assessment considers only trigger for surface water. The triggers for sediment, soil and STP	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.

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		assessment should also be already in Phase I, since the Koc study is the only study to trigger those studies and it is not a complex study to provide already at phase I. Proposed change (if any): Trigger value (and consequently Phase I) should be deleted. OR the Trigger value should be justified. If the trigger value and Phase I are retained, the triggers for sediment, soil and STP assessment should also be already in Phase I.	
126-129	36	The proposed action limit of PEC ≥ 0.01 µg/L for the Phase II assessment (section 4.2) is somewhat arbitrary and may not be justified for all active substances. Although Phase II assessment is already required for certain classes of substances (e.g. endocrine active substances and antiparasitics), the PEC action limit should ideally be determined case specifically (e.g., in comparison to clinical data, such as the therapeutic index). For example, antineoplastic (cytostatic) compounds should be dealt with extra care due to their severe adverse effects. Proposed change: The scientific rationale behind the set action limit should be clarified. At minimum, the following footnote from the previous version should be returned to the revised guideline: "The present action limit is based mainly on acute toxicity data and may be revised in future versions of guideline when a sufficient data is available". It should also be clarified whether data refers to aquatic endpoints only	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.

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		and how are the trigger values for sediment, soil and STP dealt with. In addition, the list of example active substances for which the above action limit does not necessarily apply should be supplemented with antineoplastic compounds. See further comments.	
126	42	The action limit is set to 10 ng/l in surface water, which is relatively high for identifying APIs potentially causing environmental risk. According to the 2006 ERA-guideline this action limit is based on acute toxicity data and was to be revised. There should be some justifications given for the action limit. PECsw trigger does not reflect the ecotoxicity of pharmaceuticals to terrestrial organisms. Proposed change (if any): Please give sufficient justification for limit value PECsw proposal. Limit value should be scientifically justified. Lower limit value should be considered. The triggers for sediment and soil assessment should also be already in Phase I.	The database used for maintaining the current action limit is provided in a current publication by Schwarz et al. (2021) (https://doi.org/10.1186/s12302-021-00503-0.). The investigated long-term toxicity effect data set came from studies submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. A detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.
127	1	Some substances (e.g. endocrine active substances and antiparasitics) should enter Phase…. Proposed change: The guideline needs to be clear that antiparasitics sit outside the tailored ERA for antibacterials and they only require an ERA if the PEC action limit is exceeded.	Text edited; table added for better guidance. Antiparasitics are not replaced by antibacterials, since these are different types of substances with different indications, therefore a specific assessment strategy applies for each. Antiparasitics enter Phase II regardless of their PEC, the action limit does not apply to

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		Replace antiparasitics with antibacterials as they require a tailored ERA (this terminology should be used throughout in a consistent manner)	these substances. For antibiotics, the action limit applies but they require tailored testing.
127	17	Examples for "Some substances" are indicated to be endocrine active substance and antiparasitics. The latter should be antibiotics. (See also comment on line 267-270) Proposed change (if any): Replace antiparasitics by antibiotics	Text edited; table added for better guidance. Antiparasitics are not replaced by antibacterials, since these are different types of substances with different indications, therefore a specific assessment strategy applies for each. Antiparasitics enter Phase II regardless of their PEC, the action limit does not apply to these substances. For antibiotics, the action limit applies but they require tailored testing.
127	22	"Antiparasitics" is not considered to be used in humans to a very large extent. This wording is probably inherited due to copy-paste from veterinary guidelines. Should it read "antibiotics"? Proposed change (if any): Replace "antiparasitics" with "antibiotics".	No, antiparasitics are also used in humans to some extent. E.g, ivermectin and permethrin are active substances in human medicinal products. Text edited; table added for better guidance. Antiparasitics are not replaced by antibacterials, since these are different types of substances with different indications, therefore a specific assessment strategy applies for each. Antiparasitics enter Phase II regardless of their PEC, the action limit does not apply to these substances. For antibiotics, the action limit applies but they require tailored testing.
127-129	25, 26, 42	There should be clear specifications on when a substance should enter Phase II regardless of its PEC_{sw}. Proposed change (if any): Please specify more clearly when substances are considered to fall into class "substances with specific classifications".	Based on current information on PNECs, for endocrine active substances and antiparasitics the action limit does not apply.

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127	29	Editorial issue - question: is "parasiticides" or "antiparasitics" the correct wording?	Antiparasitics is correct.
127	44	It is noted that different classes of substances require a Phase II assessment by default. In this sentence: "Some substances (*e.g.* endocrine active substances and antiparasitics should enter Phase II regardless of their PEC value" the examples given are endocrine active substances and antiparasitics, whereas elsewhere in the document different examples are given (see line 341: antibiotics). It is also noted that only endocrine active substances and antibiotics are explicitly addressed in Section 4.3. Please can the guideline be updated to comprehensively list all substance classes which would require a phase II assessment by default as well as, where required, giving a clear description of the nature of any tailored assessment that is needed (as detailed in Section 4.3). Considering that a Phase II assessment, and likewise any 'tailored' risk assessment, could trigger the generation of new *in vivo* toxicity data it is important that the substance classes which do and do not fall into this category are clearly delineated.	Endocrine active substances and antiparasitics enter Phase II regardless of their PEC, the action limit does not apply to these substances. For antibiotics, the action limit applies but they need tailored testing. Text changed, table added for better guidance. Antiparasitics are not replaced by antibacterials, since these are different types of substances with different indications, therefore a specific assessment strategy applies for each.
128	27	textual clarification Proposed change (if any): change PEC into PEC_{SW}	Agree, text edited.
129	48	This action limit is based on an aquatic concentration below which it was concluded that no ecotoxicity data on drugs for relevant standard test organisms were reported (U.S. FDA,	The used database for maintaining the current action limit is provided in Schwarz et al. (2021) (https://rdcu.be/clO90). The investigated long-term toxicity effect data set came from studies

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		1996). This concentration was further divided by an assessment factor of 100 to obtain the action limit. Is this action limit still considered to be valid? In addition, would this take into account the presence of > 1 pharmaceutical substance? Thereby giving a summed residue?	submitted in the authorisation process of human medicinal products. In this evaluation all substances were included for which the PEC action limit applies. Since a large portion of the data is based on confidential study reports from various pharmaceutical companies, the original data cannot be made publicly available. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. The regulatory ERA is product based, and thus it is impossible to test/predict environmental risks for all possible API combinations. New information on risk assessment methodologies and regulatory adaptations may change this in future.
131-133	47	Proposed change (if any): Sentence on lines 131-133 would logically start after the sentence ending on line 129 (and after appropriate modification) to read: Some substances (e.g. endocrine active substances and antiparasitics) should enter Phase II regardless of their PEC value (see decision tree, **Figure 2**), because they may affect organisms in the environment at concentrations < 0.01 µg/L. For such substances, a tailored risk assessment strategy shall be followed that addresses their specific mechanism of action (section 4.3).	Text edited; table added for better guidance. Endocrine active substances and antiparasitics need an ERA regardless of their PEC, the action limit does not apply to these substances. For antibiotics, the action limit applies but they require tailored testing. The substances for which the action limit does not apply, are not per se the same substance groups that need a tailored assessment.
134	1	The phrasing: "When a risk is identified in Tier A…" is presumptuous. Proposed change (if any):	Not agreed.

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		This sentence should begin: "When a potential risk is identified …" as Tier A is only a preliminary evaluation of possible hazards to the environment.	
134-135	25, 26	Refining the PEC-value is justified due to the "total residue approach". However, the assumptions made in the refinement stage should be verified by a third party, so that variables (e.g. Fpen) are not "optimized" to give artificially lower PEC-values.	The default Fpen (0.01) was used in previous risk assessment. The scientific basis is documented in the GL text from 2006 (EMEA/CHMP/SWP/4447/00 corr 2). Justified refinement options are explained in question of the Phase 1 decision tree and will always be assessed by a NCA.
137-139	25, 26	Currently the trigger values do not take persistence into consideration. Proposed change (if any): Persistence (e.g. in soil after sewage sludge application) and subsequent potential accumulation due to repeated load should be taken into consideration in the trigger values.	Not agreed. Rationale: Phase I is a simplified assessment calculated based on worst case defaults, metabolism and biodegradation are not considered.
142	22	Proposed change (if any): Shift place "soil" and "groundwater" to better reflect the order they are presented.	Not agreed Rationale: The chapter order has been revised to soil before groundwater.
146	44	Suggest amended wording as follows: "The PBT (Persistent, Bioaccumulative and Toxic) **hazard evaluation** concerns the identification…" Reason: to distinguish this step from the risk assessment procedure.	Comment noted. The PBT/vPvB assessment has been revised and differentiated between PBT/vPvB screening and definitive PBT/vPvB assessment.
146	48	Please consider re-wording the sentence from: The PBT (Persistent, Bioaccumulative and Toxic) assessment concerns the identification of certain intrinsic properties of the active substance	Not agreed but section edited for clarity. Rationale: Metabolism of the active substance is not considered in the PBT/vPvB screening.

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		To: A thorough PBT (Persistent, Bioaccumulative and Toxic) assessment concerns the identification of certain intrinsic properties of the active substance and/or metabolites (where appropriate).	
147	12	Persistency is not determined as an "intrinsic" property of a substance. Substances, that e.g. degrade in soils in hours to days might persist in sediment for hundreds of days due to a lack of oxygen under test conditions. So in most case its not an "intrinsic property" but a matter of specific test conditions. Proposed change (if any): delete "intrinsic property", because it is wrong.	Not agreed but section edited for clarity. Rationale: It is agreed that Persistence refers to a specific compartment, but it is still considered an intrinsic property of the active substance for the purposes of hazard assessment, in that it is independent of exposure.
147-148	25, 26	It is an important observation that PBT-properties make risks unpredictable. However, since several substances are known to be very persistent, and since minimizing environmental exposure (i.e. minimizing use) is usually not a viable option for APIs, the results of the PBT-screening should be somehow incorporated into the risk assessment and PEC-calculations. Persistence has already been incorporated into the PEC_{soil} calculations, but e.g. potential transport through soil layers, surface run-off or foodwebs should also be considered for PBT-substances.	Labelling and risk mitigation is addressed in Section 7 of the guideline. Appropriate mitigation measures should generally aim at minimising the quantity discharged into the environment.
147-148	29	For PBT substances a risk assessment is not possible/ feasible. We propose to rewrite the sentence: Proposed changes:	Comment noted. Text edited.

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		The PBT properties of a substance do not allow predicting the long-term effects in the environment, thus a risk assessment based on exposure is not applicable.'	
149	48	Please consider re-wording the following sentence: 'As the PBT assessment concerns intrinsic properties of the active substance subsequent exposure is not considered'. It is unclear what is meant by subsequent exposure.	Comment noted. Text edited.
150	22	Proposed change (if any): Write the explanation for vPvB also in this section (as is done for PBT).	Not agreed Rationale: Explanation already in chapter 3.2.
151	22	Proposed change (if any): Please include more reference "…identified in the first part of the Phase I decision tree (4.1 Q1-Q3).	Comment noted. Text edited and supplemented by PBT/vPvB screening decision tree.
151	47	Line 151. For clarity it would be necessary to define to which decision tree the text refers to. Proposed change (if any): Compounds entering the screening phase (section 5.1) are identified in the first part of the decision tree (Question 1-3, Fig. 2).	Comment noted. Text edited and supplemented by PBT screening decision tree.
154-157	20	Sentence is very difficult to understand unless one has read rest of the document. Proposed change (if any): rewrite for clarity.	Comment noted. Further explanation has been added.
154-157	22	The section needs several re-readings to be understood. E.g. the first line, "in exceptional cases for substances which do not meet the trigger for PBT assessment (log KOW >4.5)", since it is stated that this is when the trigger is NOT met, it should be described as (Log KOW <4.5).	Comment noted. Text edited.

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		Proposed change (if any): Consider rewording.	
154	44	For clarity, suggesting amending the sentence as follows: "In exceptional cases**,** [add comma] **some** substances which do not meet the trigger for PBT assessment (log Kow > 4.5) **may nevertheless still require** an assessment of PBT/vPvB properties. This will be the case if the results obtained in Phase II of the risk assessment demonstrate that the B- and T-criteria are met, or if the vB-criteria is met (see Table 16).	Comment noted. Text edited.
154–155 379–381 485–486 907–908 919–923 1078–1080 1093–1098 1106–1109	45	It is necessary to include trigger values for log K_{ow} and BCF, respectively, when a substance is considered bioaccumulative without being a PBT or vPvB substance.	Comment noted
157	27	typo Proposed change (if any): change vB-criteria into vB-criterion.	Text edited
157-158	48	TO BE AWARE: We are currently in discussions at a European Member State Level (Competent Authorities for REACH and CLP; CARACAL) about the new criteria of Persistent, Mobile and Toxic (PMT)/ very Persistent very Mobile (vPvM) that have been proposed by the German Environment Agency (UBA). These criteria have been	Comment noted. Due to overlapping timelines of the current GL revision and the regulation of the new hazard classes PMT/vPvM the GL revision does not address this.

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		proposed to identify substance that are a potential threat to drinking water and drinking water supplies. Discussions are currently focusing on whether hazard criteria are accurate and whether REACH is the correct legislative instrument to implement this.	
160	26, 30, 48	stated: "*When a risk is identified and/or a substance is classified as PBT/vPvB, this information should be 159 included in the SmPC and risk mitigation measures should be discussed*". What is SmPC? Proposed change (if any): clarify what is SmPC.	The Summary of Product Characteristics (SmPC) is a document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively. SmPC has been added to the list of Definitions.
162	10, 22	Structure of the report is described in section 9 not 8 Proposed change (if any): The structure of the risk assessment report is described in section 9.	Agree. Text edited.
164	48	The following sentence 'The ERA should be performed for the environmentally relevant chemical species, which in most cases is the parent compound', appears to directly contradict earlier text where only the active is discussed. Please also note that the text contains some inconsistency of terminology in terms of 'active substance and 'parent compound'.	Not agreed Rationale: In some cases, the pharmacologically active substance is the active metabolite and not the parent compound (e.g. prodrugs).
166	43	Section 3.2.1. Because physico-chemical properties of active substances are important drivers for fate and toxicity, the fate of metabolites and other transformation products should get more emphasis. By basing the ERA on the assumption that no metabolites are formed, a possible higher environmental	Not agreed Rationale: It is recognized that various API/active substance-derivates may have somewhat different toxicological and environmental fate properties, but it is also recognized that it practically impossible to assess environmental risks for all individual metabolites and transformation products. The total residue approach is chosen as a pragmatic solution that assumes

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		persistence and bioaccumulation by metabolites appears to be easily neglected.	that metabolites and transformation products that are generated are generally less persistent and toxic and thus pose less risk to the environment. Based on these premises, the assumption that a given parent compound is representative for all environmental exposure, will therefore introduce some conservatism in the risk assessment for most substances. The applicant may always choose to also perform an ERA for the metabolite(s). In this case, the PEC for the parent compound may be adjusted. When it is known that any metabolite will have a higher risk to the environment than the parent compound (as is the case with pro-drugs), the ERA has to be performed for the most environmentally relevant compound, which in this case would be the metabolite.
166-169	47	Chapter 3.2.1. "Total residue approach": The general assumption is that the metabolites have lower toxicity than the parent substance. On the other hand, an exception is made for prodrugs. In analogy with the prodrugs, it would be justified to do an ERA for metabolites known to have a higher toxicity than the parent. Proposed change (if any): In cases where some metabolites are known from preclinical safety testing to have a higher toxicity than the parent, an ERA for such metabolites should also be submitted.	Not agreed Rationale: This is covered in the DRAFT GL in lines 171-175 which now have been slightly altered to provide more guidance. In cases where there is confusion concerning the number of ERAs (e.g. both prodrug and active metabolite), scientific advice should be sought from the regulatory agencies.
169	48	Could you please explain how the residue approach has been justified? Is it correct to assume that the metabolites have a similar or lower toxicity than that of the parent substance?	Active substances (AS) may be/are metabolized/transformed to a relatively large degree across different conditions (e.g. in humans, wastewater treatment plants, in surface water and sediment, soil). It is practically impossible to assess the toxicological,

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			bioaccumulation and/or persistence profiles for all individual metabolites/transformation products. While it is recognized that there are examples in the ecotoxicological literature where the derivates (e.g. metabolites) of a chemical substance may be more persistent or more potent, for most active substances it may be assumed that the environmental risk of metabolites/transformation products is less than the risk of the parent compound. The applicant may always choose to also perform an ERA for the metabolite(s). In this case, the PEC for the parent compound may be adjusted. When it is known that any metabolite will have a higher risk to the environment than the parent compound (as is the case with pro-drugs), the ERA has to be performed for the most environmentally relevant compound, which in this case would be the metabolite.
171-175	15	It would be helpful if the document to clarify when both prodrug and active metabolite needs to be assessed (e.g. provide a cut-off).	Text edited for clarity. In cases where there is confusion concerning the number of ERAs (e.g. both prodrug and active metabolite), scientific advice should be sought from the regulatory agencies.
172	44	For precision, suggested rewording: "However, there may be instances where **most of the prodrug fails to be converted to the active (i.e. <50 % conversion) and is** excreted largely (**i.e. >50 %**) intact or via **a** metabolic **pathway** that **does** not generate the active moiety."	Text edited
176-177	29	Active substances of combination products should be assessed together and in specific cases tests could be	Not agreed.

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		necessary. To the current state of knowledge there is a high relevance of substance combinations in the environment. The ERA is foreseen for the product of the respective application. This is especially considered for PEC calculations (e. g. dose of the product, indication, prevalences). There is no plausible reason why in case of combinations the assessment should only focus on the separate active substances. This is not consistent. The approach should be the same as for veterinary pharmaceuticals. Proposed change (if any): In case of fixed combination products the assessment should be targeted at the combination. In Phase I the PEC values for the active substances in the product should be summed up. If scientifically justified, the ERA data might be performed separately for each compound within the product. A situation could arise where for a particular test species the RQ values for each of the active ingredients individually is lower than 1, but where the sum is ≥ 1. Unless it can be justified as to why it is not relevant it may be necessary to carry out further assessment of the risk presented by the combination of actives.	Rationale: For human pharmaceuticals, the ERA has a focus on single active substances (AS) based on several considerations: Compared to veterinary conditions (where emissions to the environment via manure are very local are with a limited number of individual products as source of the AS), emissions of AS for human use go via waste-water treatment plants. The effluent contains a far greater amount of different AS with different physicochemical/environmental fate/toxicological properties than those present in the fixed combination product. As such, assessing the specific interactions for only the human FDC AS (as opposed to all other possible mixtures) is questionable. The regulatory ERA is product based, and thus it is impossible to test/predict environmental risks for all possible AS combinations. New information on risk assessment methodologies and regulatory adaptations may change this in the future.
176	41	Unfortunately, the guideline clearly falls behind the scientific and regulatory state of the art in one particular aspect, which is the assessment of the risks of fixed combination products. As a consequence, the draft	Not agreed Rationale: For human pharmaceuticals, the ERA has a focus on single active substance (AS) based on several considerations: Compared to veterinary conditions (where emissions to the

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		jeopardizes its aim to provide a realistic assessment of potential environmental risks for those products. On page 8, line 176 it is stated that "*For fixed combination products, the ERA is performed separately for each compound within the product*". Such a sole focus on each individual compound would lead to a systematic underestimation of the environmental risk of the product, see the various recent reviews on mixture (eco)toxicology, by e.g. the OECD (OECD Series on Testing and Assessment No 296 "Considerations for assessing the risk of combined exposure to multiple chemicals", ENV/JM/MONO(2018)37.) or the EU Joint Research Centre (e.g. Bopp et al 2016. Review of case studies on the human and environmental risk assessment of chemical mixtures. In EUR 27968 EN.), but see also Bopp et al., 2019. Regulatory assessment and risk management of chemical mixtures: challenges and ways forward. Critical reviews in toxicology, pp.1-16. and a broad range of more detailed scientific papers (which I could compile on request). The fact that combinations of biologically active chemicals typically lead to a significantly increased risk is why the systematic consideration of mixture effects has already been implemented in other EU chemical regulations for almost a decade. This includes the environmental risk assessment of plant protection products, see for example the following EFSA guidelines that all implement Regulation 1107/2009: EFSA, 2009. Guidance Document on Risk	environment via manure are very local are with a limited number of individual products as source of the AS), emissions of AS for human use go via waste-water treatment plants. The effluent contains a far greater amount of different AS with different physicochemical/environmental fate/toxicological properties than those present in the fixed combination product. As such, assessing the specific interactions for only the human FDC AS (as opposed to all other possible mixtures) is questionable. The regulatory ERA is product based, and thus it is impossible to test/predict environmental risks for all possible AS combinations. New information on risk assessment methodologies and regulatory adaptations may change this in future.

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		Assessment for Birds & Mammals. EFSA Journal 2009; 7(12):1438.) and EFSA, 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290, and, most recently, the EFSA mixture assessment guideline EFSA, 2019. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 17(3):5634. Also, ECHA has published a detailed mixture assessment guideline as part of the environmental risk assessment of biocides, implementing Regulation 528/2012: ECHA, 2017. It can be found in Guidance on the Biocidal Products Regulation, Volume IV Environment - Assessment and Evaluation. doi 10.2823/033935. There is absolutely no scientific or practical reason, why the approaches detailed in these guidelines could not be also applied during the environmental risk assessment of fixed combination medicinal products, perhaps in adopted form. It should be emphasized that the first-tier mixture assessment would actually not require to generate any additional ecotoxicological data. Predictive methods for assessing the joint risk of chemicals, including pharmaceuticals, are at hand, tested and validated (see the aforementioned reviews and guidelines), but also various scientific publications.	

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		Proposed change (if any): In order to ensure a realistic environmental risk assessment of fixed combination products, line 176 on page 8 should be replaced by the following: "For fixed combination products, the ERA is performed with the aim to describe and assess the total risk of the mixture of all biologically active compounds of the product."	
176	44	For clarity, suggest rewording as follows: "For fixed combination products, the ERA is performed separately for each **active substance (or pro-drug, potentially)** within the product."	Text edited.
176	46	: It is not state of the art to assess the risks of active ingredients in combination products separately. Both drugs will reach the WWTP and the receiving surface water at the same time. As with plant protection and biocidal products some indicative tests with the mixture of the active drug ingredients should be carried out. Alternatively, the effect concentration should be calculated using concentration addition. According to various publications (e.g. Altenburger, R. et al, (2018), Mixture effects in samples of multiple contaminants – an interlaboratory study with manifold bioassays, Environment International 114, 95-106 *and* Kortenkamp, A., Backhaus, T., Faust, M. (2009): State of the Art Report on Mixture Toxicity. Report for the Directorate General for the Environment of the European Commission) in most cases the result will be on the safer side.	For human pharmaceuticals, the ERA has a focus on single APIs based on several considerations: Compared to veterinary conditions (where emissions to the environment via manure are very local are with a limited number of individual products as source of the APIs), emissions of APIs for human use go via waste-water treatment plants. The effluent contains a far greater number of different APIs with different physicochemical/environmental fate/toxicological properties than those present in the fixed combination product. As such, assessing the specific interactions for only the human FDC APIs (as opposed to all other possible mixtures) is questionable. The regulatory ERA is product based, and thus it is impossible to test/predict environmental risks for all possible API combinations. New information on risk assessment methodologies and regulatory adaptations may change this in future.
179	22	…"by or on behalf of the applicant".. is superfluous.	Not agreed.

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		Proposed change (if any): Delete "by or on behalf of the applicant"	Rationale: Studies could also be obtained through public literature. Studies that are performed specifically for the purpose of regulatory risk assessment should be GLP compliant and follow most recent test guidelines.
179	44	Regarding the statement "QSARs (Quantitative Structure-Activity Relationships) and read-across cannot replace the studies requested in this guideline."; please consider removal of this sentence. The field of animal-free methods, including *in vitro* assays, *in silico* approaches, as well as structured read-across and Weight of Evidence arguments, for the generation of key information for the purposes of chemical safety assessment is rapidly evolving. There are an increasing number of animal-free OECD test guidelines becoming available that may be relevant for generating the data required for ERAs. So that this test guideline remains relevant in the long-term, and that appropriate animal-free methods may be employed when they are available, please consider the following text instead: "**Data generation by or on behalf of the applicant in order to meet the ERA data requirements specified in this document** should be GLP-compliant **where applicable** and preferably follow the most recent test guidelines issued by the Organization for Economic Co-operation and Development (OECD) or comparable international validated test guidelines."	Partly agreed. Rationale: Currently, there are no validated and regulatory accepted methods to replace laboratory studies. Hopefully, new scientific projects like the EU PREMIER project will bring this a step further, but at the moment it is too early to refer to these methods yet. A statement regarding QSAR and 3Rs has been added to section 3.1.3. However, text proposal is accepted.

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181-183	1	Whilst it is acknowledged that QSARs are not all fully reliable at this stage, given the longevity of these guidelines and rapid progression in the innovation of alternative approaches, it feels inappropriate to completely dismiss QSARs or study types different to those specified in this guideline. It should be considered that there may be instances where read-across and *in silico* approaches may be applicable (e.g. when refining exposure considering multiple metabolites or for generating conservative supporting data) Proposed Change: QSARs (Quantitative Structure-Activity Relationships) and read-across are not, in general, considered as appropriate replacement for the studies requested in this guideline at this time. If appropriately validated alternative approaches are considered the merits and acceptability of the data or models should be discussed with the competent authority prior to submission of the ERA.	Not agreed. Rationale: Currently, there are no validated and regulatory accepted methods to replace laboratory studies. Hopefully, new scientific projects like the EU PREMIER project will bring this a step further, but at the moment it is too early to refer to these methods yet.
183-183	20	For P and B-assessment using QSARs, it could be helpful to indicate that QSARs may give additional perspective as WoE data for regulators.	Not agreed. Rationale: Currently, there are no validated and regulatory accepted methods to replace laboratory studies. Hopefully, new scientific projects like the EU PREMIER project will bring this a step further, but at the moment it is too early to refer to these methods yet. Also, for the PBT assessment, the requested laboratory studies should be performed.
185	29	Please use the current updated version of Water Framework Directive EQS	Agreed. Text edited.

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		Proposed change: cite as „European Communities, 2018"	
188-198	2	The publicly available data may be divided into three categories: 1. Scientific articles (research data) are usually characters/word - limited, therefore statistical or study endpoints are mostly presented, without presentation of raw data/analysis results or statistics to re-evaluate the results. Re-evaluation of the results is not possible. 2. Scientific reports (e.g. Masters, PhD works) published by environmental agencies, university. These reports usually have a good presentation of raw data as well as statistic evaluation. Possible re-evaluation of the results 3. Public assessment reports (PARs) published by Regulatory authorities usually present the study endpoints – re-evaluation not possible. Because PARs are published after registration procedure was concluded, the data was already evaluated and approved by the Regulatory authorities, therefore no additional re-evaluation is necessary because ERA will not change between the innovator and generic products (indication, MDD and pharmaceutical form being the same). The proposed guideline´s position eliminates the majority of publicly available ERA data and therefore forces the MAHs into study repetition which conflict with the basic	All data provided, whether these are scientific publications, data from grey literature, or GLP studies performed specifically for the ERA, should undergo a thorough reliability assessment, e.g., using the CRED criteria. Regarding endpoints published in (E)PARs or other regulatory summaries (e.g., in the biocide or PPP framework): these are not acceptable because of legal reasons: Endpoints are owned by the company who submitted them in the original procedure and cannot be used by other applicants without a letter of access. If the applicant has a letter of access, the applicant also should have the study reports available and submit those. Besides this, (1) endpoints may have been evaluated using older standards or in different frameworks and not meet current standards. (2) EPARs have not always been updated with new data or changed assessments during former procedures. Some more text on this is added in section 3.1.4 and section 6.1. To prevent repetition of studies, applicants are encouraged to share data and to construct a database to enable easy sharing.

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		principles of ERA, where protecting the environment is the main goal, with unnecessary repetition of studies (3R principles). Proposed change (if any): - Re-evaluation of criteria for acceptability of public available data - ERA database establishment, data available for the MAHs (generics can link to the published data) and for the public (growing the awareness of extensive usage of medicine for the environment)	
188-198	36	The recommendation for sharing of the ERA data (produced by the MAH) is highly relevant and should be facilitated and encouraged in all possible ways. This should be emphasized also with a view to implementation of the EU Strategic Approach on Pharmaceuticals (EC Communication 2019, 128). Proposed change (if any): Ideally, publishing the ERA data could be a mandatory requirement, but if not feasible at this point, a template that summarizes the critical information and the test protocols used (together with their justification) could be given to MAHs (e.g., as an Annex of the revised ERA guideline). In this manner, the reporting practices would be harmonized, which would significantly advance the sharing of data as well as the prioritization of most harmful substances, e.g., at the waste water treatment plants.	Agreed. The (E)PAR summarizes the ERA results. Agreed that lack of harmonization, resulting in different ERAs for the same compound with sometimes different conclusions, is undesirable. Harmonization between frameworks however cannot be solved within this guideline revision.

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		Namely, in some cases, the lack of harmonization (of the ERA reports) may result in significant discrepancies between the different sources of information. For example, according to the European Commission's Joint Research Centre, the PNEC value of diclofenac is 0,05 μg/L, whereas the PNEC value reported in the Swedish environmental classification system (fass.se) is many-fold higher, 32 μg/L. This difference likely results from the fact that different fish organs (liver vs. gill) has been used to derive the abovementioned values. Obviously, such great difference in PNEC results in substantially different risk quotient. Therefore, harmonization of the ERA data reporting practices is of utmost importance with a view to sharing the data in public domain.	
189-192	1	The draft guideline states for APIs that are already marketed, information may be available in the public domain "To prevent repetition of (animal) studies and allow identification of signals emerging from environmental monitoring and research, the Applicant should provide a complete literature review (See 191 section 6.1 on data search)." Proposed Change (if any): Can the guideline clarify whether the summary review of existing data can be submitted as part of a briefing book or pre-submission meeting document to determine if existing data is sufficient and additional studies are not needed?	During pre-submission meetings for marketing authorisation applications, no preliminary assessment is performed. The applicant can always ask for scientific advice following regulatory procedures.

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189 ff	22	It is not clear if a complete literature review is mandatory for active substances that are already marketed. That is, if data is shared from another MAH, is there a need for a literature review in order to identify signals?	Yes, the applicant should perform a literature search, also if data is obtained from another MAH. This is to allow identification of signals from environmental monitoring and research, as well as toxicity data from scientific experiments. Text in section 6.1 (Data search) has been changed to make this clear.
189-192	22	It is unclear to what extent the complete literature review should be performed and how the search strategy should be presented. Maybe instead of a requirement of a complete literature review it should read that "literature data **may** be submitted as an alternative to experimental studies"? It is unclear what is meant with "identifications of signals emerging from environmental monitoring and research". Publications dealing with environmental monitoring data could be extensive for some compounds. Lengthy literature reviews dealing with data of little relevance for the ERA is not wanted! Proposed change (if any): It should be clarified in this section that only data relevant for use in replacement or supporting the standard experimental data set may be presented.	Partly agreed. Text edited, mainly in section 6.1.
192	1	The guideline states that other marketing authorization companies who have already performed relevant studies are encouraged to share data with the Applicant. As stated in line 236, in order to avoid repetition of studies (e.g., due to concerns for animal welfare), we recommend EMA develop a transparent process that leverages available data without burdening either company.	Partly agreed. However, it is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent Authorities are not allowed to share data. Industry should find a way to share data in a way that the burden to industry will be minimized, following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme.

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		Proposed change (if any): An agreed mechanism for data transparency and accessibility is established before this guideline comes into force that places minimum burden on industries losing exclusivity of a product and generic/ biosimilar companies entering the market.	
192-194 and 235-241	4	Even though the originators/MA holders are "encouraged to share their data", there is no real motivation given why the originator/MA holder should do so. As mentioned in the row before an obligation to publish the ERA results could circumvent this issue.	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data.
192-194 and 236-237	10	Encouraging MAH to share data from already performed studies is not sufficient. In order to avoid unnecessary repetition those data should be made publicly available by either the MAH, the authority or both. A database hosted by EMA or European Environmental Agencies compiling a matrix of all data on environmental studies of an API would be very useful. Access to relevant studies should be possible by cost sharing. Furthermore, a valid exposure assessment is filed in PSUR and assessed by competent authorities, so that an overview on the exposure to the environment is documented.	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data.
194-196 and 1200-1201	4	If PARs and EPARs cannot be used without the underlying studies, the applicant again has to rely on the originator/MA holder to get access to the ERA dossier, which most likely will not be granted. In order to prevent unnecessary repetition of animal studies one should be able to cross-reference to recent PARs and EPARs. In case the ERA needs	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data.

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		to be updated the authority will let the applicant know, which tests have to be performed additionally.	Regarding endpoints published in (E)PARs or other regulatory summaries (e.g., in the biocide or PPP framework): these are not acceptable because of legal reasons: Endpoints are owned by the company who submitted them in the original procedure and cannot be used by other applicants without a letter of access. If the applicant has a letter of access, the applicant also should have the study reports available and submit those. Besides this, (1) endpoints may have been evaluated using older standards or in different frameworks and not meet current standards. (2) EPARs have not always been updated with new data or changed assessments during former procedures. Some more text on this is added in this section and section 6.1.
204-206	25, 26	This is a sensible assumption, but it makes it very important to use proper methods in estimating the exposure. PEC_{sw} should not be directly used in estimating soil exposure.	A soil assessment is needed for substances with high release to the sewage treatment plants, even in scenarios where the adsorption to the solid fraction is limited (lower than a Koc value of <10 000 L kg-1). Therefore, a soil assessment is triggered based on a set of trigger values depending on a combination of chemical-physical substance properties (Koc) and the predicted concentration in surface water
204-206	45	"It is assumed that active substances with limited use and/or limited environmental exposure will have limited environmental effects, and thus the risk assessment will stop in Phase I." It is important to consider that the use can change over time and the guideline also need to take this into consideration.	Not agreed Rationale: Environmental risk assessment is based on predicted environmental concentration (PEC) and the available scientific knowledge at the time of application. The PEC is calculated using the maximum daily dose of the active substance and Fpen. For either of these factors to change, a line extension or a type II

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			variation application must be submitted, for which an updated ERA is required.
204	48	Please consider re-wording the following sentence: 'It is assumed that active substances with limited use and/or limited environmental exposure will have limited environmental effects, and thus the risk assessment will stop in Phase I'. It is misleading to assume that pharmaceutical substances that inherently have a narcotic effect may have limited environmental effects. This is dependent on efficacy and dose of the substance and also whether it reaches a target organism. The wording of the assumption therefore needs to be tightened.	Agreed, sentence deleted, and text edited for clarity.
207	27	Comment: Phase I risk assessment does not consist of a decision tree, this is an illustrative aid. Proposed change: The Phase I risk assessment is *presented* as a decision tree in Figure 2.	Agreed. Text edited.
212	13	Figure 2, Q1: not every natural substance is unproblematic. There are ingredients (e.g. in plants) which are used as pharmaceuticals. In lines 215 – 222 it is explained which kind of substances are meant. Proposed change (if any): Including a word such as "unproblematic" in Q1 of the Figure resulting in a question like "Is the active substance a naturally occurring unproblematic substance?".	Not agreed Rationale: Figure 2 should be 'read' together with the descriptive text for the boxes below the figure. The description for Q1 provides examples of naturally occurring substance for which a risk to the environment is not anticipated.

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212-213	17	Figure 2: Q2c asks if the default Fpen was used, and in case "yes", the assessment may be stopped in Phase I. However, the default Fpen is not always applicable. What about indications which have a prevalence higher than 1%? Proposed change (if any): Reconsider using Q2c as a decision criterion. Q3b not only considers biodegradation, but also excretion, which is included in the text but not in the figure. Proposed change (if any): Include the criterion of <10% excreted to box Q3b	Regarding Q2c: No change introduced in Figure 2. This decision-section is concerned with Art 10 substances that come with a previous ERA. Box Q2d makes it clear that whether the refined Fpen in the earlier ERA is > or < 0.01, it is a resulting increase in PECsw that matters. If there is an increase, this is handled by boxes Q5 and Q6. Regarding Q3b in Fugure 2: Not agreed. In the interest of readability, not all information can be included in the figure.
212 (Figure 2)	29	Comment: PBT button The PBT button is confusing. We propose to draw another decision tree for PBT screening "PBT screening decision tree". For differentiation, the decision tree in figure 2 should be amended and named Risk assessment decision tree. Proposed change (if any): See below in the annexes.	Agreed. Text edited and PBT screening decision tree added, see chapter 5.1
212-341	47	Figure 2 could be simplified e.g. according to the figure suggested above. The steps from Q1 to Q3 could be combined in one box. Q7 is essentially the same as Q4, and could be combined into one question. Proposed change (if any): Change the upper part of Figure 2 e.g. with the figure given above (Specific comment no 4).	Combining Q1-Q3 in one box would not simplify the Decision tree since there are several questions where answers determine different routes in the tree.

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		Change Q4 to read: **Q4: Is the PEC_{sw} action limit of 0.01 µg/L applicable for the active substance?** For active substances that can affect environmental organisms at concentrations < 0.01 µg/L, the action limit may not be applicable. A tailored risk assessment is required for compounds with a specific mode of action (e.g. endocrine active substances, antibiotics, and antiparasitics). More information on identification and tailoring of studies for EAS and other specific active substances can be found in section 4.3. and delete the redundant Q7 (from the Figure and the text).	Change of Q4 as proposed is not supported. The general text in section 3.2.1 that describes which substances that the action limit does not apply for, and which substances that have a specific toxicity profile requiring tailoring of studies, has been changed to provide more clear guidance.
212/215	48	Is the Active Substance a naturally occurring substance? It would be helpful to understand whether this category addresses synthesised natural substances, which are regulated under REACH. Could further clarification be given? There are examples of many natural substances that have properties of PBT/vPvB or an Equivalent-level-of-Concern e.g. phytoestrogens, polyaromatic hydrocarbons, sterols which if being emitted to the environment a risk assessment should be performed beyond that of Phase 1.	It is noted in the descriptive text for Q1 below Figure 2 that there may be exceptions for substances considered environmental hazards/risk under other frameworks.
215-222	1	The phrase "naturally occurring" is an ambiguous term. It is not clear whether it covers both substances found in nature, or those obtained *from* natural sources. It should also be clarified the extent to which substances can be modified – e.g. is a 40 amino acid drug which occurs as	The descriptive text for Q1 below Figure 2 covers these aspects. The Guideline cannot describe or be kept updated on all modifications that are not considered to have an impact on environmental risk. When not submitting ERA studies, the Applicant is expected to submit a justification.

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		part of a much larger chain in nature considered to be "naturally occurring". Are taxol-class drugs obtained from yew-tree bark considered to be naturally occurring?	
216-222	10	The examples for naturally occurring substances given in Q1 mention more or less chemically defined substances used as APIs and exempts them from the requirement to conduct ERA studies. The reason given for this is: "that due to the physico-chemical nature of the API these products are unlikely to pose a risk to the environment or based on the environmental fate and/or common presence in the environment these products are unlikely to alter the concentration or distribution of the substance in the environment. This also applies for more complex naturally occurring substances like e.g. tinctures made from animal or human material which are used in homeopathic or anthroposophic medicinal products. It is therefore justified to exempt these also from the requirement to conduct ERA studies. To make this sufficiently clear, such tinctures should be added to the list of examples. Proposed change (if any): In the case of medicinal products comprised of naturally occurring substances such as vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates, lipids and tinctures from animal or human material, as active pharmaceutical ingredient(s) (API), the ERA may consist of a justification for not submitting ERA studies, e.g. that due to the physico-chemical nature of the API these products are unlikely to pose a risk to the environment or based on	Not agreed Rationale: The current wording of Q 1 is considered sufficiently clear as it is already stated that "*As defined in Directive 2004/24/EC, the same criteria apply to herbal medicinal products. However, there may be exceptional cases where further justification for the absence of studies might be necessary, e.g., when a compound is classified as being a carcinogen, mutagen, or toxic for reproduction (CMR) or PBT/vPvB (see section 5).*"

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		the environmental fate and/or common presence in the environment these products are unlikely to alter the concentration or distribution of the substance in the environment.	
216-222	20	We do not agree that being a naturally occurring substance is reason to terminate the risk assessment. Many natural substances give cause for concern, such as antibiotics and hormones. It is difficult to see how a reliable conclusion can be reached in the absence of the data that would need to be submitted for other APIs. Will this exemption apply to substances that are naturally occurring but synthetically produced or only if extracted from organisms? What about modified naturally occurring molecules? Also, how will stereoisomers be addressed, as they have in many cases been demonstrated to have different effects, and that while molecules of biological origin often will have predominately one direction, synthetic molecules will often be a mixture. Further, how will the natural presence of a substance be proven and how will the term natural be defined? Proposed change (if any): reconsider if such broad exemptions are warranted.	Not agreed. Rationale: The descriptive text for Q1 below Figure 2 covers these aspects. The applicant must provide justification for not providing ERA studies.
223	17	"The same criteria applies" Proposed change (if any): "The same criteria apply"	Agree, text edited.
223	27	typo	Agree, text edited.

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		Proposed change (if any): change criteria into **criterion**	
226	22	The concept of CMR might need further clarification.	CMR is explained under Definitions.
228	1	Comment: The criteria for requiring a justification for exclusion for adjuvants needs to be defined clearly and should include only those for which data already exist in other frameworks and indicate a potential risk. Proposed change (if any): Clarification needed either for the inclusion or exclusion of adjuvants.	Text edited. Criteria for the absence of ERA studies for adjuvants of vaccines are given.
230	27	typo Proposed change (if any): change 2001/83 EC as amended into **2001/83/EC, as amended**	Text edited.
231-232	16	Comment: According to Directive 2001/83/EC as amended, applicants are also required to submit an ERA for applications under Art 10(1) and 10(2) - generic medicinal products. … We have accessed the ERAs of all authorised pharmaceutical products and note that many EPARs state the ERA will be done post approval; and, some ERAs included in the EPAR even state CHMP critical remarks of the applicant not performing an ERA. Proposed change (if any): According to Directive 2001/83/EC as amended, applicants are also required to submit an ERA for applications under Art 10(1) and 10(2) -	Not agreed. Rationale: This aspect is covered by questions 2b and 2c of the decision tree.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		generic medicinal products (if there is a completed ERA and the data is shared)	
235-241	2	The environmental risk assessment (ERA) according to the current guideline (1) as well as in the proposed revised version (2) is mandatory for each dossier, and as such regarded as product specific. However, an identical ERA outcome for all products containing the same indications, maximum daily dose (MDD) and therapeutic regimen (identical ERA for innovator and generic products) exist. In particular, the ERA phase II studies are API specific and their endpoints are used in ERA reports independent of the product, consequently the ERA does not differ between the innovator and generic products. A generic product itself will not lead to an increased consumption of an active compound (API), because the market demand of a specific API does not change significantly and is independent from the number of Marketing Authorization Holders present on the market. After termination of data exclusivity the market share of the innovator product (100%) divides between the new MAHs resulting in approximately 5-15% for each MAH. Based on the fact that a generic product does not increase the risk for the environment and because of the fact that the ERA is API specific and does not differ between the innovator and generic product having the same indications, MDD and pharmaceutical form, the request for performing an ERA for each generic product does not result in any benefit for the environment, since this result is unnecessary study	Not agreed Rationale: According to Directive 2001/83/EC, applicants are required to submit an ERA for all initial MAAs, applications under Art 10(1)-generic medicinal products are not exempt, likewise an ERA is required for Art 10c-informed consent applications. For environmental exposure market penetration by active substance is considered but the market share of a specific product is not. After termination of data exclusivity, the market penetration can increase. However, Q2b of the decision tree was revised to include the following in relation to generics: "*In the specific instance of generics where data sharing is not agreed, if a relevant ERA3 was considered satisfactory by an EU National Competent Authority and the applicant is able to justify that the scientific conclusions reached for the relevant ERA remain applicable to their generic product, repetition of ERA studies will generally not be required. In such cases, it is expected that appropriate information and/or risk mitigation measures should be included in the product information of the generics (SmPC, PL) and aligned with those reflected in the relevant ERA.*"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		repetitions. These actions are also is in conflict with the basic principles of ERA, where protecting the environment is the main goal, with unnecessary repetition of studies (3R principles). Proposed change (if any): Generic products should be exempt of performing an own ERA, because they do not increase the risk for the environment. If the generic product has the same indications, MDD and pharmaceutical form as the innovator product and also demonstrates essential similarity with the innovator product the ERA conclusions of the innovator product can be applied also for the generic product (cross-reference to SPC and other published documents of the innovator product). This is also the case for new fixed combination products intended for substitution indication where a cross reference to proposed documents of the available mono-compound products can be drawn.	
236-241	15	The experience from data sharing under REACH is that it was often difficult for the parties to reach an acceptable compromise. Will the Agency set up a mechanism to make sure the fees for data sharing is based on the principle of fair, non-discriminatory cost sharing.	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data.
238	1	If the environmental assessment is approved by EMA and a letter of access given, no study reports should be required to be submitted. Underlying study reports should not be required if the filing meets the requirements of Article 10 of	Not agreed Rationale: There may be cases that the studies have not been available to respective assessors, e.g. due to ERA finalization post approval.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Directive 2001/83/EC. In addition, reference to the PAR, EPAR or other previously accepted summary should be acceptable in lieu of the full ERA if it is not available as there is no mechanism of obtaining it. Proposed Change: Remove "(including study reports)"	
239-241	16	Comment: If a generic medicinal product applicant conducts missing studies and/or updates the originator's ERA, it is unlikely that the generic applicant will share the data with the originator or other applicants / MA Holders. Proposed change (if any): If the reference ERA is not complete in accordance with the current guideline (e.g. studies are missing, or increased environmental exposure may be anticipated) the originator should conduct the missing studies and/or update the ERA, and be required to make this data available to the public.	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data. It should be considered that there is no legal basis to make ERA issues conditional" Update of ERAs depends on voluntary actions."
239	48	Comment: A letter of access is mentioned. Are there any plans for a regulating the cost reimbursement mechanism as this has been a challenge under REACH?	This guideline cannot provide legal obligations to share data, but only encourage companies to do so, for example following the industry's own e-ERA proposal under the EcoPharmacoStewardship programme. It is not the remit of EMA but of the industry to design a procedure for sharing of data. Competent authorities are not allowed to share data.,
242	48	Please consider adding the following text: The market penetration factor (Fpen) is defined as the percentage of the population receiving the active substance daily. The default value when calculating the PEC_{SW} is 0.01, reflecting	Text edited. **The market penetration factor (Fpen) is defined as the fraction of the population receiving the active substance daily.** If the default Fpen (0.01) was used in this earlier risk assessment…

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1% of a population. This value may then be refined as per text under Q6	
243-244	7	Implication is that a revised ERA is required where the indication has changed but the default Fpen was used previously. It is unclear what would change in such an assessment? If no new prevalence data is available, then the default Fpen would still apply. Proposed change (if any): If the default Fpen (0.01) was used in this earlier risk assessment, and provided that the ~~indication~~ dosage is the same, the outcome of the risk assessment will not change and the risk assessment stops. However, if a refined Fpen was used, this Fpen may change and thus the outcome of the risk assessment may change.	Text edited. If the default Fpen (0.01) was used in this earlier risk assessment - and provided that the ~~indicationindication and dosage~~ **dosage of the new indication is** the same - the outcome of the risk assessment will not change and the risk assessment stops.
245-246	27	Additional clarification proposed. Proposed change: However, if a refined F_{pen} was used, the applicant should verify if the respective F_{pen} is still appropriate, and if not, update accordingly (see Q6). The outcome of the risk assessment may change.	Text edited. However, if a refined Fpen was used**, the applicant should verify whether the respective F_{PEN} is still appropriate, and if not, update the F_{PEN} accordingly (see Q6).** The outcome of the risk assessment may change.
251-255	1	Could the Agency clarify whether the revised ERA should be provided to the previous Member States as well?	If a new MS is added in an MRP or DCP procedure which changes the prevalence data and the refined Fpen, a variation would be required to update the ERA for all MS.
251	27	typo Proposed change (if any): add space between If and a	Cannot find typo.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
256-260	1	Could clarification be given about what is considered to be a non-natural peptide? Are these examples or a comprehensive list? Is the guideline only considered relevant with conjugation and/or increased biostability? Proposed change: Clarification is needed as outlined above.	It is outside the scope of the ERA guideline to list all or a large number of possibilities (e.g. all possible chemically modified peptides). In case of uncertainties, it is generally the responsibility of the applicant to justify their choices.
257	17	Please define non-natural amino acids. When is an amino acid non-natural? How many and what type of modifications should have been made to the molecule to make it non-natural? Proposed change (if any): consider including a definition for non-natural amino acids.	It is outside the scope of the ERA guideline to list all or a large number of possibilities (e.g. all possible chemically modified peptides). In case of uncertainties, it is generally the responsibility of the applicant to justify their choices.
262-263	13	The sentence is strange. Pharmaceuticals are released into sewage and enter the environment via STP. A pharmaceutical does not enter a STP via the environment. Proposed change (if any): Change of environment and STP resulting in: … that they will be quickly degraded in STP and will not enter the environment.	Agreed. Text edited.
263	12	"will not enter STP". Two lines later the OECD 301 test is mentioned. This is a test with sewage sludge and it cannot be concluded based on that test that a substance will not ENTER the STP. Proposed change (if any):the substance will not LEAVE the STP if passing the 301 test.	After text edit in line 263, it is not necessary to mention the 301 test specifically.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
263	22	Please define STP.	STP has already been defined earlier in the document.
263	27	'will not enter the STP' is an incorrect statement. The additional screening step proposed (ready biodegradability testing) is agreed, but it models behaviour in the STP. Hence, the outcome demonstrates whether or not the substance is emitted into the environment after STP passage in appreciable amounts. Moreover, note that a ready substance still passes the STP in small amounts: ready biodegradable does not mean zero emission. Proposed change: replace 'will not enter the STP' with will not enter the environment in substantial amounts.	Text edited
263	29	We propose to change the compartments "environment" and "STP". If an active substance is quickly degraded in the STP it will not enter the environment. Proposed change (if any): '…will be quickly degraded in the STP and will not enter the environment"…	Text edited
264	13	High doses of a pharmaceutical have to be applied to get sufficient high amounts to the target. Is it guaranteed that amounts < 10 % don't affect soil organisms?	While there are no absolute guarantees, the 10% threshold is considered to provide a conservative limit and follows the EMA approach for what is considered relevant metabolites (>10% of administered dose).
264-265	20	Comment: does the 10% relate to the unchanged substance or also to metabolites and conjugates? Proposed change (if any): clarify	Phase I only considers unchanged substances. Proteins and peptides are not considered to form Phase II & II metabolites in the same sense as chemical compounds in the ERA.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
266	27	typo applicable for the active Proposed change (if any): change applicable for into applicable **to**	Agreed, proposed change implemented.
266-270	36	Antineoplastic (cytostatic) compounds are missing from the list of 'active substances with a specific mode of action' that should undergo a tailored risk assessment. Proposed change: The list of example active substances that can affect environmental organisms at concentrations < 0.01 µg/L should be supplemented with at least antineoplastic (cytostatic) compounds. See further comment.	Not agreed Rationale: The currently available information on antineoplastic substances does not show that they have effects below the action limit (see Schwarz et al., 2021 (Environ Sci Eur 33:68)). Thus, for these substances the action limit applies.
267-270	17	This section deals with substances that may affect environmental organisms below the action limit. The focus is on EAS and antiparasitics (which are also named antibiotics in the document). In the existing guideline, EAS were indicated as examples – implying that other types of substances that may affect reproduction below the action limit should also be considered. Although the Q&A documents later explained that the assessment for specific concern was mainly aimed at sexual endocrine disruptors, it was never really clear if other types of substances should be included as well. Does the new proposal mean that the tailored assessment is restricted to endocrine active substances and antibiotics, and that other types of substances do not need to be considered for potential concern below the action limit?	Antiparasitics are not replaced by antibiotics, since these are different types of substances with different indications, therefore a specific assessment strategy applies for each. Antiparasitics enter Phase II regardless of their PEC, the action limit does not apply to these substances. For antibacterials (antibiotics), the action limit applies but they need tailored testing (see Q 7). Text changed and table added to section 3.2.1 for better guidance. It is explained that there may be other substances for which the action limit does not apply. Applicants are encouraged to seek Scientific Advice in such cases.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Replace antiparasitics by antibiotics; include further lines of guidance on other types of substances for which the action limit is not applicable (if intended).	
269	1, 22	Antiparasitics appears in the text again. Should this read "antibacterial" or "antibiotics"?	It should read antiparasitics. Text has been edited for better guidance.
274	27	typo: receive Proposed change (if any): change receive into **receives**	Text edited.
274	45	For some common diseases, e.g. diabetes mellitus, the prevalence may be higher than 1%. If the worst possible scenario should be the basis, then the proposed percentage is too low.	The default Fpen is based on a 95 percentile. More information can be found in the Note at the end of the first version of the guideline.
280 (Eq 1)	10	Equation 1 is used to calculate the PEC_{SW} value in mg L^{-1}. This value must then be compared and evaluated against the action limit of 0.01 µg/L. For the purpose of simplicity, it should be explicitly stated that a conversion from mg L^{-1} to µg L^{-1} is required before evaluation with the action limit can take place. Alternatively, the equation could be modified such that the end result is automatically calculated in µg L^{-1}, e.g. by requiring the daily dose to be employed with the unit µg inh^{1} d^{1}. It makes little sense to provide an equation which calculates a value which then has to be converted before evaluation of the result can take place. It should be possible to directly compare the result of the equation with the action limit.	No change to the guideline. Rationale: All equations relate to ECHAs "Guidance on Information Requirements and Chemical Safety Assessment Chapter R.16: Environmental exposure assessment" (2016). For better transparency the same units have been used. Dosages in SPC are usually also given in mg/L which can be used directly in the calculations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
280, 332, 544	21	Fpen is related to the fraction of the population using the product and emitting to one STP or directly to a surface water body (i.e. 10000 inhabitants in the standard modelling environment = Ninhab). The number of inhabitants is not shown in the equation since it is evened out by the number of inhabitants creating the daily wastewater amount (= 10000 inhabitants = Ninhab). The equation as provided is correct but seems a bit confusing since Fpen, related to a population, seems to be applied to only ONE inhabitant. Proposed change (if any): Either change the equation into DOSE x Fpen x Ninhab / WASTWinhab x Ninhab x DIL or add an explanation e.g. in a footnote that Ninhab is evened out in the equation as the equation provided is already a shortened version and presumes already a calculation step.	Text edited. The PEC_{SW} is calculated using default values and the following assumptions: • 1% of a population receive the active substance daily. • The sewage system is the main route of entry of the active substance into the surface water. **The calculation is based on an average wastewater flow of 200 L per inhabitant per day for a population of 10 000 inhabitants.**
282	2	It is not clear on what maximal daily dose (MDD) should be used in the PECsw calculation, when the initial (loading) dose is different to the long-term dose. For example when a starting dose (lasting 2 weeks) is 100 mg/day, after which the patients switches to 40 mg/day (lasting several years). Additionally in the case of specific drugs that are used intermittently *"… (such as antibiotics), an assumption of constant daily use will produce an overestimate of the PEC"* (1). For these cases a further explanation is required on what MDD should be used in the PECsw calculation.	Not agreed Rationale: Q5 with Equation 1 should base on the maximum daily dose of the active substance. All treatment regimes and dosing schemes which are clearly documented in the SPC can be used for refinement in Q6.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): We propose that the maintenance dose is to be used as the MDD for the PECsw calculation since, the environment is mostly exposed to this dose level (with regards to duration of treatment).	
282	7	All tables listing parameters used in calculations have no references. Previously the guideline had references included. Proposed change (if any): Suggested that references for all default values are included to maintain continuity and historical traceability of the source of defaults. – THROUGHOUT	Not agreed Rationale: All equations relate to ECHAs "Guidance on Information Requirements and Chemical Safety Assessment Chapter R.16: Environmental exposure assessment" (2016).
282, Table	27	Comment: $DOSE_{AS}$ has an incorrect unit. The dose is expressed in mg per patient per day, not mg per inhabitant! This is corrected in Eq 1 by using the (correct) unit for F_{pen}: patient per inhabitant (pat inh^{-1}). See page 12 of EMA/CHMP/SWP/44609/2010 Rev. 1 (Q&A on ERA) where this is already specified. F_{pen} is the ratio of the number of patients per total number of inhabitants in a region. Proposed change: adapt the following units throughout the document: • $DOSE_{AS}$ from mg inh^{-1} d^{-1} to mg pat^{-1} d^{-1} • F_{pen} from [--] to pat inh^{-1}	Agreed. Text and equations edited.
282	29	The table below line 282 introduces the dilution factor DILUTION. The actual value of 10 is proposed. There is strong evidence, that at least for German rivers this factor	See also comment from stakeholders 25 and 26 to lines 292-293 (Q6) and lines 512-513. No change to the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is significantly smaller if representing a realistic worst case default. Please cp. DOI: 10.1016/j.scitotenv.2017.04.180	Rationale: The default value has not been changed to be in line with other legislatives which also refer to the dilution factor given in ECHA Exposure Assessment Guideline (R16). If the dilution factor will be revised by ECHA amendments will be made for human pharmaceuticals as well.
282-283	34	Values of default factors used in Phase I decision tree: Two of the parameters used in eq. 1 (lines 282-283) seem to be on the rather "non-conservative" side: First, a dilution factor of 10 is rather high. In small streams, it can be as low as 2. Second, the amount of wastewater per inhabitant and day (i.e., 200 L/d*inhabitant) seems too high. In most European countries, actual household wastewater is much lower (e.g. water use in Germany 120 L/d*inhabitant, in France 140 L/d*inhabitant, Eurostat, Water statistics). 200 L might be a valid value if industrial wastewater is included, but this is not a reasonable assumption here since the risk assessment is targeted towards assessing exposure to activate substances originating from human excretion. Both of these values should be checked against available data, and most likely lowered to make for a sufficiently conservative phase I assessment.	See also comment from stakeholders 25 and 26 to lines 292-293 (Q6) and lines 512-513. No change to the guideline. Rationale: The default values has not been changed to be in line with other legislatives which also refer to the dilution factor and the amount of wastewater per day given in ECHA Exposure Assessment Guideline (R16). The amount of wastewater per inhabitant and day is the sewage flow rate including not only household wastewater but also industrial wastewater which is produced in a standard town of 10 000 inhabitants.
282	46	The default value for F_{PEN} is set to 0.01 which means that not more than 1% of the population will ingest the drug. This is OK for nearly all HMPs but not for pharmaceuticals against flu and other diseases with possible epidemic outbreaks. For such HMPs a F_{PEN} of 0.05 is proposed.	Not agreed Rationale: see comment line 274

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
285	22	A medicinal product is not necessarily prescribed but could be available over the counter. Proposed change (if any): Consider replacing "prescribed" with "recommended".	Text edited. it is assumed that the medicinal product is unlikely to represent a risk for the environment following its **recommended** usage in patients and no further risk assessment is required.
285	27	typo 'risk for the environment' Proposed change (if any): change risk for the environment into risk **to** the environment	Text changed
287-338	2	The PECsw uses the maximum daily dose (MDD) and Fpen default value of 0.01 which results in a PECsw above the phase II trigger value for the majority of the currently available APIs on the market. The currently proposed PECsw refinements based on prevalence data and treatment regime are disease and not API specific. Meaning that available prevalence data do reflect the distribution of a particular disease/illness within a population for a certain period. But the available prevalence does not necessary correlate with the amount of population that was actually treated with the particular API. Additionally, several different APIs may be prescribed for the same indication. Proposed change (if any): The possibility of PECsw refinement based on prevalence data may be additionally upgraded with API prescription data for a particular indication.	Not agreed Rationale: It should be noted that the PEC initital in Phase I is a trigger value which should be based on worst case assumptions: Prescription data as also sales data are subject to annual fluctuations and do not consider 100 % market share (compare EMA/CHMP/SWP/44609/2010 Rev. 1, Q4.). Additionally, for new active substances only prevalence data gives a reliable forecast for a realistic worst case environmental exposure scenario. For risk assessment further refinements are available in Phase II.
287-331	27	In this section, in most cases 'the F_{pen}' can be replaced by 'F_{pen}'.	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): change 'the F_{pen}' into F_{pen} in cases where this is appropriate.	'the F_{pen}' has been changed into F_{pen} in cases where this is appropriate.
287-338	30	Q6: the PECsw can be refined already at Phase I. This is not acceptable so far the scientifically unsound trigger value of 0.01 µg/L exists. Proposed change (if any): Delete the PECsw refinement from Phase I.	Not agreed Rationale: The current action limit is still appropriate as demonstrated in a publication by Schwarz et al (2021) - https://doi.org/10.1186/s12302-021-00503-0. The refinements in Phase I are limited to prevalence and are a scientifically sound solution for rare diseases.
289	18	For medicinal products which can be used for more than one indication, the calculation of refined PEC_{SW} should take into account all designated indications for the product.	Text edited. For medicinal products which can be used for more than one indication, the calculation of refined PEC_{SW} should consider all designated indications for the product.
289-292	26	Very important information is stated on lines 289 - 292: "*For medicinal products, which can be used for more than one indication, the 289 calculation of refined PECSW should take into account all designated indications for the product. The 290 total PECSW is the sum of the PECSW for each indication, which should be calculated using the maximum 291 prescribed dose for each indication.*" This should be brought up more clearly in whole document", not only in section 4.1.	Not agreed Rationale: The consideration of all designated indications applies only if the PECsw will be refined. For the unrefined PECsw the Fpen of 1% covers all indications. If further refinement is needed in TIER B references to refinement options in Phase I are given already (see section 4.2.3.2.).
292-293	25, 26	The default values aim to represent national/EU-wide average conditions, and not a worst case exposure scenario. The values used in PEC-calculation vary greatly between countries, and per capita water consumption of 200 l/d is often an overestimation. Also the dilution factor	Not agreed Rationale: See similar comments to lines 282-283 (Q5).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		depends completely on environmental conditions, and in some cases may be close to zero. Due to these uncertainties, the PEC-calculation may result in underestimations. It should be possible (and encouraged) to take regional differences in environmental conditions (such as dilution factor) into consideration, e.g. in a similar way as regional consumption differences are instructed to be taken into consideration on rows 302-303. Proposed change (if any): "The other default values *represent estimated average conditions in the national/EU-wide scale, and may be replaced with more relevant ones representing local conditions, or when estimating worst case exposure scenarios.*"	
295	22	Parasiticide again (see previous comment on antiparasitics). Proposed change (if any): Replace "parasticide" with "antibiotic".	No change to the guideline but text edited from "paraciticide" to antiparasitics. Rationale: Antibacterials are covered by Q7.
296	22	A medicinal product is not necessarily prescribed but could be available over the counter. Proposed change (if any): Consider replacing "prescribed" with "recommended".	Text edited.
297-312 and 522-527	5	It states that the PEC_{SW} can be refined but only assuming 100% disease prevalence or market share on a daily basis. This assumption is unrealistic and will result in over-	Not agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		estimating the risk to the environment. In many cases the disease prevalence is over 1% of the population which would exceed the default PEC value, limiting its utility. In reality, the active pharmaceutical ingredient is only prescribed to a fraction of the disease population on a daily basis. In addition this guidance is a big departure from the current EMA ERA guidance which recommends using sales/marketing data to revise the PEC_{SW}. Proposed change (if any): We recommend instead of assuming 100% prevalence or market share that sales/marketing data be used to derive the refined PEC_{SW}. This is consistent with current EMA guidance.	Rationale: In the current EMA guidance market data are not allowed for Fpen refinement, compare EMA/CHMP/SWP/44609/2010 Rev. 1, Q4.
303-304	22	It is not agreed that prevalence data from the member state with the highest prevalence can not be used if this member state is not involved in the authorisation procedure, since this will represent an acceptable refined worst case. Proposed change (if any): Delete this sentence.	Not agreed Rationale: This approach in not new, it is unchanged from what was included in the Q&A document (EMA/CHMP/SWP/44609/2010 Rev. 1).
309	27	COMP: Add reference to EMAs website where adopted COMP opinions are published Proposed change (if any): Add reference to COMP opinions on EMA website.	Text edited, as adopted by the Committee for Orphan Medicinal Product (COMP; www.ema.europa.eu/en/committees/committee-orphan-medicinal-products-comp).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
314	22	"this is easily done…" assuming that products for single use are only used once a year, that is maximum one diagnostics?	No change to the guideline. Rationale: The assumption that a diagnostic product is only used once per year by 1 % of the population has proven itself since the revision of the Q&A document (EMA/CHMP/SWP/44609/2010 Rev. 1). It is not known that the environmental exposure is underestimated by this.
316-317	29	Change the example for treatment regimen, because too inaccurate "For example, an anti-cancer drug administered for five days in monthly cycles, tTREATMENT equals 5 days and nTREATMENT would be 12 year^{-1}." Proposed change (if any): "For example, an anti-cancer drug administered for five days in a 28-day-cycle, tTREATMENT equals 5 days and nTREATMENT would be 13/year^{-1}."	Text edited. For example, an anti-cancer drug administered for five days in a 28-day-cycle, $t_{TREATMENT}$ equals 5 days and $n_{TREATMENT}$ would be **13**/year^{-1}."
317	48	Please define 'posology' and the context is which it is to be taken into account with the SmPC	Rationale: Posology = the knowledge about how medicines are dosed, is a well-known medicinal term. Information about posology can be found in the product information according to the current QRD templates (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-templates-human) in section 4.2 of the SmPC and section 3 of the PL.
320	27	consultation of clinical experts, preferably those involved in evaluation of the product under assessment is advisable. Add footnote Proposed change: Add footnote after 'independent source.'	No change to the guideline. Rationale: Guidance is considered as clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		*Clinical experts should be consulted where necessary; the ERA is preferably brought in line with the clinical assessment of the product.	
330	20	Comment: Eq2 – this seems to assume that all release to the environment comes from use. Perhaps an additional factor from the, unwanted but still relevant, practice of flushing medicines should be included?	No change to the guideline. Rationale: See comments line 296 and 338: '… that the medicinal product is unlikely to represent a risk for the environment following its **recommended** usage in patients …' .
331	22	Include comment that this is the same as Eq1 except for Fpen-refined (consider deleting the descriptions of the parameters in the table below).	Not agreed Rationale: Comment may confuse.
338	22	Consider replacing "prescribed" with "recommended".	Text edited.
339 (and Fig. 2)	22	Is the Q7 necessary? Or are the alternatives already covered by Q4?	Q7 is necessary – it concerns the need for a tailored testing strategy for compounds with a specific mode of action (e.g. endocrine active substances and antibacterials). Q4 also relates to specific assessment strategies, but it concerns the applicability of the action limit. For active substances that can affect environmental organisms at concentrations < 0.01 µg/L, the action limit may not be applicable. These substances enter Phase II regardless of the PEC, (although tailored testing may not be required, e.g. antiparisitics). Text changed and table added to section 3.1.1 for better guidance.
340-341	25, 26	A tailored ERA is required for substances with a specific mode of action. Similarly, a tailored ERA should be required for substances with PBT-properties.	Not agreed Rationale: For all substances, both a risk assessment and a specific hazard assessment for PBT/vPvB properties is required. The tailored testing strategy is part of the risk assessment. The

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			outcome of the PBT assessment does not influence the risk assessment, therefore if a compound is PBT/vPvB but does not meet the trigger value for Phase II risk assessment, no Phase II risk assessment is necessary.
341	1	", … antibiotics" this differs to antiparasitic used elsewhere, could terminology be used consistently or well defined if the difference is intentional.	Text has been changed for better guidance. Antibiotics have been replaced with antibacterial to make the distinction to antiparasitics clear.
344	27	fate concerns environmental fate, in this context. This is the common way of expressing in the field. Proposed change (if any): change fate into environmental fate	Agreed. Text edited.
351-355 and 430-433	45	When using other test guidelines, approaches and methods, it must be clearly stated in the ERA report that they are acceptable.	Justification of all non-standard tests should be provided in the expert report. Section 6.2: *All tests, including non-standard tests, should undergo a reliability evaluation and can only be used if deemed 'reliable' or 'reliable with restrictions'.*
352-355	26	Using different methods may be justified, but the aim should also be to produce information that would enable comparisons between different substances. Proposed change (if any): The following sentences are to be deleted: "*It is recognised that there are other test guidelines, approaches and methods, which are capable of providing an equivalent environmental risk assessment. If methods other than those described in this section are used, a justification*	Not agreed. Rationale: The aim of the assessment is not to compare between different substances.

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		should be included in the Environmental Risk 354 Assessment Report"	
353-355	25	Using different methods may be justified, but one aim should also be to produce information that would enable comparisons between different substances. Proposed change (if any): "If methods other than those described in this section are used, a justification *and an estimation on comparability of the results presented and the results produced by the methods described in this section is to* be included in the Environmental Risk Assessment Report."	Not agreed. Rationale: The aim of the assessment is not to compare between different substances.
356 (Table 1)	1	Vapour Pressure, although not a mandatory study, is required as a parameter in SimpleTreat for soil exposure assessment where soil assessment is triggered. Could there be an option for a default (very low volatility) or *in silico* modelling approach to be used in the first instance? (e.g. EpiSuite) Proposed change (if any): Suggest clarification text is supplied also for the 'not mandatory' studies under section 4.2.1.1. The inclusion of default "worst-case" values or options for non-experimental derivation where possible would be welcomed.	Not Agreed. Rationale: The new SimpleTreat manual in the annex gives a default value for Vapour pressure, which for soil evaporation can be assumed to be negligible. Also, the current GL states that 'If methods other than those described in this section are used, a justification should be included in the Environmental Risk Assessment Report'.
356 (Table 1)	1	Ready biodegradability studies – only OECD 301 is discussed in the table, yet elsewhere in the document it is stated that OECD 301 can be waived for OECD 308/314 as required.	Not agreed. Rationale: Table 1 lists all mandatory tests which are needed for the Tier A risk assessment. The text on ready biodegradability

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		Proposed Change (if any): Please provide further clarification on when and how OECD 308 or 314 will be suitable for replacement of 301 and include all options in the guidelines section of Table 1. The ready biodegradation tests also include the OECD 310 study and this needs to be referenced within the table. It would be useful if in addition, the Agency could confirm that OECD 308 can be waived if OECD 301 shows the compound to be readily biodegradable, as stated in question 8 of the EMA Q&A on the 'Guideline on the environmental risk assessment of medicinal products for human use'.	(section 4.2.1.2) has been edited and amended with OECD 302 and 310 (see also responses on comments for lines 419 and 557). There is more detailed information given.
356 (Table 1)	1	A number of the physico-chemical properties studies listed are regularly performed as part of the standard CMC data package for drug development, but potentially not under either GLP conditions or possibly not according to OECD guidelines. Could clarification be given to the use and acceptance of such data? Proposed change (if any): Allow the inclusion of non-GLP physico-chemical studies generated for the CMC data package.	Not agreed. Rationale: It is stated that "If methods other than those described in this section are used, a justification should be included in the Environmental Risk Assessment Report". In addition, it is added that "All tests, including non-standard tests, should undergo a reliability evaluation and can only be used if deemed 'reliable' or 'reliable with restrictions. (as described in section 6.2)."
356 (Table 1)	1	Fate Properties (4.2.1.2) studies include OECD 106 utilizing 3 soils and 2 sludges. Comments throughout this document question the need for Koc data for soils over or instead of Koc for sediment. Unless there is a scientific justification for 3 data points from soils, changing the OECD 106 requirements to 2 (or 3) of sludges and 2 sediments with the option to include 2 (or	Not agreed. Rationale: The OECD 106 is not formally extended to use sediments. Therefore, this guideline cannot propose to test sediments instead of soils in the OECD 106 test, see also response on comment line 582. However, testing sediments instead of soils can be supported by providing a justification, see also comment above.

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		3) soils should be considered. The availability of sediment partitioning data will inform the sediment ERA and the need for soil partitioning data may not be critical for APIs not requiring a terrestrial ERA. Flexibility should be allowed to conduct sediment exposure modelling using either soil or sediment partitioning data as availability of data may vary; especially for existing APIs. Proposed Change: Adsorption - Desorption Using a Batch Equilibrium Method with 3 soils and 2 sludges should be changed to Adsorption - Desorption Using a Batch Equilibrium Method should be conducted with 2 (or 3) sludges, 2 (or 3) sediments and/or of 2 (or 3) soils when warranted.	
356	1	EMA states that for log Kow, "a calculated value is generally not acceptable." Proposed change (if any): Please describe the circumstances under which a calculated log Kow is acceptable, and the model(s) that may be used. Please provide an analysis that supports EMA's rationale for not embracing QSAR *in silico* modelling.	Not agreed. Rationale: A reliable experimental study is needed, and this situation only applies to rare cases, e.g. when the substance cannot be tested reliably.
356 (Table 1)	12	Under fate properties 4.2.1.2. OECD 106 is suitable for soils only. Sludges cannot be tested according to the scope of the guideline. No guidance at all is given for sludges with the consequence, that test submitted will not be valid as each lab has to find its own way how to deal with sludges (pre-treatment before the test?). So the produced "numbers" are totally useless.	Not agreed but text edited. Rationale: see response for comment on line 582.

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		Proposed change (if any): the KOC in sludges can be estimated by OECD 121. Add here.	
356 Table 1	27	Typo in OECD 201 Proposed change (if any): Add space between OECD and 201	Text edited.
356 + 421-422	7	The text (lines 421-422) regarding the waiving of OECD 301 is not in line with TABLE 1 (Line 356). Suggest that clarity is provided in TABLE 1 as to the acceptable biodegradation data. Proposed change (if any): Update Table 1 to include OECD 314B and 308. Include further clarification text to make clear in which circumstances study data from 314B or 308 would be considered acceptable in place of 301.	See comment above.
356, 680-683, 935	19	*Hyalella* is not mentioned as a standard test organism in the guidance anymore, but used to be in the previous guidance. This may be due to the absence of an applicable OECD test guidance. Recently *Hyalella* is revisited and may become a suitable test organism for a new OECD test guidance (at least for bioaccumulation). Proposed change: Keep mentioning *Hyalella* but make the reservation that it can be used only after a suitable OECD test guidance has been adopted.	Not agreed. Rationale: The test with *Hyalella* has been removed from the guideline as no final version of the OECD draft had been adopted at the time of the revision.

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356	25, 26	OECD 308 has been removed from the list of mandatory tests (table 1). To my understanding OECD 301 covers only aerobic conditions. Therefore OECD 308 would give valuable and more comprehensive information than performing only OECD 301. Proposed change (if any): Include OECD 308 into the list of mandatory tests.	See comment above.
356	36	The OECD 308 test, which was among the recommended tests for assessment of fate properties in the previous version of the guideline, is not included in the list of mandatory tests in Table 1. This test gives critical information on the fate, persistence and transformation of the active substances in the aquatic compartment and should therefore be included in the mandatory tests. Since transformation products are often more persistent than the parent compound (see, e.g., Berkner and Thierbach, 2013), the Ready biodegradability (OECD 301) is not sufficient for assessment of the fate properties. Proposed change: The OECD 308 test should be included in the list of mandatory tests in Table 1.	Not agreed. Rationale: Before the test was used to assess whether sediment testing was needed. Now the test is not needed to assess the sediment compartment. For PBT assessment the test may still be performed.
356	45	It is necessary to have trigger values for toxicity, i.e. when a pharmaceutical is considered to have very high toxicity, high toxicity, moderate toxicity or low toxicity to aquatic organisms (aquatic toxicity [4.2.1.3]).	Not agreed. Rationale: There is no trigger value needed for toxicity to decide on further assessment.
356	46	According to Table 1 and the following text (section 4.2.1.2) in phase II, tier 1 the only biodegradability test to be	Not agreed. See above.

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		conducted is a ready test. This is clearly not sufficient to get sufficient information on the fate of pharmaceuticals which are expected to potentially exceed the action limit of 0.01 µg/L. As hitherto a water-sediment test (OECD 308) is necessary to get sufficient information on fate and is highly recommended.	
356	48	It is unclear why the OECD 302 Inherent Biodegradation Studies have been omitted from the text of the risk assessment. In combination with the OECD 301 studies, they can give you a valuable insight into the microbial density required (increased chance of the presence of the competent degrader being present) in order for biodegradation to occur.	Partly agreed. Text is edited. Not in table 1 but in the chapter below (4.2.1.2), see also response on comment line 557 (Table 5).
360 (4.2.1.1)	22	The non-mandatory characteristics are not further described. When are they supposed to be done? Or are the information only required as "nice to know"?	All three are marked with an asterisk, indicating they are not mandatory.
362	27	This concerns water solubility, which should be added. Proposed change (if any): Change 'The solubility' into 'The water solubility'	Text changed.
364	48	The defined pH range is correct. However, data should be accepted for study data generated in the wider range of pH 4 to pH 9 as this is the environmental pH range for assessment under REACH and Plant Protection Products. This comment is also applicable for the K_{OW}	Not agreed. Rationale: In this guidance the range 5-9 is considered environmentally relevant.
365-366	27	An important notion is that water solubility should be determined before determining the octanol-water partitioning coefficient, see also the introductions of OECD TGs 107 and 123. A small extra sentence is proposed.	Agreed. Proposed change accepted.

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		Proposed change: Aqueous solubility should be determined before determining the octanol-water partitioning coefficient. Both values should be compared to evaluate the plausibility of their respective results. Besides this, information on solubility and partitioning should be taken into account when designing and/or evaluating fate and ecotoxicity tests.	
367	20	For determining the log KOW, considering the crucial role that is given to this single value, not only variation with pH should be considered. Several other factors may also affect the logKOW value; such as salinity and temperature. See also example from literature: http://www.ijesd.org/papers/267-CD0081.pdf Proposed change (if any): Include, in addition to pH, relevant salinity and temperature as factors to describe log DOW.	Not agreed. Rationale: It is not possible to test all possible varying environmental factors, nor to model these effects. Also, other frameworks do not demand such comprehensive Kow testing.
367	27	Octanol/water partitioning coefficient typo: the coefficient is called partition coefficient. The process is called partitioning. Proposed change (if any): Throughout the document: change partitioning coefficient into partition coefficient.	Text edited.
368-372	10	The proposal in the guideline to no longer accept log P values determined using the HPLC method (OECD 117) makes little scientific sense and should not be implemented. In reversed phase HPLC, the retention of analytes on a non-polar stationary phase is based predominantly on the lipophilicity of the particulate analyte	Not agreed. Rationale: The problem is described in section 14. of OECD 117: "It is preferable that these reference substances should be structurally related to the test substance." This is difficult to realize with molecules as complex as active substances often are."

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		and is described by the retention factor, k, according to the equation 1, *Kc* is equal to the equilibrium distribution coefficient of the substance, *Vs* is the volume of the stationary phase and, *Vm,* is the volume of the mobile phase. $k = K_c \frac{Vs}{Vm}$ Equation 1 (Ph. Eur 9.0, 2.2.46) The capacity factor therefore describes the distribution of the analyte between the non-polar stationary phase and the polar mobile phase and is a valid descriptor of the lipophilicity of a substance. It is true that complications may arise for acidic, basic or zwitterionic compounds, which may be pH sensitive, or which may undergo polar interactions with non-endcapped silanol residues on the stationary phase. However, in recent years the development of base deactivated and sterically protected stationary phases has reduced residual silanol interactions in C18 columns to an absolute minimum. Such difficulties do not arise for neutral, non-ionic compounds and the use of the HPLC procedure to measure the partition coefficients of neutral species should be permitted. As an analytical procedure, HPLC is widely used in the scientific community as a valid method for determining log P values and there is a vast plethora of peer-reviewed literature demonstrating its usefulness and validity [1-6] . The shake flask procedure is a laborious, time-consuming procedure requiring relatively large quantities of analyte and octanol, which is classified as an irritant and environmentally hazardous solvent [7]. This is a major disadvantage in cases where only small quantities (pg) of analyte are available, or the analyte is extremely	OECD 117 is only considered as screening method and only results from OECD 117 are not considered sufficient.

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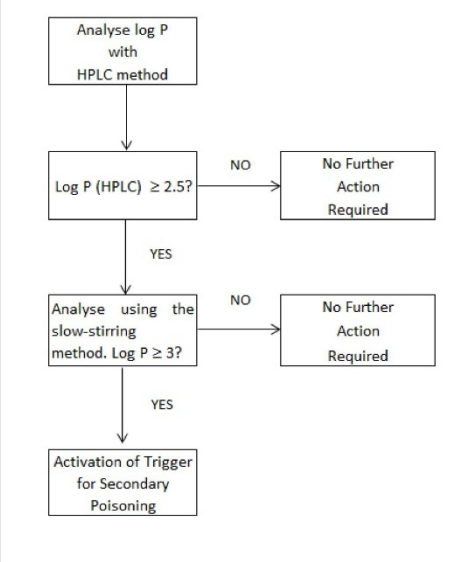
		expensive. Furthermore, The treatment and disposal of octanol is both expensive and environmentally unfriendly. Another disadvantage of the shake-flask procedure is that it is sensitive to impurities in the analyte sample and is not easily used for samples which degrade very quickly in an aqueous environment. In such cases, RP-HPLC is a far superior alternative since pg or ng quantities of substance can be analysed quickly without the need for strong organic solvents. It also has the added advantage of allowing the analysis of several compounds simultaneously. It therefore provides a quick, accurate and cost-effective procedure for measuring and ranking the lipophilicity of neutral molecules. One argument often used against the HPLC procedure is that it is less accurate as compared to the shake-flask or slow-stirring methods. However, the procedure has a documented accuracy of ± 0.5 log P units as compared directly to the shake-flask method in appropriate ring tests [8]. To ban the use of the procedure, *per se,* would therefore be a major mistake. A much better alternative would be to allow the use of the HPLC procedure for substances with log P values up to 2.5, which equivalent to the trigger value for evaluation of secondary poisoning minus the uncertainty of the HPLC measurement, i.e. 3.0 - 0.5 = 2.5. It could be stipulated that all values measured by HPLC up to and including 2.5 are acceptable without further analysis. For values above 2.5, where the true log P value could theoretically be 3.0, the value of the HPLC procedure would need to be confirmed using the slow-stirring procedure. This would allow the HPLC procedure to be employed for non-critical substances. An example of how this might work is provided in the decision tree in Figure 1.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		 Figure 1 Decision Tree for the determiniation of the suitability of the HPLC method Furthermore, we want to encourage to establish a database to publish the data on API (e.g. like octanol/water partitioning) which represent characters of the substances and can be regarded as natural constants. There is no need that these tests are repeated for each application for marketing authorisation. This supports to avoid the use of organic solvents.	
370	29	We propose to delete the sentence for the OECD 117 as it can only be used for indicative purposes. As OECD 107 or 123 are mandatory this information is not required.	Agreed. See response to comment on line 368-372.

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371-372	10	The term "all environmentally relevant pH values" should be specified according to line 378 Proposed change (if any): The octanol/water partitioning coefficient, Kow, should be determined experimentally using the shake-flask method (OECD 107) or the slow-stirring method (OECD 123). A calculated value is generally not acceptable. The results from the HPLC screening method (OECD 117) may only be used for indicative purposes, e.g. for compounds, which are highly soluble and have a predicted log Kow < 1 at all environmentally relevant pH values (at least pH values ranging from pH 5 to 9).	Agreed Text edited: '… relevant pH values (pH 5 to 9)
375-376	27	Proposed to include additional guidance on how to derive an ion corrected D_{ow}. Proposed change: Add a footnote behind 'should be reported' stating: Calculate K_{ow} as ion corrected D_{ow} using the determined D_{ow} value, the pK_a and the pH at which the D_{ow} value is determined by $K_{ow} = D_{ow}$•(1+10^(pH-pK_a)). This is applicable to monoprotic acids and bases for the proton releasing (acidic) reaction. In more complicated situations assistance may be sought by QSAR software or data published in scientific literature.	Agreed. Text edited For dissociating compounds, Log Dow values should be determined as a function of pH covering an environmentally relevant pH-range (at least 3 pH values ranging from pH 5 to 9), e.g. by measuring the pH-lipophilicity profile (log D as function of pH). In addition, ion-corrected log Dow for the neutral molecule should be reported together with the respective dissociation constant (pKa) value(s). The ion-corrected Dow is equal to Kow and can be calculated with Equation 4. For neutral molecules, Dow will approximate Kow. $K_{ow} = D_{ow}$•(1+10^(pH-pK_a) (Eq 4) Footnote [4:] This equation is applicable to monoprotic acids and bases for the proton releasing (acidic) reaction. In more complicated situations,

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			assistance may be sought by QSAR software or data published in scientific literature.
375	29	Explanations on logDow seems confusing. Proposed change: For dissociating compounds, the log D_{ow} for the neutral undissociated molecule (equals the log K_{ow}) should also be determined. This is achieved by choosing the respective pH value as described in OECD 107.	Not agreed. See response above
375	48	Please include the correction equation to calculate ion-correct logD_{OW} in this section. Please also confirm how pKa value should be determined i.e. are computer calculated acceptable and if so which software is preferred?	Agreed. See above response.
376	27	if ion correction of a D_{ow} value is performed, the calculation is done with a single pK_a value. Hence 'value(s)' should be changed into value. Proposed change: change 'value(s)' into 'value'	Agreed. See edited text above.
377-388	5	It states that the Dow value (log Kow ≥ 3) at any pH between 5-9 triggers a secondary poisoning assessment. However, the focus should be on neutral pH (i.e., 7) as this is the most physiological relevant pH in the aquatic environment. Proposed change (if any): Change from logKow at any pH to logKow at pH 7.	Not agreed. Rationale: Other pHs are also environmentally relevant. Therefore, any of the Dow values is relevant for screening of secondary poisoning

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377-381	17	This section is not entirely clear, since the preceding text indicates that for dissociating compounds, an ion-corrected logDow for the neutral molecule should be reported; the ion-corrected Dow is stated to be equal to the Kow. In the last paragraph of this section, it is indicated that the logDow value (at pH 5-9) is directly compared to the logKow trigger. Please clarify. Further, please clarify how the ion-corrected logDow should be derived, as this is not covered by this guideline nor by the test guidelines. Proposed change (if any): Please clarify what value needs to be compared to the logKow trigger: the logDow value or the ion corrected logDow value.	Agreed. See edited text above.
377	27	In this sentence it is better to speak of D_{ow} rather than log D_{ow} as one does not determine a log value in the experiment, but this is a way of reporting and further use only. Proposed change (if any): D_{ow} values should be determined as a … etc.	Agreed. See edited text above.
378	27	This text was taken from the Q&A rev1. Proposed to slightly rephrase as it is not entirely correct, and the phrase 'pH-lipophilicity profile' is redundant. Proposed change (if any): Log D_{ow} values should be determined as a function of pH, covering an environmentally relevant pH-range: at least 3 pH values ranging from pH 5 to 9.	Agreed. See edited text above.
379	27	In this sentence, 'log D_{ow}' should be used	Agreed. See edited text above.

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		Proposed change: If the log D_{ow} value (for dissociating substances) at any pH value between pH 5 and pH 9 meets the trigger values for…etc.	
379-380	27	Behind this statement (when log D_{ow} itself exceeds either of the two triggers), the consequence of the ion corrected log D_{ow} (described one section above) should be added. Proposed change: Add 'or ion-corrected D_{ow} value' (bold below) to the sentence in line 381: If the D_{ow} value (for dissociating substances) at any pH value between pH 5 and pH 9**, or the ion-corrected D_{ow} value,** meets the trigger…	Agreed. See edited text above.
379-381	47	Comment: Lines 379 - 381: D_{ow} and log K_{ow} seem to be used in an inconsistent way. If I understand the message right, the sentence could be rewritten as below: Proposed change (if any): If the log D_{ow} value (for dissociating substances) at any pH value between 5 and 9 meets the trigger values (> 3 for secondary poisoning or > 4.5 for assessment of secondary poisoning), further assessment is required (see Section 4.2.8 and 5).	Partly agreed. Log Kow is the neutral substance, log D both neutral and ionisable. For clarity the triggers are still named with Kow. See edited text above.
382	48	It would be valuable to define in the section how these data are used, variations that can be observed when examining salt over free base/acid form when dosed into Fate and Ecotox studies.	No change to the guideline.

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383-385	17	It is indicated that the dissociation constant is used to verify exposure concentrations in fate and ecotoxicity tests. Please explain what is meant, as verification of test concentrations is usually done using analytical equipment, taking samples from exposure solutions. Is this remark intended to indicate that the pKa can be used to determine what chemical species of the molecule must have been present during the tests? Proposed change (if any): Consider rephrasing the remark on verification of exposure concentrations.	No change to the guideline.
383	27	It is relevant to clarify that the determined dissociation constant(s) should be reported for the acidic (proton releasing) reaction, i.e. as pK_a value. In addition, it should be clarified to which molecular moiety the pK_a value applies, i.e. the reaction of the atom releasing the proton should be given for the reported pK_a value. Proposed change: The dissociation constant should be determined for dissociating compounds and should be reported as acid dissociation constant (pK_a) along with the appropriate reaction in the molecule to which the pK_a value applies.	No change to the guideline.
386 ff	29	In the draft guideline the intended fate assessment in surface water is basically reduced to information about sorption behaviour and ready biodegradability as properties of the active substance. This is not sufficient for assessing fate & behaviour, degradation and transformation of active	Not agreed Rationale: Although it is acknowledged that the OECD 308 study results in a lot of information about the fate of an active substance in the water/sediment system, the information generated with the recommended tests are considered sufficient. The OECD 308 study is an extensive study for which much of the data is not used in the

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		substances and its transformation products in the environment. Keeping OECD 308 in the base data set could be a solution. Data from OECD 308 can further be used to assess the relevance of transformation products for surface water and for groundwater. Consequently, more explanations are required in an own chapter. It is acknowledged that especially OECD 308 has been subject to criticism and that there is room for improvements in terms of the performance of the test, evaluating and reporting the results. Currently, research is ongoing on improving the standardisation, evaluation and transferability of results to environmental conditions in rivers (Fenner et al., 2017 (=P-Ident I Bericht), Honti et al., 2018, https://www.eawag.ch/en/department/uchem/projects/pident2/). Proposed change: New chapter Transformation in water sediment systems OECD 308 provides information on distribution of the substance between water and sediment, on half-life values, transformation products formed, mineralisation and non-extractable residues. Therefore, half-life values in water, sediment and total system, the amount of CO_2 evolution and the amount of NER formed should be reported. Furthermore, the half-life	risk assessment. If however, an OECD 308 study is performed, for example in the hazard assessment, the data may be used.

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		should be calculated for both, active substance and transformation products >10%, if possible. SFO kinetics are preferred, if applicable. The identification and quantification of transformation products are particularly important when a transformation product is present in amounts >10% of the mass balance and/or appears to be persistent, e.g., if it is present at several time points throughout or increasing towards the end of the study. If identification of the molecule is not feasible, it should be documented, and a justification should be provided in the ERA. Extraction methods like pressurized liquid extractions with organic solvents (polarity depends on substance characteristic) are preferred to allow for including potentially reversible fractions from the sediment. Fractioning of humic substances is not required. Determination of the Koc for the sediment used in OECD 308 is preferable as this can help to reduce uncertainties in the evaluation of the study results (Honti et al., 2016).	
386	30	4.2.1.2 Fate studies: In this revised draft GD OECD 308 has been deleted from Phase II A without no explanation. That leads to the situation that there is no information on fate or transformation of the APIs in the aquatic compartment. Even if this study is not used in the risk assessment in Phase II A, it gives essential information about the persistence of possible transformation products. According to the Berkner and Thierbach, 2013, for 45% of the API, transformation products are more persistent than the parent.	See comment above.

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		Proposed change (if any): Add OECD 308 to the Phase II A test requirements	
390-408	1	Given that the sediment risk assessment is now always required it would be considered reasonable to also discuss the use of sediments within the OECD 106 study; and for use of the data in the sediment exposure calculation. Sludge should always be required as this is the trigger for terrestrial assessment. But soil and/or sediment data may be available for some substances. It seems logical to be able to use soil or sediment data, where this is available, for PECsediment calculation. It also appears logical that applicants should be allowed to provide sediment data, either in addition to or in lieu of soil data, for calculation of PECsediment, for example where no terrestrial assessment is triggered. This should be a permissible option and it should be made clear whether sorption and desorption data are required. Proposed change (if any): Recommend that a statement be included to state that adsorption data in sediment can also be considered relevant if data is available; in addition, modify the default requirement for soil adsorption data to allow flexibility for either soil or sediment or both to be generated. Ideally, Adsorption - Desorption Using a Batch Equilibrium Method should be conducted with 2 (or 3) sludges, 2 (or 3) sediments and/or of 2 (or 3) soils when warranted.	Not agreed. Rationale: See also response to comment line 356.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
392	48	Sediments appear to have been removed from solid matrices required in the OECD 106, should it be clarified why sorption assessment in sediment is not required. It should also be made clear that the PEC calculation for sediment is then based on the sorption results from soil.	See also response to comment line 356.
400-402	25	As stated, sorption varies between different matrices. Therefore, using Kd values produced using soil samples might not represent realistic sorption in sediment environment.	See also response to comment line 356.
401-402	27	Adsorption data determined using soil ($K_{oc\ soil}$) are also used in the exposure modelling calculations of PEC_{soil}. This should be added. Moreover, it is more precise to state that these adsorption data are used in the exposure assessment, rather than the risk assessment. Proposed change: Adsorption data for at least 3 soils are needed for equilibrium partitioning calculations in the sediment and soil exposure assessment (Section 4.2.4) and refinement of PEC_{GW} in Tier B (section 4.2.6.2).	Not agreed. Rationale: Koc_{soil} is not used for calculation PECsoil, only Koc_{sludge} (see also response on comment on line 482).
408	48	Propose rewording 'organic carbon content of the soil sample' to organic carbon content of the solid matrix being assessed.	Not agreed. Rationale: Current text is considered simpler and correct.
409 (Table 2 footnote)	1	Please provide the scientific basis for use of the geometric mean values for sludge and soil. Proposed change (if any): Include reference and/or justification for footnote	Not agreed. Rationale: See also response to comment line 584.

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409 (Table 2)	1	Trigger for sediment is identified as Koc soil. Proposed Change (if any): Trigger for sediment should be Koc sediment and/or Koc soil instead of Koc sludge.	Not agreed. Rationale: Sediment risk assessment is always required and not triggered.
409 (Table 2)	1	The data used from OECD 106 as specified in Table 2 is only adsorption data. Where does the EMA see value in the desorption parts of the study? Proposed change (if any): As desorption is not used in the ERA (as continuous exposure is assumed), it should not be mandatory to include this as part of the OECD 106; data should only be requested that is used in the ERA.	Agreed. Tables edited.
409 (Table 2)	27	With regard to table 2. Please add bullets, and one parameter ($K_{oc\ soil}$) for soil, Tier A. $K_{oc\ soil}$ is used in EqP calculations between soil and porewater when PEC_{soil} is calculated; which is contained in $K_{soil\text{-}water}$ in the exposure model. Proposed change: In row 4 (soil), column 2, Tier A, add a bullet: 'PEC_{soil} calculation: $_{Koc\ soil}$ ** is used in equilibrium partitioning calculations between soil and groundwater.'	Agreed. Text edited with bullet points. Not agreed. Rationale: Kocsoil is not used for calculation PECsoil, only Kocsludge (see also response on comment on l 482). Table 2 has changed for revised groundwater risk assessment.
409 (Table 2)	47	Line 409, Table 2. A word seems to be missing in the first column.	Text edited.

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		Proposed change (if any):Heading of the first column: "Absorption **data** needed in Phase II"	
409 (Table 2)	48	Table 2 – Please clarify which laboratory study values are input into calculation and models. Please clarify which values are then generated by the model and are results.	Not agreed. Rationale: These are all OECD 106 studies. What is calculated is given, when necessary.
419	20	OECD TG310 is also a ready biodegradation test and should be considered.	See also comment to table 1 Agreed. OECD 310 added. OECD 310 specifies: this Guideline is a screening method for the evaluation of ready biodegradability of chemical substances and provides similar information to the six test methods described in OECD Test Guideline 301 A to F. Text edited: '... should be determined according to OECD 301 (or 310).'
419-421	25, 26	Pre-exposing microbial communities to contaminants often changes the biodegradation rate. Therefore it should be stated completely unambiguously, whether or not the community should be pre-exposed to the studied substance. Proposed change (if any): "The microbial community *must* not be pre-exposed…"	Not agreed. Rationale: Current text is considered sufficient, stating 'should not'
422-423	27	The results of OECD 301 are used for … add to this sentence: 'the PBT assessment.' In addtion, according to REACH R.11: A substance that is readily biodegradable or if criteria for ready biodegradability are fulfilled with the exception of the	Agreed. Text edited: The results of OECD 301 (or 310) are used to trigger the soil and groundwater assessment, both **as PBT screening information** and in the SimpleTreat calculation.

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		10 day window is generally considered as not fulfilling the persistency criteria (P and vP). But REACH R.11 should always be checked for correct, case by case interpretation. Proposed change: • The results of OECD 301 are used for triggering soil and groundwater assessment, the PBT assessment and the calculation in the SimpleTreat.	
424	27	Please consider to remove the word "classified", as it may cause confusion with regard to the classificaton and labelling framework. Proposed change: Not readily biodegradable substances are considered potentially persistent.	Agreed. Text edited: Not readily biodegradable substances are considered potentially persistent in the PBT screening (see 5.1).
424	27	Add reference to REACH R.11 guidance for this statement, as this is the source upon which it rests. Proposed change: Add reference to REACH R.11	Agreed, edit included.
424 and 1126-1128	45	It is necessary to have trigger values for when a substance is considered persistent and potentially persistent respectively, for the different test protocols used for persistence.	Not Agreed Rationale: The triggers for P are given in Table 16.
425-461	15	It is not clear if section 4.2.1.3 refers to all ecotoxicological studies in the ERA or just the aquatic studies. Comment:	Text edited. "The risk assessment for the aquatic and sediment compartment is based on chronic exposure and effects because the emission of pharmaceutical residues into surface water is assumed to be continuous."

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		There is little information or guidance on sediment or soil studies in the relevant section for those studies. ~~I am guessing this refers to all ecotox studies~~. Many of the soil guidelines do not call for analytical measurements or only in cases where there is not stability in the soil compartment. Consequently, one would be following the guidance if they conducted the test but did not measure composure concentrations. I am unsure if that would be acceptable from a regulatory standpoint based on how the document is currently worded. Proposed change (if any): Suggest clearer and more defined language for this section as it relates to all potential ecotoxicological studies in the ERA.	"Concentrations should be measured analytically. Results should preferably be based on measured concentrations, but nominal concentrations can be used if measured concentrations are within 80-120% of nominal concentrations."
426-441	7	It is appreciated that the application of ECx in risk assessment is being considered in a pragmatic way, for example, where reliable, replacing NOECs even if the value is higher. However, some consideration should be given to whether a 10% effect is the correct level. Little evidence is available, to date, to demonstrate that a 10% threshold for all endpoints is appropriate for risk assessment. The % effect threshold should be chosen based on (i) the relevance of such a change at the population level and (ii) consideration should be given to the ability of the standardised studies to detect such a change.	No change to the guideline. Rationale: The EC10 stipulation is based on, and in line with ECHA REACH recommendation in the R.10 guidance document ("p.11, Table R.10-1") which promotes EC10 over NOEC.

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		Some consideration of this second point has been considered here however the justification of the population relevance of a 10% effect has not been given sufficient consideration. Proposed change (if any): Suggest a proposal for further research in this area is called for and a statement that an EC10 appears appropriately protective in the absence of such justification but the value of x can be amended if data suggests an alternative value is appropriate.	
429	48	It may be helpful to specify that within the "continuous" exposure, there will be peaks and troughs in exposures levels over periods of time.	Text edited.
431	27	to footnote nr. 1 text (the note is contained in this line). a 'reliable endpoint' is too shorthand. Choose different wording. Moreover, 'behaviour' is a very wide description of endpoints. There may be behavioural endpoints that can be linked to effects relevant at population level (e.g. reburial activity), so the gross generalisation made seems not adequate. Consider rephrasing. Proposal given below. Proposed change: Many ecotoxicological behavioural endpoints have not yet been established to indicate changes relevant at population level and have not yet been standardised.	Text edited. [6] *"Many ecotoxicological behavioural endpoints have not yet been established and standardised to indicate changes relevant at a population level. Such endpoints may however be very relevant for neuro-active substances and when standardised guidelines become available, be taken up in a tailored testing strategy for neuro-active substances."*

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432-433	29	Please use the current updated version of Water Framework Directive EQS Proposed change: cite as „European Communities, 2018"	Text edited
432-433	47	Lines 432-433; the reference seems not exactly to correspond to the reference given in the list of References. Could be given more precisely.	Text edited.
434-436	5	It states that if validity criteria should be reported and if not met, the test should be repeated. In many cases, the validity criteria may not be met for practical reasons but a scientific analysis shows that the results are still valid. Automatically requiring re-conducting tests would result in unnecessary testing and use of animals. Proposed change (if any): Please change lines 435-436 to: If the validity criteria are not met, a scientific analysis should be performed to determine if the results are still valid. If the results are not considered valid, then the test should be repeated.	No change to the guideline.
435-436	1	"Validity criteria as described in the test guidelines should be reported and if these are not met, the test should be repeated." This should not necessarily be the default position, particularly for vertebrate studies. Small deviations from validity criteria may be acceptable, for example where large margins of safety exist, or where the ecotoxicity test in	No change to the guideline.

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		question does not drive the assessment (Burden et al., 2017). Proposed change: Validity criteria as described in the test guidelines should be reported and if these are not met, **the validity of the test should be fully justified and considered in the context of the overall risk assessment or consideration should be given to repeating the test (repeat vertebrate studies should be avoided where possible)**.	
437	22	Should there be a requirement to validate analytical methods and including these reports?	No change to the guideline. Rationale: Additional submission of information on analytical methods beyond those mention in the respective OECD technical guidelines is not necessary.
437	44	So that the most appropriate test design is followed, please consider adding the following text: "Special care should be taken when handling 'difficult to test' substances when performing ecotoxicity testing (in particular for any *in* vivo vertebrate testing). For example, if a substance is known to be unstable then a continuous or semi-continuous test design may be appropriate whereby the test medium is refreshed throughout the course of the experiment (noting that analytical measurements throughout the course of the study may be required).	No change to the guideline. Rationale: Such aspects are covered in the OECD technical and guidance documents.
439	1	Please define "reliable concentration – response curve". Is there specific statistical power that should be met in order	Text edited.

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		to use the EC10 value? What specific statistical criteria for model fit is EMA envisioning, recognizing that in some instances, no concentration-response model provides a reasonable fit to the ecotoxicity dataset? Proposed change: More detailed guidance is required on the specific statistical criteria for model fit is EMA envisioning .	Rationale: General recommendations for ECx regression modelling are included in OECD technical documents and do not need to be repeated in the guideline. A short clarification added to text. **New text:** "When a reliable concentration-response curve is observed (see e.g., recommendations on statistics in OECD technical test guidelines), the NOEC as well as the EC10 should be reported."
440-441	15	Line 440 states that EC10s are preferred over NOECs. Comment It is very difficult to get EC10 values for plant studies that are not extrapolated below the lowest concentration. Industry experience is that due to the inherent variability of plant studies, endpoints below an EC20 are unreliable (~~I believe this is why OECD 208 does not require EC10 or EC20 as endpoints~~). Proposed change (if any): To clarify that NOEC values will be acceptable for use in the risk assessment if an EC10 value cannot be determined from the available data.	Text edited. A short clarification added: **"**Unless the quality of the data does not allow the determination of EC10, the EC10 is preferred over the NOEC for PNEC derivation, even if the former is higher than the latter."
442	27	Proposed change: A limit test or a preliminary test is sometimes used to determine the correct exposure concentrations	Text edited.
442-451	27	What guidance can be given for the situation where the limit concentration exceeds the aqueous solubility? It may prove difficult/impossible to derive a concentration response relationship. This situation is not hypothetical. Proposed change:	No change to the guideline. It is up to the applicant to justify that a toxicity test (based in limit concentration or concentration-response relationship) is not feasible due to solubility issues (see also OECD GD23 for guidance).

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		Add guidance for the described situation.	
444-445	7	NOECs are by definition the observed concentrations therefore should not be expressed as ">" or "≥" values. LOECs, where not observed (i.e. no tox at highest concentration), can be expessed as ">" values. Proposed change (if any): If a PNEC is based on an 'unbounded' value, e.g., a ~~higher than~~ study which has a NOEC but no observed LOEC (~~NOEC~~LOEC > X mg/L), the…	No change to the guideline. Rationale: When the limit concentration is a LOEC, then a concentration-response study has to be conducted unless the applicant can prove that this is not technically feasible.
445	48	First use of RQ. Please define. Proposed change (if any): Risk Quotient (RQ)	Text edited. Definition included.
446-448	7	Comment: This will not always be possible for compounds where solubility confounds the ability to test sufficiently high. It should be made clear here that repeat studies (particularly vertebrate) should not **always** be required; it may be more appropriate to refine the PEC in such situations before repeating studies or may be impossible to repeat studies due to solubility or low toxicity Proposed change (if any): Remove "always" and include text to highlight that PECs could also be refined to avoid repeat testing, particularly in the case of vertebrates	Text edited. Rationale: A clarification has been added that states that requirements of experimental studies may be ignored if it is proven that a given study is technically non-feasible.
444	27	extend sentence to be fully clear Proposed change: add text at the end of this sentence:	Text edited.

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		… and no risk is identified when this limit concentration is used to derive the PNEC and risk quotient.	
445	27	a higher than or equal to NOEC (≥) is also an unbounded NOEC. Proposed change: rephrase: 'a higher than or higher than or equal to NOEC (NOEC > X or NOEC ≥ X mg/L)	Text edited.
445	27	in the sentence 'If a PNEC is based on…', the statement: 'would also become' is incorrect. 'Also becomes' is correct. Moreover, If should be replace by when. Proposed change: When a PNEC is based on an unbounded value, e.g., a higher than or higher than or equal to NOEC (NOEC > X mg/L or NOEC ≥ X mg/L), the RQ also becomes unbounded (PEC/PNEC < YY or PEC/PNEC < YY).	Text edited.
454	7, 29	Initial growth rate is incorrect. Proposed change (if any): …~~initial~~ <u>average</u> specific growth rate…	Text edited.
454	27	initial growth rate is an incorrect statement. Please remove initial. The endpoint determined is the specific growth rate. Consult OECD TG 201. Proposed change: replace initial growth rate with specific growth rate.	Text edited. See also comment above.

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454	27	be more explicit here. The endpoint 'yield' is included in the OECD 201 guideline for US purposes. It is not used in the ERA. Proposed change: rephrase as follows: In both situations, specific growth rate is the preferred endpoint. The OECD 201 endpoint 'yield' (biomass) is not used in the ERA, even if the endpoint yield (biomass) results in lower (no-)effect concentration (see also section R.7.8.4.1. in ECHA, 2017b)	Text edited.
456	27	add text Proposed change: The high growth rate of algal cells under optimal laboratory testing conditions makes it possible…	Text edited.
457-458	7	Could clarity be provided to what extent recovery should be disregarded? How is recovery to be determined to have taken place? Proposed change (if any): Provide further clarity	No change to the guideline. Rationale: The algae are supposed to represent all aquatic photoautotrophic organisms (including those with longer generation time). Furthermore, the ERA framework pre-supposes a more or less continuous environmental exposure, limiting the use of recovery scenarios and considerations.
458	29	Editorial issue: please include "studies" Proposed change: "… recovery studies should be disregarded, as algae act …"	Text edited.

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460	48	For endocrine active substances (EAS), the fish early life stage (FELS) test should be replaced by other more sensitive test(s), see section 4.3.2.	No change to the guideline.
467-477	20	Propose to include some text to help make clear the connection between soil and WWTPs	Text edited: Human pharmaceuticals enter wastewater after use and excretion. In STPs, they can be partially or completely transformed into transformation products. In the STP, the parent compound and transformation products are either bound to sewage sludge or emitted with the STP effluent.
468-469	25, 26	As APIs often have an electric charge, they may be effectively bound to solids even when they do not have a high affinity for organic carbon. Also, quickly degradable substances may also pose momentary risks to soil environment (e.g. ethinylestradiol). Proposed change (if any): Please revise the text in a way that does not overlook the potential short-term risks of biodegradable substances.	Text edited: Active substances with high affinity for organic carbon **or solids** have a greater likelihood of accumulating in sludge and ending up in the soil, … Further amendments to the text are not made. Rationale: The current approach does not take biodegradation into account, at least in the first Tiers, as it follows the so-called total residue approach and assumes no degradation/transformation in the STP. However, charged substances may bind to soils despite a moderate or low affinity to organic carbon. The OECD 106 specifically addresses this issue by stating: For ionisable test substances, the selected soils should cover a wide range of pH, in order to evaluate the adsorption of the substance in its ionised and unionised forms. By following the OECD 106, this adsorption issue is covered.
469	27	it should be made more explicit that 'readily biodegradable' is a trigger for not performing soil and groundwater risk assessment.	Text edited: Active substances with high affinity for organic carbon **or solids** have a greater likelihood of accumulating in sludge and ending up

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			in the soil. **In cases where the active substance is readily biodegradable, a soil assessment is not required.**
472	27	statements between brackets (K_{oc} value) is incomplete. It is a combination of overall half life and adsorption coefficient (rather than K_{oc}). Proposed change: change text between brackets: (overall degradation half life and adsorption coefficient)	No change to the guideline. Rationale: While release is dependent on a combination of physical-chemical and fate properties of the active substance, as well as functioning of the local STP. In the context on selecting a pragmatic approach for a trigger value, a few key indicators have been chosen at the first Tier. These are; Koc - determined in OECD 106 test, and the total consumption of the pharmaceutical, here expressed by the PECsw, as there is a direct correlation between Tier A PECsw and the estimated consumption of the HMP (Eq. 3).
474 ff	18	The PEC_{SW} calculated in Phase I does not directly reflect these parameters, as it disregards processes such as biodegradation or retention of the active substance in the STP. Hence, the PECSW is used in combination with Koc to trigger assessment for the soil compartment, see Table 3 and section 4.2.7.	No change to the guideline.
476	27	typo Proposed change (if any): to trigger assessment **of** the soil compartment	Text edited: to trigger assessment **of** the soil compartment
477	46	Section 4.2.6 should be replaced by 4.2.7.	No change to the guideline. Rationale: The soil chapter was moved ahead of the groundwater assessment chapter.
478 (Table 3)	1	From initial investigations into the KOCsludge and PEC_{soil} values resulting from the proposed triggers, it is unclear what justifies these triggers as levels of concern? The	No change to the guideline. Rationale: The trigger value in the draft guideline is discussed in Schwarz et al. (https://doi.org/10.1186/s12302-021-00503-0). The provided data evaluation shows that the new approach assures a higher protection of the terrestrial environment and is

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		resultant KOCsludge values at the different triggers are not equal for example. Proposed Change (if any): In the interest of transparency, the EMA should provide the scientific rationale, and evidence supporting these soil assessment triggers, and cite the peer-reviewed publications that support and validate this approach.	more scientifically sound. However, if a reliable database is available in future, obtained in compliance to the data requirements of the new guideline, a refinement of the trigger value at a later time stage might be possible.
478	1	The science and risk-based evidence to justify revising the soil triggers from current values is unclear. The VICH veterinary medicines guidelines has a PEC_{soil} action limit of 100 µg/kg. To increase harmonisation between the human and veterinary medicines guidelines, a common soil PEC Action Limit should be considered. It is considered reasonable to align this action limit for both guidelines and is possible to calculate a PEC_{soil} before triggering further testing. Initial investigations of available soil organism toxicity data with pharmaceuticals (limited data set from 3 companies) indicate that this limit would be a highly protective limit. 15 human pharmaceuticals – Lowest NOEC > 1 mg/kg (most well above 10 mg/kg) Proposed change (if any): Align the soil triggers with veterinary medicines guideline, impose a PECsoil action limit of 100 µg/kg where Kocsludge <10000 or Kdsludge <3700	No change to the guideline. Rationale: The precautionary approach is agreed but the entry paths of veterinary and human pharmaceuticals to the soil environment clearly differ, which is reflected in different trigger values. Veterinary pharmaceuticals enter soil directly via faeces, therefore a Phase II assessment is triggered without considering data on the fate of the active substance (e.g. Koc). Human pharmaceuticals enter soil bound to sewage sludge after a residence time in the STP, therefore data on biodegradation and adsorption are considered. More information on the trigger for the soil assessment can be found in the supporting information of Schwarz et al. (https://doi.org/10.1186/s12302-021-00503-0).

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478	17	There is a typo for the higher Koc sludge value in the fourth row of the table: 5,0000 should be 5,000 Proposed change (if any): Correct typo	Text edited: **5,000**
478	18	Table 3: Combined trigger values for substances entering a risk assessment for soil organisms *It is appreciated that PEC is now taken into account in addition to Koc regarding the trigger for studies in soil organisms*	Comment noted.
478-479	20	Table 3 – Use Log-values for consistency and to be in line with other texts	No change to the guideline. Rationale: The GL revision is consistent with the current guideline.
478	25, 26	The trigger values should also take persistence and ecotoxicity into consideration. E.g. carbamazepine (reported Koc-values ranging from ~100 to ~1300) has been estimated to have the potential to accumulate into soil and cause risk to the soil environment, when sewage sludge is applied repeatedly. According to the trigger values presented in table 3, this substance might be overlooked, depending on the Koc-result. While carbamazepine is not one of the substances with the highest affinity for solids, it may be rather persistent. Proposed change (if any): Please revise the trigger values so that they also take persistence and ecotoxicity also into consideration.	No change to the guideline. Rationale: An additional revision of the soil trigger is not applied. While the importance of persistence and ecotoxicity is acknowledged, the request for additional (laborious) studies in Tier A data is not be supported. The use of exposure-based trigger values is a pragmatic approach, as such triggers are introduced in order to avoid unnecessary (ecotoxicological) testing.

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478 (Table 3)	27	There is an error in header of Table 3. The risk assessment is not performed for soil organisms. The protection goal is the soil ecosystem (and its functioning), which is usually denoted as 'soil compartment'. Proposed change: Table 1: Combined trigger values for substances entering a risk assessment for the soil compartment.	Text edited: Table 3: Combined trigger values for substances entering a **Phase II** risk assessment for the soil **compartment**.
478 (Table 3)	27	Add ready biodegradability as a criterion	No change to the guideline. See comment above.
478 (Table 3)	27	The word trigger in the 2nd row causes confusion and can be left out. In the 1st row below the header, the entry should rather be: 'all PEC_{sw} values'. The entry in the last row is confusing. The meaning of the current text to us seems to be equal to that in the 1st row. However, with respect to the last row, we believe that this is erroneous. A risk assessment for the soil compartment is triggered when appreciable amounts of active are emitted to the STP and adsorb to sludge. This is not the case when $K_{oc\ sludge}$ < 1000 L/kg. In these situations, a risk assessment for 'soil' should not be performed. The current statement means that even for hardly adsorbing compounds with very low PEC_{sw}, a soil risk assessment is triggered. This cannot be the intention. Proposed change in table: • replace 'Trigger irrespective of PEC_{sw}' with '**all PEC_{sw} values**'	Text edited: Due to changes in groundwater assessment, table 3 has been revised. Table has been extended with clear guidance regarding which risk assessment for soil and/or groundwater is required.

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		• in last line of Table e.g. state 'No risk assessment for soil'.	
478 (Table 3)	27	We have performed modelling to validate the background of the proposed trigger values. This led us to assume that modelled soil-porewater concentrations are probably the basis of the proposed $K_{oc\ sludge}$ – PEC_{sw} combinations. We can support the use of soil porewater concentration as the actual trigger for performing a soil risk assessment. But explanation on the background of these triggers is highly desirable. Proposed change: Add text explaining the basis of the trigger values in Table 3 (presumably the link to corresponding porewater concentrations).	No change to the guideline. Rationale: More information can be found in SI of Schwarz et al. (https://doi.org/10.1186/s12302-021-00503-0).
478	48	Table 3 – It is could to see these values presented in this way. However further explanation is needed to indicate how to interpret and understand what these trigger values mean and how they are then used.	Comment noted. Table 3 has been updated.
482, 729	21	Concerning the need of performing a groundwater assessment, please find for your information the following document including similar decision criteria for biocides: https://echa.europa.eu/documents/10162/22002949/cut-off_criteria_for_groundwater_assessment_of_biocides_en.pdf In summary: For biocidal active substances the cut-off criteria **DT50 <21 d** at 20°C and **Koc >500 L/kg** are used for application rates up to 100 kg a.s./ha per year. For	This information is appreciated. The most relevant entry into the groundwater is considered to be via bank filtration. The cited cut off criteria from biocides assessment are for groundwater leaching and therefore not applicable. Furthermore, the cut off criteria have been derived for groundwater concentration of 100 ng/l as limit value. In this legislation the PECgw is needed for risk calculation even if PECgw < 100 ng/L.

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		substances fulfilling these properties, no leaching to groundwater is expected (validated by FOCUS simulations). Proposed change (if any): For information, take into account when considered appropriate.	
482	27	The K_{oc} trigger for a groundwater assessment should not be based on $K_{oc\ sludge}$. This specific partition coefficient is determined on activated sludge, while entry into groundwater (either via bank infiltration of surface water, or via equilibrium partitioning via soil) is described much more accurately with a K_{oc} determined using soil as adsorbing matrix. The properties of activated sludge are very different from soil and lead to different K_d as well as (normalised) K_{oc} values. Proposed change: • replace $K_{oc\ sludge}$ with $K_{oc\ soil}$ • add a footnote to $K_{oc\ soil}$ stating: n_{soil} ≥3: geometric mean, n_{soil} <3: worst-case (lowest K_{oc}).	No change to the guideline. Rationale: The Koc trigger for soil and groundwater assessment bases on a Koc derived on sludge because it describes the partitioning in a sewage treatment plant between sewage sludge (relevant for terrestrial compartment) and the aqueous phase (relevant for aquatic compartment) more accurately than a Koc derived from soil. However, the section on groundwater triggering has been redrafted. Triggering of groundwater assessment via two exposure routes is now foreseen in a combination of Koc sludge and PECsw.
485 and 907	1	The potential for harmonising the log Kow trigger for an OECD 305 Fish Bioconcentration Study with the veterinary ERA guidelines should be considered. In principle, the triggers for evaluating the potential for secondary poisoning and PBT assessment should be the same with a trigger of log Kow ≥ 4.5. The log D vs. log BCF for 46 pharmaceuticals were reviewed by Constantine et al. (see Appendix B) and support use of BCF trigger equal to log D ≥ 4.5 determined at 1 or more relevant pH's.	No change to the guideline. Rationale: This approach is in line with trigger for secondary poisoning for EQS as defined in section 2.4.3.1 of Guidance Document No. 27- Deriving Environmental Quality Standards - version 2018 (https://rvs.rivm.nl/sites/default/files/2019-04/Guidance No 27 - Deriving Environmental Quality Standards - version 2018.pdf)

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		However, in keeping with the EMA CVMP/VICH Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (Nov 2004), Section 3.3.2, a Phase II BCF trigger of log Kow ≥ 4.0 is appropriate for human medicinal products. Please note there is no scientific basis for human medicinal products to have a lower trigger for fish BCF studies than any other chemical class. Proposed change (if any): Harmonise the trigger for a Phase II fish bioconcentration study and secondary poisoning assessment with the veterinary medicines ERA guideline; specifically revise the trigger from log Kow ≥ 3 to ≥ 4.0. Alternatively, harmonise to REACH and PBT assessment with a log Kow >4.5 trigger limit. If the current trigger limit is to remain with a log Kow ≥ 3 then scientific opinion and rationale should be publicly available to support this decision.	
485	27	The trigger for performance of a secondary poisoining assessment is not correct. Line 485 does not match with section 4.2.8, lines 907-915, where the correct route is explained. At log K_{ow} ≥3, performance of a BCF study should be triggered. If the outcome of the BCF study is a BCF ≥100L/kg, assessment of secondary poisoning is triggered. Proposed change: Adapt trigger as described above.	Text edited: If the octanol/water partition coefficient (log Kow) is ≥ 3 (see section 4.2.8), a BCF needs to be determined experimentally. If this BCF is ≥ 100 L/kg, a secondary poising assessment is requested.

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488-493	20	In addition to the continuous exposure, build-up over time is also an issue for persistent compounds Proposed change (if any): include persistence and build-up over time as a part of the argument for chronic tests. Also, consider extra assessment factor for persistent compounds	No change to the guideline. Rationale: It is not necessary to include an additional assessment factor for persistent compounds because accumulation is not considered in the PECsurface water calculation due to the short retention time in surface water compartments.
492	1	Lines 491-493 state "When the PEC/PNEC ratio is ≥ 1, a risk to the aquatic compartment as a whole (not a particular sensitive group of species) is indicated. If a risk is identified in Phase II Tier A, a refined assessment may be performed in Phase II Tier B." It is unclear based on the last part of the statement if an assessment required. Proposed Change: Rephrase "may be" to "is needed in a Phase II Tier B evaluation."	No change to the guideline. Rationale: The applicant may choose whether to accept a risk (and possibly have to apply risk mitigation measures) or whether to refine the risk assessment. Thus, the term 'may be' is appropriate.
494	30	4.2.3.1 Phase II Tier A Surface water - It seems that marine risk assessment is not considered at all (no testing requirements for marine species or not even an extra assessment factor). Pharmaceuticals reach coastal and open sea waters, as ultimate sinks. For example, the Baltic Sea ecosystem is particularly sensitive to pharmaceutical pollution because of its low biodiversity, with low functional redundancy and many species experiencing an increased physiological stress due to the brackish water environment. The water exchange rate in the Baltic Sea is slow, meaning that there is a long retention time for persistent substances. This makes the	No change to the guideline. Rationale: It is agreed that marine systems also receive pharmaceuticals via freshwater and also by direct emission. However, adding an additional AF to the PECsurface water would be cancelled out by an additional dilution factor for marine systems. Text edited in chapter 3.1.1: The marine environment is not assessed separately, the freshwater assessment is considered sufficiently conservative to also address risk to the marine environment *due to the additional dilution in open marine waters*.

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		Baltic Sea ecosystem more susceptible to hazardous substances in comparison with other marine areas. A status report on pharmaceuticals in the environment in the Baltic Sea Region was published by UNESCO and HELCOM http://www.helcom.fi/Lists/Publications/BSEP149.pdf . The report was developed jointly by Helcom and EUSBSR PA Hazards. It served as a case study within the framework of UNESCO Emerging Pollutants in Water Series under UNESCO-IHP's International Initiative on Water Quality (IIWQ) Project on 'Emerging Pollutants in Wastewater Reuse in Developing Countries'. According to the report, in a recent non-target screening conducted in Norway, a relatively large number of pharmaceuticals were found in sea birds (Miljødirektoratet, 2013). These results, together with the results presented on pharmaceuticals in blue mussels in the Baltic Sea, suggests that pharmaceuticals may be transferred in aquatic food chains up to seabirds. Proposed change (if any): Add marine species to testing requirements (e.g. EN ISO 10253 and EN ISO 16712) or add an extra AF of 10 to the risk quantification.	
504	29	Ionisable test substances should be tested at pH values where the test substances are present in neutral state and at an environmentally relevant pH (5-9). Please add therefore the following sentence.	No change to the guideline. Rationale: For ionisable test substances, care should be taken that when possible, testing is performed at pH values where the test substance is present in neutral state considering the recommended pH ranges of the test guidelines, and in addition the

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		Proposed change: please add "For ionisable test substances, care should be taken that testing is performed at pH values where the test substances are present in neutral state and at an environmentally relevant pH (5-9)."	conditions outlined in OECD guidance document 23 should be considered. More information has been added to chapter 4.2.1.3
505	7	Table could clarify that the endpoints should be based on growth rate Proposed change (if any): ErC10	Text edited.
512-513	25, 26	If the PEC-value used in calculating RQ was derived using the default values, an RQ_{sw} < 1 means only that the large scale average concentration is below the PNEC. In areas where e.g. dilution factor is lower or regional consumption is higher, the PNEC may very well be exceeded. Since an ERA result of RQ<1 is interpreted to exclude risks, the default values used in calculations should be chosen more conservatively, and justification for each value should be given. Proposed change (if any): Please consider reselecting the default values more conservatively.	No change to the guideline. Rationale: According to general risk assessment terminology, the PNEC reflects a reasonable worst-case scenario. There may be locations where the PNEC is exceeded. In that instance, actual measurements of pharmaceuticals can be compared to the PNEC for a retrospective risk assessment. If indeed a risk is identified, risk mitigation may be performed on a local scale (e.g., upgrading sewage treatment plants), and the information may feed into an eco-pharmacovigilance programme.
514	20	Include persistence and build-up over time as a part of the discussion. Further, consider extra assessment factor for persistent compounds	No change to the guideline. Rationale: It is not necessary to include an additional assessment factor for persistent compounds because accumulation is not considered in the PECsurface water calculation due to the short retention time in surface water compartments.
516-520 (624-625)	25, 26	All of the options for refining PEC seem to aim at decreasing the PEC. Also per capita water consumption and dilution	No change to the guideline.

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		factor should be taken into consideration to ensure a sufficient level of environmental protection. An increase in the PEC should also be a possible outcome of the Tier B assessment.	Rationale: Market data and revision of the Fpen may also result in a higher PEC. The default values are relevant for EU wide calculations.
518	1	Market forecast data and consumption data should be used to inform the environmental exposure assessment. In many cases, environmental exposure and hence environmental risk are over-estimated, resulting in unnecessary risk refinements and in some cases risk labelling. Market forecast data of peak year sales is used in the exposure assessments for FDA submissions. Proposed change (if any): Include a bullet for market forecast data capturing peak year sales in the EU country with highest predicted use.	No change to the guideline. Rationale: In Phase I, a market share of 100% is always assumed. Hence, market research data cannot be used for the refinement of Fpen as this will not take into account competitive products with the same API. Additionally, market shares may change quickly, so 100% market share must always be assumed. Sales forecast data cannot be used for refinement in Phase II since these data are impossible to verify.
518, 521-531	22	Inconsistency with the statement on line 88 where it reads that an ERA is not required for renewals. When would refinement based on consumption data be applicable? Define, or delete paragraphs dealing with refinements using consumption data. Proposed change (if any): See comment.	Text edited: Option to refine the Fpen at the renewal of a marketing authorisation for a medicinal product is now removed. Rationale: As an ERA is not required for renewals the option to submit consumption data at renewal would only be applicable in rare instances.
521	17	Equation 5 concerns refinement of the Fpen based on consumption data. This equation was stated to be similar to equation 2 in the last Q&A document (2016) and has since been used by some applicants in Phase I or Phase II Tier A when applying for authorisation of a generic product. Does moving to Phase II Tier B mean that this equation (eq 5)	No change to the guideline. Rationale: The possibilities for refinement of the Fpen in Phase I (Prevalence/ Treatment regimen) are outlined in Q6 of the Phase I decision tree (Equation 2). Refinement of the Fpen using consumption data is not accepted in Phase I, this is unchanged from the previous version of the guideline.

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		cannot be used in Phase I anymore? Also, it is now stated that it can be used for renewal applications, while we experience that it was also used for generic applications. Proposed change (if any): Please clarify.	Regarding renewals see comment above.
521 ff	29	No ERA is required for renewal - see line 88. The chapter of Fpen refinement with consumption data for renewals should be deleted.	Text edited, see comment above.
522-527	10, 18	Line 88 states that an ERA is not required for renewals of marketing authorisations. However, line 522 ff state that for renewals consumption data on the active substance to refine Fpen (and consequentially PEC_{SW}) may be used. There is also no reason why this approach may not be allowed generally for generic MA applications since consumption data should always be available in these cases.	Text edited, see comment above.
522-524	36	It is stated that 'At the renewal of a marketing authorisation for a medicinal product, consumption data on the active substance **may be used** to refine F_{PEN} (equation 5) and the PEC_{SW}, with the possibility of a consequential impact on the conclusion of the previous ERA'. Proposed change: It is worth considering whether the refinement of F_{PEN} should be obligatory at the renewal of the MA, and the revision of the PEC_{SW} conditional on the result of F_{PEN} refinement, since the original PEC_{SW} is always a fairly rough estimate only.	Text edited, see comment above.

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524-525	1	When using consumption data to estimate environmental exposure, not all accurate and reliable data are available in the public domain. Proposed change (if any): The guideline should recognise that some proprietary data (e.g. IMS Health data), which are not in the public domain are suitable for environmental exposure assessment. The guideline should state explicitly that physician prescribing or sell-in / sell-out data (e.g., IMS Health data) can be used for these purposes.	Text edited, see comment above.
525	29	In case consumption data will be still applicable for refinement: Please be more detailed – What means stable consumption? Decreasing is not included. No quantitative definition is given on „stable".	Text edited, see comment above.
529-531	27	The value 365 in eq. 5 also has the unit d y^{-1}, which should be added to the table with Parameter used in Table 5. If this is omitted, the outcome of eq. 5 has incorrect units. Please refer to parameter names used in the previous version of the guidance. Why not stick to these? In addition, year is represented as 'yr' in earlier equations. Please harmonise. We would propose to use 'y'. Proposed change: Add 365 and its unit d y^{-1} to the Table at line 530. Consider giving the parameter a name.	Text edited.
532-546	9	As per the proposed Guidelines, refinement of the PECsw using metabolism data may be used instead of the total residue approach, however, for metabolites present at	No change to the guideline.

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		≥10%, a full Phase II risk assessment of the metabolite(s) is required to support the refined PECsw. In most, if not all cases, sufficient test material of such metabolite(s) is not available nor is it feasible to synthesize. Therefore, testing of metabolite(s) is typically not a viable option. During the drug development process, data may be generated to understand the activity of mammalian metabolites relative to the parent drug substance, i.e., a specific metabolite is shown to have x% the activity of parent in a given activity assay. If such data are available, the option to refine the PECsw based on the % excretion of the specific human metabolite, corrected for % activity relative to parent should be an additional option to Phase II testing of a human metabolite. Proposed Change (if any): Revise numerator in Eq. 6, line 544, to include metabolism factors; ($F_{\text{metabolite excreted}}$ x faction of activity metabolite) and add this additional factor to subsequent Table of Parameters (line 546) $$PEC_{sw\text{-}refined} = \frac{Dose_{AS} \times Fpen \times (F_{excreta\ active} + (F_{metabolite\ excreted} \times F_{metabolite\ activity}))}{WASTEW_{inhab} \times Dilution}$$	Rationale: It is unknown how the activity of the metabolite(s) relates to the activity of the parent compound in environmental organisms.
532-542	20	Please expand on why 10% is set as a threshold for metabolites. REACH guidance indicates 0,1% w/w for the assessment of metabolites if technically possible, and in no case above 10% as a cut-off. A further requirement is that metabolites/transformation products that increase during the test period for simulation tests must be identified, as	No change to the guideline. Rationale: The 10% threshold for metabolites is comparable to other frameworks, such as biocides & plant protection products. This threshold has also proven itself for HMP. The guidance for Metabolism in REACH is not comparable as human metabolites are different to technical mixtures.

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		this may indicate persistence. Also, how does the 10% relate to conjugates formed in the liver? Are the conjugates calculated as a whole or only the relevant part of the new molecule, i.e. the original substance? This is relevant as a conjugate may considerably affect the molecular weight of the compound.	Conjugates are not considered as they may retransform into the parent compound in the STP.
532-542	36	The decision on whether or not the total residue approach is abandoned has critical impact on the overall ERA assessment. This decision is particularly important with a view to the potential ecotoxicity of the metabolites. For example, the toxic effects of many chemotherapy agents is often associated with their metabolites (rather than the active substance). Proposed change: The decision on whether or not total residue approach is abandoned should be more explicit and based on the known metabolic profile in human, i.e., if the active substance is primarily (e.g., >50%) eliminated as metabolites, it should be mandatory to abandon the total residue approach and refine the PEC_{SW} and PEC/PNEC ratio accordingly. The use of total residue approach should be limited to those cases only, when the active substance is primarily eliminated unchanged.	No change to the guideline. Rationale: The total residue approach assumes that metabolites have similar or lower toxicity that that of the parent substance, therefore it is not mandatory to abandon this approach even if the active substance is primarily eliminated as metabolites, unless the metabolite is the pharmacologically active substance (e.g., a pro-drug), in this case the ERA should be performed for this metabolite (see section 3.2.1).
532	44	If the total residue approach is abandoned and instead the metabolites are to be specifically considered, it may be worthwhile amending the guideline to provide: • Clarity regarding the link between any observed human-relevant ED effects (e.g. from mammalian	Text edited. More details and guidance regarding endocrine concerns from other sources like non-clinical or human-relevant data are mentioned in section 4.3.2. However, it is not always possible to dispense with fish tests for exact risk derivation, even if endocrine

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		studies, or in vitro etc) and any anticipated ecological endocrine disrupting effects, in particular what the ramifications could be for triggering any new fish toxicity testing study (ideally, new endocrine disrupting tox studies would not be triggered without very good cause for concern, which may not be warranted based on only human-relevant data). • Explicit descriptions of any toxicity data required for risk assessment of the metabolites, and the methods for generating the required data that would be acceptable (in particular, any non-animal data generation or read-across methods). • Preferred approaches to metabolite risk assessment that do not require new data generation, such as assuming worst-case toxicity (i.e. as toxic as the parent substance), or reasonable worst case toicity (half as toxic as the parent substance).	activity has been demonstrated in the preclinical part of the dossier. Additionally, considerations of 3R principles and weight of evidence approach are mentioned in sections 3.1, 3.2.3 and 4.3.2.
535-536	17	Why should a full Phase II risk assessment be conducted for metabolites when the whole residue approach is abandoned to demonstrate there is no risk for the active pharmaceutical ingredient? Could this not be restricted to the compartment for which the refinement is needed? What if the PECsw of the metabolite(s) is below the Phase I trigger of 0.01 µg/L? Should a Phase II assessment still be conducted? Could part of the assessment be based on QSAR data, in order to determine which substance (i.e. API, any metabolite) is expected to carry the highest risk?	No change to the guideline. Rationale: A full Phase II and not only a compartment specific ERA is required for each metabolite constituting ≥10% of the administered dose is required because their fate and effects may differ to the active substance. The action limit is not relevant for metabolites as at this point the assessment is already in Phase II, and the action limit step already passed. Regarding QSAR see response for comment 181-183.

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		Proposed change (if any): Consider accepting refinement based on metabolism data for specific compartments only; abandon requirement to conduct metabolite studies in compartments for which no concern was identified. Please also consider what should be done if the PECsw for the metabolite(s) is below the Phase I trigger.	
535-536	47	line 535-536 reads: If the total residue approach is abandoned, a full Phase II risk assessment is required for each metabolite constituting ≥10% of the administered dose. The percentage given could be misinterpreted since in metabolism and disposition studies percentage of metabolites could mean several things - in vivo the most relevant percentages would be those for the circulating ones. In this guideline the excreted metabolites are relevant which could be clarified. Proposed change (if any): If the total residue approach is abandoned, a full Phase II risk assessment is required for each **excreted** metabolite constituting ≥10% of the administered dose.	Text edited.
536	48	This wording is unclear. Proposed change (if any): a full Phase II risk assessment is required for metabolite excreted at ≥ 10%.	Text edited, see previous comment.
544	24	One should connect this eq to the text by adding a reference for the corresponding text/paragraph. Applies to all equations although those follow the paragraphs in question.	Text edited.

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546	24	A bit more specific expression would favour understanding the metabolism in this equation Proposed change (if any): "Fraction of parent substance excreted"	Text edited.
548 555-556 588-596 617-618	19	The human metabolites have to be considered as parent substance as long as the "whole residue approach" is not abandoned, but on the other hand any environmental transformation (potentially leading to the same breakdown products) used in SimpleTreat calculation would allow PEC mitigation. Proposed change: This inconsistency should be corrected anyhow. If the primary degradation as considered in SimpleTreat will be carried forward, also all true structurally changed human metabolites should be considered for $F_{excreta}$ reduction. Alternatively I propose that only identified metabolites and/or transformation products, for which the human target activity has been shown to be 10% or less compared to the API, may be disregarded for the PEC calculation. However this would implicate that SimpleTreat cannot be used straight-forward anymore.	No change to the guideline. Rationale: Only in rare cases MAHs submit other tests than an OECD 301. Over 90% of all active substances are not readily biodegradable, so there is not unequal treatment of metabolites in SimpleTreat.
548	21	Note that the new default value for the concentration of suspended solids of 7.5 mg/L as suggested in SimpleTreat 4.0 is based on data mainly from the Netherlands. For	It was decided that for the environmental risk assessment of human pharmaceuticals as far as possible default values need to

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		biocides this new default value was not accepted since the database for changing this default value was considered not extensive enough to represent a European situation. For biocides the former value of 30 mg/L was therefore kept and used in SimpleTreat4 (implemented as changeable default value in EUSES 2.2.0). For REACH, SimpleTreat 3.1 is currently still applied, using also the former default values. Proposed change (if any): Verify if the changed default value for the concentration of suspended solids in SimpleTreat4 based on data of mainly one member state in the EU, thus not representing the whole EU situation, is acceptable for EMA.	be used when running SimpleTreat 4.1, this includes the suspended solids concentration in effluent of 7.5 mg/L.
548, 579	21	The previous guidance document for HMP referred to EUSES. Note that ECHA took over EUSES form JRC and is releasing a new EUSES version 2.2.0 including also SimpleTreat 4 in September 2019. The advantage of using EUSES for the exposure and risk assessment is that the whole assessment could be performed with one model. A default emission scenario for release via STP or release to surface water is included in EUSES 2.2.0 which could – following adaptation – be used also for HMPs. Note also that if EMA is interested to have their emission scenarios per se included in EUSES, please notify ECHA accordingly (for a potential future update of EUSES). Proposed change (if any):	No change to the guideline. Rationale: It was decided that emission scenarios remain as stand-alone guidance.

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		Add a reference to EUSES 2.2.0 in the final version of the guidance if considered appropriate (ECHA to provide the link to the related ECHA webpage once finalised).	
549	29	We propose an additional sentence for more clarity. Proposed change (if any): Refinement of PEC_{SW} may also be performed with a model simulation using the latest version of SimpleTreat. (Download: https://www.rivm.nl/en/Topics/S/Soil_and_water/SimpleTreat; instruction: https://www.umweltbundesamt.de/publikationen/application-of-simpletreat-40-in-european-551 substance) The output of SimpleTreat is the *Fraction of release directed to water by STP* ($Fstp_{WATER}$) and will be derived by incorporating:"…	Text edited.
554	27	Make very clear that it concerns $K_{oc\ sludge}$ in this line. The table below also lists $K_{oc\ soil}$, which is fine for the purpose of that table, but less informed users should be aware that $K_{oc\ sludge}$ are to be entered in SimpleTreat, not $K_{oc\ soil}$ data. Proposed change: Add $K_{oc\ sludge}$ between 'the' and 'data'	Text edited.
557 (Table 5)	1	Not all relevant studies are listed. Proposed Change (if any): Add 314(B) to the table.	Text edited: Information on optional OECD 314B or 302 has been added in footnote: 'OECD 301 can be replaced by OECD 314 or OECD 302.'

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557	27	Please add in Table 5 OECD 314 B as a separate entry. Proposed change" Add a line to Table 5, listing OECD 314 B. The endpoints needed from the study to be used in the SimpleTreat exposure modelling are 1) a first order degradation rate constant valid for the combined aqueous and sludge phase and 2) the test temperature.	Text edited, see previous comment.
557	48	Please explain why the OECD 302 inherent biodegradability studies are not referenced as relevant to the persistence assessment?	Text edited, see previous comment.
559-563 and 566-570	20	Identical text in two paragraphs – this is a little confusing. Proposed change (if any): Suggest rewriting the second paragraph so it is not identical.	Comment noted. First paragraph has been rewritten. Text edited. For local scale assessments, it is assumed that one point source is releasing its wastewater to one STP. The local release of the active substance to surface water ($Elocal_{WATER}$), needed as a required input value in Simple Treat, can be estimated as follows: Eq 7: The concentration in the influent of the STP, i.e. the untreated wastewater, can be calculated from the local release to wastewater and the influent flow to the STP. The influent flow equals the effluent discharge. Eq. 8:
559, 566, 573	27	Comment:	Text edited.

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		these subheaders can be left out. A short explanation text above the equation suffices. The header in line 548 covers the entire section. Proposed change (if any): • delete headers at lines 559, 566, 573 • add ' (*E*local$_{water}$) ' after the text 'wastewater' in line 562. This introduces eq. 7.	
560-564 and 567-571	1	The text in these two sections is identical, even though the first section (lines 560-563) is to address "Calculation of emission of API per day" and the second section (lines 567-570) is to address "Calculation of the STP influent concentration." Therefore, it is not clear when Equation 7 needs to be used and if/when Equation 8 needs to be used. Proposed Change: Refine text in each section to properly address the issue (emission of API and STP influent modelled or predicted concentration" and the corresponding equations in lines 564 and 571.	Text edited. First paragraph has been rewritten.
564, 571, 576	1	Are these (or can these) equations run through the Simple Treat model or do the calculations need to be shown in the ERA? Proposed change (if any): The guideline should indicate what needs to be calculated using the given equations or what can be provided as a model output?	Text edited: Calculations have been shortened and ClocalEFF can now be derived as output from SimpleTreat. Additional guidance is provided in the SimpleTreat manual in the annex.
564	47	Line 564, Eq. 7, the CAPACITY$_{STP}$ should be given a definition in the text preceding the equation, not only in the table following some 2 pages after the equation.	No change to the guideline. Rationale: Information available in Q5 of the Phase I decision tree.

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564	48	It would be helpful if these were defined up front. If this is not possible, please indicate to the reader which page the definitions can be found on.	No change to the guideline. Rationale: As general structure the definitions of input values are summarized at the end of each chapter.
567-570	27	This section can be deleted as it is a repetition of lines 560-563. That section can serve as an introduction for equations 7 and 8. Text in between these equations is not needed Proposed change (if any): delete lines 567-570.	Text edited. First paragraph has been rewritten
571	17	Equation 8 misses a factor of 10^6 in the numerator, as now it yields $Clocal_{INF}$ expressed in kg/L. Proposed change (if any): Correct equation to include x 10^6 in the numerator.	Text edited.
573-575	27	not every equation needs introduction with a header. Simply delete line 573 and give the introductory lines (574-575) above eq. 8. Proposed change (if any): Remove line 573.	Text edited.
581	27	Proposed change (if any): delete '(consideration of volatilization)' as this information is redundant and not provided with other parameters.	Text edited.
582	12	OECD 106 is not suitable to determine sewage sludge KOC. Please read the scope of the guideline Proposed change: review the entire document as on several places the risk assessment is based on a parameter that	Text edited. Rationale: Comment for formal reasons accepted. The current GL proposes to use OPPTS 835.1110 (EPA) to determine the adsorption/desorption on sludges. Since the current GL came into

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		cannot be determined by the guideline proposed! If it is applied anyway, data will not be reliable.	force a lot of adsorption measurements have been performed following the OECD 106 for soils. Up to now OECD 106 is preferred but has not been formally extended for the use of sludges. The specific EPA-GL is now mentioned in Table 1 of the revised GL as optional alternative.
582	47	Line 582: why is the word "Adsorption" in bold?	Text edited.
584	27	The EMA guideline only requests 2 K_{oc} values for sludge, it seems odd to stipulate the averaging is done when 3 values are available. In risk assessment practice, NL takes the geometric mean of the two $K_{oc\ sludge}$ values. Proposed change: The geometric mean of the available K_{oc} sludge values should be used (also when the requested 2 values are submitted).	No change to the guideline. Rationale: It is statistically not forbidden but clearly not recommend calculating a mean with two values. More than two are needed for more analysis e.g., for variance and evidence. In other legislations the mean is based on at least 4 values.
588-590	27	When the result of a OECD 301 or 302 simulation study is available, the rate constant entered should be selected from the pre-defined values shown in the pull down menu in SimpleTreat 4.0. These half-life values are agreed within the REACH and BPR (biocides) frameworks for the various types of outcomes (e.g. readily biodegradable meeting the 10 d window, readily biodegradable, failing the 10 d window, inherently biodegradable, etc.). No temperature needs to be entered when selecting from this pick list. Proposed change: Add reference to the pre-defined half-life values available in SimpleTreat 4.0 for OECD 301 / 302 outcomes.	Agreed. Additional guidance is given in the SimpleTreat manual in the Annex of the guideline.
598	27	Proposed change:	Text edited.

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		• add, after distribution: 'of the mass of active substance • change distribution for 'into distribution over' 'In the output-sheet the distribution of the mass of active substance over four compartments:'	
604-609	1	This section describes calculating the refined surface water concentration. Lines 605-609 state "The starting point for the calculation is the concentration of the API in the STP effluent. Dilution in the receiving surface water and adsorption to suspended matter are then considered. The partition coefficient between suspended matter and water, KpSUSP, may be estimated from the Koc of the API, determined for soil by taking into account different organic carbon contents of the media. The lowest Koc derived from soil should be used." As the path of a pharmaceutical product to STP effluent includes exposure to, and removal of, sludge but not soil, is the Koc of soil the most appropriate variable? Proposed Change (if any): Utilize the Koc of sludge instead of soil for these calculations.	No change to the guideline. Rationale: In the STP the removal by adsorption to sludge is considered. After STP emission, the removal by partitioning to suspended matter in the aquatic environment is relevant. This suspended matter resembles soils more closely than sludge. For this media a Koc derived for soil is closer than a Koc derived for sludge.
609	27	We do not agree to use the lowest of three available, valid K_{oc} values for soil. The geometric mean value should be taken here. Moreover, it is quite strange to start averaging from 4 available values or more, while the guideline requirement is 3 K_{oc} values. Average K_{oc} and *DT*50 values should preferably be used in exposure assessment (when the minimum amount in	See comment line 584.

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		variation is indeed covered) in order not to end up with worst case calculations instead of realistic worst case. Proposed change: • change lowest into geometric mean of 3 K_{oc} values. • Note, this also pertains to lines 636-637	
610	48	Comment: First use of oc. Please define and add to the "definitions" section. Proposed change (if any): organic carbon (oc)	Text edited in 4.2.1.2 and oc added in list of Definitions.
610	48	Comment: First use of Kf. Please define and add to the "definitions" section. Proposed change (if any): Freundlich constant (Kf)	Text edited and list of Definitions updated.
613	17	Equation 11 misses a factor of 10^{-6}, as Kp_{SUSP} is expressed as L/kg and $SUSP_{WATER}$ is expressed as mg/L, and its product does not yield a dimensionless value. Proposed change (if any): Correct equation to include x 10^{-6} on the $SUSP_{WATER}$	Text edited.
613 Eq. 11	27	The units in equation 11 are incorrect, a conversion factor from mg to kg is missing. It can be displayed as a value (10^6), but this value has the unit mg kg^{-1}. It can also be added as a parameter, e.g. $CONV_{kg\text{-}mg}$, with the value 10^6 and unit mg kg^{-1}. Proposed change: • Adapt eq. 11: divide the product $Kp_{susp} \times SUSP_{water}$ by $CONV_{kg\text{-}mg}$ (unit mg kg^{-1})	Text edited.

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		• Add the parameter for unit conversion to the Table at line 616.	
613	47	Line 613. Eq 11. The equation for the FACTOR seems mathematically incorrect; this factor should not have any unit, but Kp_{SUSP} should be in L/kg and $SUSP_{WATER}$ in mg/L. Thus, $Kp_{SUSP} \times SUSP_{WATER}$ has the unit mg/kg which is added to a unitless number. Proposed change (if any): Check the equation and amend as needed.	No change to the guideline.
616 (Row 12)	1	Proposed Change (if any): Change Kocsoil to Kocsludge. Change Partition coefficient between organic carbon and water derived from soil to … from sludge.	No change to the guideline, see comment line 604-609
616 Table	27	See also comment at line 613 Proposed change: Add conversion factor from mg to kg (and vice versa).	Text edited.
616 Table	27	Foc_{susp} has the unit $kg_{oc}\ kg_{dw}^{-1}$ K_{psusp} has the unit $L\ kg_{dw}^{-1}$ $K_{oc\ soil}$ has the unit $L\ kg_{dw}^{-1}$ $SUSP_{water}$ has the unit $mg_{dw}\ L^{-1}$ Check e.g. Table 5 from the TGD (2003) or Table 3 from BPR Vol IV, Part B&C or REACH table R.16-8. In those guidances, 'solid' is used, which is also an option as 'solid' is further used to denote the dry part of different matrices. Presenting the full units helps preventing calculation errors. See comm. line 282: the unit of $DOSE_{AS}$ and F_{pen} should be adapted accordingly.	Text edited.

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		Proposed change: Change units as presented above and align with REACH and BPR guidance.	
616	29	Comment: Please correct the unit of $Elocal_{water}$ to: [mg d^{-1}]	Text edited: Corrected with added $CONV_{kg/mg}$
616	48	The $CAPACITY_{STP}$ is set at 10,000 inhabitants. Has any consideration been given to the variations in the amounts of pharmaceuticals that a STP may receive resulting from the local population variation?	No change to the guideline.
629-700	20	Sediments on the marine and freshwater environments may be very different. Suggest that the applicant state the type of sediment meant to be represented by the assessment. For clarity and ease of assessment by regulatory risk assessors. Proposed change (if any): Suggest that the applicant state the type of sediment meant to be represented by the assessment	Text edited. Rationale: The stated difference is acknowledged, just as large differences exist between various freshwater systems (streams, rivers, lakes etc.) and marine systems like brackish or deep sea. The presented calculations, however, all refer to PECsw, which is a standard surface water scenario for fresh waters unless otherwise specified. This is now specified 3.2.1. No changes are made to this chapter.
634-644	1	This section (4.2.4.1) provides instruction for a Phase II Tier A assessment for sediment. The first part of the section explains how to complete an exposure assessment for sediment. Lines 636 states ”Koc should be determined for a minimum of three soils (see section 4.2.1.2).” Lines 642 and 643 provide a calculation on how to determine the concentration of the API in sediment and the calculation ultimately incorporates Kocsoil.	No change to the guideline, see comment for l 356 (table).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		As the media of concern is sediment, and the calculations are provided to determine the concentration of the API in sediment, it is unclear why the use of Koc for soil would be preferable with the use of Koc for sediment to determine the concentration of the chemical in sediments. The option to use soil or sediment Koc data should be allowed. Proposed Change (if any): Allow the use of Koc sediment or Koc soil to calculate PEC sediment.	
638-639	1	The document states "If the adsorption to soil does not correlate with the organic carbon the solid-water partitioning coefficient should be used as KpSUSP (highest Kd = KpSUSP)." This is unclear and/or not well defined. What are the parameters that would allow one to decide that adsorption to soil does/does not correlate (or correlate well enough) with organic carbon? Proposed Change: Please clarify this statement.	Text edited. The solids/water partition coefficient for suspended matter is calculated according to equation 16.* More details how to assess oc correlation are linked in added footnote: * If four or more KFOC values derived from soil are available, the geometric mean may be used and the correlation between KF (or KD) and organic carbon (OC) may be assessed. If KF does not correlate with OC, KF should be used as KpSUSP. This can be assessed with the Excel-tool Input_Decision freely available: https://www.bvl.bund.de/EN/Tasks/04_Plant_protection_products/03_Applicants/04_AuthorisationProcedure/08_Environment/01_Tool_input_decision/ppp_Tool_Input_Decision_node.html
638-639, 649-350	25	Repetition ("If the adsorption to soil does not correlate with the organic carbon the solid-water partitioning coefficient should be used as KpSUSP (highest Kd = KpSUSP)" Proposed change (if any): Remove the first one (638-639)	GL text changed, see comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
643, 647	27	In Eq. 14: the value of 1000 (Eq. 14) has a unit (L m^{-3}) and should be added to the table explaining the variables. In Eq. 15, the value 10^{-3} has a unit (m^3 L^{-1}). Propose to use it as in Eq. 14: 1000 (L m^{-3}), by dividing the product $F\text{solid}_{susp}$x$K\text{p}_{susp}$xRHO_{solid}. This also aligns the equation (in form) with its source (REACH/TGD). Proposed change: Use 1000 L m^{-3} in both eq 14 and 15 and it to the table listing the variables.	Text edited.
647	27	the brackets in eq 15 can be removed, they are redundant Proposed change (if any): remove brackets.	No change to the guideline.
655 (row 10)	1	Allow the use of the most appropriate partitioning data. Proposed Change: Change from Koc soil to Koc sediment (or change to Koc sediment or soil). Change from Partition coefficient between organic carbon and water derived from soil to … derived from sediment (or … derived from sediment or soil).	No change to the guideline, see comment for line 356 (table).
655 Table	27	It is very important to note that RHO_{susp} is a wet (bulk) density. This should be added to the description of the parameter. Please align with the source: REACH R.16 or the former TGD (2003). Preferably add ww in the unit: kg_{ww} m^{-3} This is a different density than RHO_{solid}, as the former is a total compartment density, resulting in a wet weight value, which results in a wet weight result for $PEC_{sediment}$. It would	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be good to make this distinction now and be correct, for less experienced users. Prevent that lengthy discussions and re-explanations are needed in the future. Also *F*oc$_{susp}$ had the unit kg$_{oc}$ kg$_{dw}^{-1}$ or kg^{oc} kg$_{solid}^{-1}$ to align with REACH (R.16) Proposed change: Adapt description of RHOsusp: 'wet bulk density of suspended matter' and align description of other parameters and their units with source (R.16).	
657	27	Indeed, *PEC*$_{sed}$ is expressed as a *wet weight* concentration in freshly deposited suspended matter. But not in 'solid' suspended matter, because it is calculated as a wet weight concentration, <u>including the water phase.</u> Hence, delete 'solid' from this line. Only after the conversion to a dry weight concentration in suspended matter (Eq 17) we can state that the concentration is expressed in solid suspended matter. Proposed change: delete solid from line 657	Text edited.
659-662	27	This is confusing. There is one equation too many. The latter equation is redundant, the others should be slightly rewritten. The first equation should present: *CONV*$_{susp}$ = *RHO*$_{susp}$ / (*F*solid$_{susp}$x*RHO*$_{solid}$) Of which the outcome (4.6) is already presented correctly in the table.	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The 2nd equation should state: $PEC_{sed\_DW} = PEC_{sed} \times CONV_{susp}$ Proposed change: Change equations as stated above.	
663 Table	27	uniformise typography of subscript for dry weight and wet weight. Proposed change: kg w.w. into kg_{ww} and kg d.w. into kg_{dw}	Text edited.
663 Table	29	Reference for PECsed is Equation 14 instead of Eq. 13. Proposed change (if any): See EQ. 14	Text edited.
665	17	"The fraction bound residue that may have been determined in fate studies"; a water-sediment study is no longer indicated, except to address PBT concerns. Please consider rephrasing. Proposed change (if any): Consider rephrasing.	No change to the guideline. Rationale: The sentence indicates a "may" wherefore the sentence is valid. No changes made.
667	48	Please note that when deriving a $PNEC_{SED}$ for REACH purposes the value is normalised to the organic carbon content of the matrix	No change to the guideline. Rationale: The PNEC is normalised to standard OC content like in REACH by normalising all input data (NOEC/EC10).
669	27	Proposed change (if any): insert 'toxicity' between one study: **one toxicity study**	Text edited.
673-674	29	Ionisable test substances should be tested also at pH values where the test substances are present in neutral state. Please add this in the sentence.	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: please change to "For ionisable test substances, care should be taken that testing is performed at pH values where the test substances are present in neutral state and at an environmentally relevant pH (5-9)."	
676-683	1	The option of a 3rd sediment dwelling species has been removed from the sediment risk assessment. Previously a third species was possible (*Hyalella*) to enable further reduction of the assessment factor to 10, in-line with the REACH Guideline (R10.5.2.2) Proposed change (if any): Please add *Hyalella* to Table 3 and note that if three long-term tests are conducted (e.g., *Chironomid*, *Lumbriculus*, *Hyalella*) then an AF of 10 may be used in setting the PNEC.	Not agreed. Rationale: The test with *Hyalella* has been removed as no final version of the OECD draft has been adopted. Therefore, no additional guidance is given on the use of a lower assessment factor of 10. In exceptional cases where data from a *Hyallela* test, conducted in line with an international validated test guideline from an institute comparable to OECD (e.g. US EPA), is available, expert judgement may be used to decide on the reliability and relevance of the study, and potential use of a lower assessment factor.
676-678/Table 7	24	I acknowledge that all the tests in this guide are OECD tests as those are globally (OECD countries) accepted in different jurisdictions but particularly with sediments, ERA would benefit from the ISO tests. Especially crustacean test (*Hyalella azteca*) would be a good choice as neither Lumbriculus nor Chironomus are known to be sensitive species.	See above.
676/696	48	Table 7 presents the standard species that are used. There is currently work undergoing using the *Hyalella* shrimp, which would allow refinement of the effect assessment and completes representative organisms living in/on the	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sediment. This refinement as an adjustment factor is in the REACH guidance text.	
680-683	19	As the same assessment factor (AF) applies to the OECD 218/219 and OECD 233 studies, the higher tier status of the life-cycle study is not acknowledged. This seems unjustified. Proposed change: Implement a reduced AF if the life cycle study has been used.	No change to the guideline. Rationale: The choice of Chironomid test is voluntary. The use of AF follows the recommendations in the REACH program. No changes made.
688 Table	27	give units of F_{oc} (see earlier tables with parameters and comments on those) Proposed change: unit of F_{oc} is $\mathbf{kg_{oc}\ kg_{dw}^{-1}}$	Text edited.
694-697	1	Line 694 states "If the risk quotient is ≥ 1, risk refinement may be performed in Phase II - Tier B" and Lines 696-697 state "If a risk is identified in Tier A, refinement of PEC_{SW} (see section 4.2.3.2) may also be used for Tier B sediment assessment." As with the comment below (re Lines 752-755), the use of "should" is inconsistent. For instance, in Lines 752-755, if the RQ is > 1, further evaluation is needed in Tier B. However, in the above statement (Line 696) a Tier B assessment is not clearly stated to be a required action. Proposed Change: The word "should" be revised to "need(s)" or "is mandatory" or a similar phrasing that removes ambiguity	It is not mandatory to continue to Tier B. The Applicant can enter the risk:benefit evaluation already after Tier A. However, the point is valid, and the text is changed to: If the risk quotient is ≥ 1, **any** risk refinement **must** be performed in Phase II - Tier B.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		throughout the document when what is being requested is a required action.	
696	27	clear guidance should be added how to calculate PEC_{sed} in Tier IIB. See proposal. Proposed change: Add sentence, after 'sediment assessment': The $PEC_{sed\ refined\ IIB}$ is calculated using eq. 14, using $PEC_{sw\ refined\ IIB}$ as PEC_{sw}. An alternative option is to present a new equation: PEC_{sed} in Tier IIB is calculated using Eq. X: $PEC_{sed\ refined\ IIB} = \frac{K_{susp\text{-}water}}{RHO_{susp}} \times PEC_{sw\ refined\ IIB} \times 1000$	No change to the guideline. Rationale: It is clearly stated that the Applicant should use a refined PECsw.
702	27, 48	typo Dash between The and microbial Proposed change (if any): remove dash	Text edited.
704	22	Should the activated sludge inhibition test be performed only for anti-microbial substances? Proposed change (if any): If that is the case, consider moving the entire paragraph to 4.3.1 (Tailored assessment for antibiotics). Otherwise clarify the paragraph.	Text edited: "In order to evaluate the anti-microbial effects of ~~anti-microbial~~ substances, the activated sludge respiration inhibition test (OECD 209) should be used."
709	27	'as there is no dilution of effluent with surface water'. This is stated confusingly and can be seen as incorrect; the effluent is diluted with surface water and the default dilution factor used is 10. A text proposal is given: Proposed change:	Text edited: "This is achieved by multiplying the PEC_{SW} ~~with~~ **by** a factor of 10, as ~~there is no dilution of 710 effluent with surface water~~ **the PEC_{SW} is derived from the calculated STP effluent**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		replace text in line 709 after the comma, with: 'as the surface water concentration was calculated from the STP effluent concentration by applying a default dilution factor of 10 (See e.g. eq. 3).'	**concentration by applying a default dilution factor of 10 (see Eq. 3).** "
712	22	Proposed change (if any): Change "PNEC" to "PNECmicroorganisms" for clarity.	Text edited.
712	27	typo Proposed change (if any): replace for by with respiration inhibition test with activated sludge	Text edited.
721-722	1	Lines 721-722 state "When the risk quotient is ≥ 1, risk refinement options as described for surface water may be used in Phase II Tier B." Are the risk refinements required? If so, text should reflect. Proposed Change (if applicable): Change statement to "When the risk quotient is ≥ 1, risk refinement options as described for surface water are needed to complete Phase II Tier B" or similar statement.	Text edited: "When the risk quotient is ⩾ 1, **a Phase II Tier B assessment is required and** risk refinement options as described for surface water **(section 4.2.3.2)** may be used ~~in Phase II Tier B~~."
727	17	$PEC_{AERATION\ TANK}$ is indicated to be equal to $Clocal_{EFF}$, with reference to Eq. 7; this should be Eq. 9 Proposed change (if any): Correct reference to equation from 7 to 9	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
727 Table	27	Within the table, there is incorrect reference to equation nr. 7. Reference should be made to eq. 9, where *C*local$_{eff}$ is calculated. Use automatic referencing to equation numbers. Proposed change: change eq. 7 into eq. 9	Proposed correction implemented
729	29	Highly appreciated by UBA. This approach is now in line with the current assessment for veterinary pharmaceuticals. The present concept considers clearly the current state of knowledge. The new approach includes the higher sensitivity of groundwater ecology and gives new options for refinement in Tier B which are not available in the current guideline.	Text edited.
729-753	30	Phase II Tier A and B assessment for groundwater: Finnish authorities are of the opinion that the risk assessment approach in the draft Guideline in groundwater contradicts both the spirit and letter of the EU Groundwater-Directive 2006/118/EC. Furthermore, the Finnish environmental legislation concerning the contamination of groundwater is very strict. According to the Finnish Environmental Act (17/2014) the **pollution** of groundwater is forbidden, that means entry of hazardous substances must be prevented, no risk assessment is taken place. The obligation of Groundwater-Directive 2006/118/EC Article 6 GWD to prevent inputs of hazardous substances especially for compounds listed in Water Framework Directive (WFD) Annex VIII is a mandatory obligation and has strictly to be complied with also when applying other	No change to the guideline. Rationale: The comment is acknowledged; however, this guideline utilises a risk-based approach.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		EU legislation. While the WFD Annex VIII point 9 lists only biocides and plant protection products, the same active ingredients may be used also as pharmaceuticals. Therefore, an active ingredient of a medicinal product belonging to the listed compounds of Annex VIII WFD must not enter into groundwater and a "zero-emission" of hazardous substances into the groundwater is demanded. Using the risk assessment approach as it is in GL may mean that an accumulation of a medicinal active substance in the groundwater can be accepted if RQ < 1. Such an approach clearly contradicts the prevention obligation of Article 6 GWD for hazardous substances which also considers for substances which are not classified as hazardous according to the Water Framework Directive (2000/60/EC): "all measures necessary to limit inputs into groundwater so as to ensure that such inputs do not cause deterioration or significant and sustained upward trends in the concentrations of pollutants in groundwater.". Furthermore, it is scientifically not sound to assess risk with the surface freshwater species to surrogate other kind of (unknown) ecosystems, like groundwater. In line with the precautionary principle, it is questionable why 0.1 µg/l is an absolute quality standard for pesticides and biocides but is not applied to other biologically active substances such as pharmaceuticals. There is evidence from pesticide monitoring that once the substances have entered the ground water, they will degrade extremely slow. Any contamination with all chemicals, including pharmaceuticals is difficult to reverse.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): For the reasons stated above, **Finnish authorities recommend not to follow the risk assessment approach as it is now but follow the precautionary principle where the utmost upper concentration should be 0.1 µg/L.**	
730	1	There is a lack of justification that this exposure pathway, surface water to ground water via bank infiltration, is relevant enough to justify a detailed European-wide assessment as provided in the Guideline. Groundwater has been evaluated as a potential source of PIE and under typical conditions of use and is not found to demonstrate a risk to human or ecological health, although some APIs are found at low concentrations. As the surface water is the starting point, if risk to surface water is acceptable, then risk to groundwater would also be acceptable (see comment regarding assessment factors for groundwater organisms, below).	No change to the guideline. Rationale: From surface water to groundwater/bank filtrate via bank filtration is the most common and conservative exposure pathway also in other legislations. Regarding the risk assessment for groundwater ecosystems, please refer to comments below.
730	21	It is not fully clear why the concentration in groundwater is not calculated via the pore water concentration in soil following sewage sludge application but only via bank infiltration (for substances with Koc values below the proposed trigger value). Have comparative calculations taken place proving that the release to groundwater via bank infiltration is always higher compared to release via sewage sludge application and thus represents the worst case?	Text edited. See chapter 4.2.7.3. Additional groundwater assessment following sewage sludge application has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): If applicable, explain that release via bank infiltration represents the worst case compared to release via sewage sludge application or reconsider including an assessment for groundwater also following sewage sludge application (if not the worst case).	
730-733	27	Disregarding the entry of actives in the groundwater via soil (STP sludge spread onto soil) is not agreed. The compartment should not simply be neglected, because K_{oc} values are high and 'concentrations low'. Proposed change: Add the calculation of $PEC_{pore\ water}$ based on PEC_{soil} (using assumptions and equilibrium partitioning equations and from REACH/BPR guidance), when Tier IIB for soil has been triggered. This also gives a PECgroundwater estimate. The highest of the two (bank infiltration or soil leaching) is taken forward in the risk assessment.	Text edited. See chapter 4.2.7.3. Additional groundwater assessment following sewage sludge application has been added.
730	27	Proposed change: bank **infiltration**	No change to the guideline.
731	1	Define which Koc (soil or sludge). Can be confused with soil since text discusses bank filtration and high sorption affinity in soil.	Text edited. Changed from Koc to $Kfoc_{SLUDGE}$.
731	1	Proposed change (if any): Suggest removing average or replacing "with an average Koc" with "where the appropriate Koc_{SLUDGE}" to avoid confusion with Table 2.	Text edited. Proposed deletion of "average" implemented.
731-732	30	"It is assumed that the exposure of groundwater via sewage sludge incorporated into soil can be disregarded	Text edited.

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		with reference to the high sorption affinity of these active substances to the soil." Is this based on the scientific grounds or is it just an assumption? As there is no reference to any scientific literature, it seems it is an assumption, and we consider it very weird assumption. For the veterinary medicines, PECgw is assessed after the manure application (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.1, 2016), which is comparable to the sewage sludge application. Proposed change (if any): The assessment of groundwater contamination through the sewage sludge application should be added to this GL also.	See chapter 4.2.7.3. Additional groundwater assessment following sewage sludge application has been added.
734-746	25, 26	PEC_{gw} and $PNEC_{gw}$ calculation are extremely simplistic. They should be given some justification. E.g. comparisons between MEC_{sw} vs. MEC_{gw} and same for PNECs. Proposed change (if any): Give justification for the selected methods. Otherwise they will seem completely arbitrary. If there is no justification for the selected method, delete Phase II Tier A for ground waters, and move directly to current Phase II Tier B (SimBaFi etc.).	No change to the guideline. Rationale: The stepwise assessment (Tier A/Tier B) follows the general assessment procedure of the guideline. In Tier A a realistic worst-case scenario is used followed by a refinement in Tier B. The simple estimation for groundwater by a factor of 4 has been used in the guideline since 2006. It was reconsidered during the revision and is still considered valid.
734	48	We are concerned that the 0.25 multiplication and additional assessment factor presented for the exposure and effects concentrations for the $PNEC_{GW}$ are overly precautionary. Ground water systems are, as a rule of thumb, considered non-viable due to a dramatic decrease in	No change to the guideline. Rationale: The stepwise assessment (Tier A/Tier B) follows the general assessment procedure of the guideline. In Tier A a realistic worst-case scenario is used followed by a refinement in Tier B. The simple estimation for groundwater by a factor of 4 has been used

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		temperature (2–4°C) and low microbial density. These systems may lack the ability to degrade a substance but eventually groundwater will return to being a surface water. This philosophy may be driven by the Persistent, Mobile and Toxic/ very Persistent and very Mobile criteria. However, we do not think it is appropriate to include it here.	in the guideline since 2006. It was reconsidered during the revision and is still considered valid.
736-745	1	It appears that EMA is attempting to align with the Vet Meds approach, but it is critical to point out that the exposure pathways and anticipated levels in groundwater are completely different. For human health, this level of effort is not commensurate with the level of risk. If bank infiltration is the only pathway considered (as it is in the Guideline), concentrations in groundwater will always be lower than concentrations in surface water, and therefore, without strong scientific proof of greater sensitivity of groundwater organisms, the PEC_{GW} and $PNEC_{GW}$ should not be more restrictive than the PEC_{SW} and $PNEC_{SW}$, respectively.	No change to the guideline. Rationale: Groundwater ecosystems are very specific and unique (endemic species, low reproduction rates etc.), lack the ability to recover from perturbations and are therefore more vulnerable than surface water ecosystems. Groundwater ecosystems are highly sensitive to (chemical) stressors (low resilience) and chemical substances have very high residence times in groundwater (much higher compared to e.g. surface water) (see references provided in chapter 4.2.3 of the groundwater guideline for VMPs (EMA/CVMP/ERA/103555/2015: Kolar and Finizio, 2017; Culver and Pipan, 2009; Gibert et al., 1994). As a result of this vulnerability, an additional assessment factor of 10 is applied to extrapolate the PNECgroundwater from the PNECsurfacewater. To strengthen the groundwater assessment, the additional exposure path of sludge on soil has also been added.
738	21	What is the basis of the factor 0.25, was this value validated and if yes how? Proposed change (if any): Add an explanation on how the factor 0.25 was derived.	No change to the guideline. Rationale: The simple estimation for groundwater by factor of 4 has been used in the guideline since 2006. No new information has become available that would lead to a deviation from this.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
740-745	1	Daphnids are an appropriate indicator species for groundwater, as copepods are common organisms found in groundwater ecosystems. Moreover, the OECD 211 daphnid reproduction test is a chronic study, which would indicate if long-term effects are expected if a groundwater system was unable to recover from perturbations (this is no different from surface water impacted with continuous release of API as is assumed in the Guideline). Therefore, it is valid to continue using the OECD 211 chronic daphnid study with AF of 10 to calculate a PNECgw and determine a potential risk. Please provide additional scientific justification for the additional AF and the inclusion of fish in the derivation of PNECgw. Based on this additional AF of 10, predicted groundwater risks will exceed surface water risks; this is counter-intuitive. Deharveng et al. (2008) stated "…the total number of described stygobiotic species in the six countries was 930… Groundwater stygobiotic biodiversity was dominated by Crustacea with 757 species in 122 genera…" so over 75% of all species so far recorded in this EU review of GW biodiversity are crustacea. Proposed change (if any): In the absence of any scientific evidence to support the guideline proposals the PNECgw should be based on the daphnia NOEC with an AF of 10.	No change to the guideline. Rationale: Please see comment above.
740	32	Proposed change (if any): My comment concerns paragraph 4.2.6.1. "Phase II Tier A assessment for groundwater /	No change to the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Effect assessment for groundwater". I appreciated the fact that the PNECgw has been calculated in a precautionary manner, by dividing the PNCEsw by a factor of 10. In this way, the peculiarity and fragility of groundwater ecosystems are acknowledged. However, I have some concerns about Equation 22. The PNECsw of Equation 22 is based on the most sensitive taxon among three functional groups, one of which consists of photosynthetic organisms not represented in groundwater ecosystems that are devoided of light. Another functional group is represented by fish, that is large predators, which do not occur in European groundwater bodies. I therefore believe that the use of Equation 22 can lead to unrealistic scenarios. Groundwater ecosystems, especially European ones, are dominated by crustaceans. I suggest using *Daphnia* to calculate the PNECsw in Equation 22. Ecotoxicological studies with stigobiotic species are indeed scanty and this implies the need to use surface water surrogates. However, such studies should be encouraged as much as possible, and the data obtained should be preferred for the PNECgw estimate. I would suggest taking into account the following scientific literature for the possible development and/or integration of this paragraph. 1. Di Lorenzo T., Di Marzio W.D., Fiasca B., Galassi D.M.P., Korbel K., Iepure S., Pereira J.L., Reboleira A.S.P.S., Schmidt S.I., Hose G.C., 2019. Recommendations for ecotoxicity testing with stygobiotic species in the framework of groundwater environmental risk assessment. Science of	Rationale: Comment noted and shared references are appreciated. If daphnia is the most sensitive taxon, it will be used. Please see also comment above.

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		the Total Environment, https://doi.org/10.1016/j.scitotenv.2019.05.030. 2. Di Lorenzo T., Cifoni M., Fiasca B., Di Cioccio A., Galassi D.M.P., 2018. Ecological risk assessment of pesticide mixtures in the alluvial aquifers of central Italy: Toward more realistic scenarios for risk mitigation. Science of the Total Environment, 644: 161–172. 3. Di Marzio W.D., Cifoni M., Sáenz M.E., Galassi D.M.P., Di Lorenzo T., 2018. The ecotoxicity of binary mixtures of Imazamox and ionized ammonia on freshwater copepods: implications for environmental risk assessment in groundwater bodies. Ecotoxicology and Environmental Safety, 149: 72-79 (Q1).	
740	46	The effect assessment for groundwater is only based on ecotoxicological data (Eq. 22). In the head paragraph (line 730) bank filtration is mentioned which indirectly indicates that groundwater is widely used for drinking water abstraction. In Germany groundwater resources are used for 75 % of drinking water. This makes it necessary to include a toxicological effect assessment similar as it is carried out in section 4.2.8 (secondary poisoning, lines 938-945). Also the PBT assessment in section 5.2 includes a consideration of toxicological data (Table 16).	No change to the guideline. Rationale: The scope of the guideline is the evaluation of potential environmental risks posed by the use of medicinal products and not on potential impacts on human health.
742	21	What is the protection goal related to groundwater, is it indeed the organisms living in groundwater? For biocides, REACH and plant protection products the "target organism" or protection goal when performing a groundwater assessment are human beings, consuming drinking water derived from groundwater. Therefore the default values	Text edited. Rationale: The scope of the guideline is the evaluation of potential environmental risks posed by the use of medicinal products and not on potential impacts on human health. However, a detailed explanation for the groundwater assessment has been added in chapter 4.2.2.

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		provided in the drinking water directive are e.g. used as trigger values against which the PEC in groundwater is compared. Is the exposure of "non-target" human beings taking up drug residues via drinking water also considered in any way in the groundwater assessment of HMPs? Proposed change (if any): Provide an explanation on the protection goal of the groundwater assessment (i.e. are these indeed groundwater living organisms and not human beings, if yes which organisms are these?).	
743-744	15	The additional assessment factor of 10 to extrapolate the PNEGW from the PNECSW could have the unintended effect of making the groundwater risk assessment more important than the surface water risk assessment form pharmaceuticals that enter the environment via a sewage treatment plant.	Comment noted. See responses above for further explanations.
752-755	1	The use of should, need(s), mandatory, etc is inconsistent throughout the document. For instance, lines 752-753 state "if the risk quotient is > 1, risk refinement options should be used in Phase II Tier B as described below." Line 755 states "If the RQgw is > 1, further evaluation is needed in Tier B using one or more of the options below." Proposed Change (same as Lines 694-697): The word "should" be revised to "need(s)" or "is mandatory" or a similar phrasing that removes ambiguity	Text edited. Alternative phrasing to "should" implemented.

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		throughout the document when what is being requested is a required action.	
754-791	27	See previous comment (to lines 730-733). The Phase II Tier B calculation of $PEC_{pore\ water}$ (taken equal to PEC_{gw}) based on $PEC_{soil\ Tier\ IIB}$ via equilibrium partitioning to groundwater is the second option and should be added to this section. The possibility of $RQ_{gw} \geq 1$ can also be triggered via deposition of sludge onto soil. It is noted that in REACH and BPR framework, $PEC_{pore\ water}$ is calculated as the time averaged concentration over 180 days. The extra calculation is not complicated as PEC_{soil} exposure modelling is already present, $K_{soil\text{-}water}$ has already been calculated for that purpose, only PEC_{soil} should be time averaged over 180 d. As both exposure routes (bank infiltration and leaching from soil) can occur concomitantly, the *highest PECpw resulting from both options* should be selected for the risk assessment. Proposed change: Add calculation routine of $PEC_{gw} = PEC_{pore\ water}$ from a time averaged PEC_{soil} over 180 days via equilibrium partitioning, acc. to REACH and BPR exposure models.	Text edited. Additional groundwater assessment following sewage sludge application to soil has been added. The additional comment to remove from Tier IIB: PECgw = 0.25 * PECsw refined, was not agreed, as this equation is part of Tier A (section 4.2.6.1, line 761).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Add guidance that the highest of both PECpw values calculated, should be used in Tier IIB groundwater risk assessment. In addition: remove from Tier IIB, when PEC_{soil} has been calculated the option of PEC_{gw} = 0.25 * $PEC_{sw\ refined}$. This is a lower tier assessment, redundant in Tier IIB.	
757-759	1	The requirement to conduct "groundwater modelling for a realistic worst-case scenario according to SiMBaFI" begs questions regarding whether it has been independently validated in the decade since its creation (Müller et al., 2010). Also, in the line 759, the link to the SiMBaFi – a bank filtration simulation model, does not work. Please update the link to a working one. Proposed change (if any): Provide a link that works for the SiMBaFI model.	Text edited. Working link has been updated.
757-780	30	For the phase II Tier B assessment SIMBaFi -model is suggested. We are not familiar of the model, is it representative enough for the whole Europe? Has the model been validated?	The results are available in a peer reviewed publication (https://doi.org/10.1007/s11270-010-0568-9). The model includes no specific regional characteristics and is very simple. For regional marketing authorisations the model can be adapted to representative local settings if knowledge on groundwater flow time is known.
759	2	In the line 759, the link to the SiMBaFi – a bank filtration simulation model, does not work. Please update the link to a working one. Proposed change (if any):	Text edited. Working link has been updated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Provide a link that works for the SiMBaFI model.	
762	27	Determination of a Freundlich (OEC 106, step 3) adsorption constant has absolute priority over point estimate K_d values. To enhance reliability of the exposure modelling, applicants should not be encouraged to stop after step 2 of the OECD106 guideline, which is often seen in practice, but to follow the guideline and produce adsorption isotherms and Freundlich adsorption constants (K_f). Proposed change: Adapt text to express that the outcome of OECD 106 is a K_f value and the 106 guideline should be conducted including step 3 (detemination of K_f). Only when it is practically impossible to determine K_f values, K_d values may be used. This also pertains to other guidance parts where K_f / K_d are needed.	Text edited. K_D and K_{OC} have been changed to K_F and K_{FOC} throughout the GL. Explanation added to chapter 4.2.1.2
763	1	How widely used is the SiMBaFI model and is there any published science that has validated its use within a regulatory context to protect against environmental risks? This guideline and the use of this model appears to have a focus on human health. Should it be defined here when to use Kf over Kd? SiMBaFi manual only uses Kd.	The publication of SiMBaFi has been accompanied with a peer reviewed publication: https://doi.org/10.1007/s11270-010-0568-9.
765	12	Kd derived from sludge ? Based on which guideline? 106 is not possible. Proposed change: delete sentence	No change to the guideline. Rationale: The comment is not understood. Adsorption data on sludge cannot be used independent from the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
766-769	17	An OECD 308 study is no longer required in Phase II, except in certain cases (PBT assessment). Still, to refine PECgroundwater calculations, the results of the OECD 308 are indicated to be used. Does this mean EMA wants applicants to conduct an OECD 308 study to address concern for the groundwater compartment? Does this mean that groundwater exposure should only be considered for bank filtration, and is it assumed that groundwater will not be exposed after application of sludge to soil? Please note that other PECgroundwater models (FOCUS pelmo and FOCUS pearl, mentioned in the documentation on SiMBaFi, which is the indicated model for human medicines) use a DT50 value in soil for groundwater assessments. An OECD 307 study is expected to be conducted more frequently than the OECD 308 under the revised guideline. Please explain why the OECD 308 is indicated as the source of the DT50. This is not well explained in the revised guideline. Proposed change (if any): Explain why for refinement of the groundwater assessment the DT50 should be determined in an OECD 308 study rather than in an OECD 307 study.	No change to the guideline. Rationale: The SiMBaFi model was developed using DT50 values determined in an OECD 308 study. Water content in bank filtration systems is much higher than in soil simulation systems according to OECD 307, therefore the system in OECD 308 seems more suitable for a bank filtration model. However, if a soil assessment is required and data from OECD 307 are available, the applicant can scientifically justify why data from OECD 307 can be used. The highest DT50 should be used independently from the number of tested soils as the SiMBaFi model is not developed for the use of OECD 307 data. If OECD 308 data are available, they should be used, if not the data from OECD 307 can be used.
766-767	25, 26	It is stated that the OECD 308 DT50 is to be normalised to 12°C. It should be specified how this is to be carried out. Proposed change (if any):	Accepted. A link to the Arrhenius equation is now included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please specify how the normalisation is to be carried out. (Using the Arrhenius equation as in section 5.2.2.1, or some other way?)	
766	27	A water-sediment simulation study is needed here. Does this mean that for this section, performance of OECD 308 is triggered? This should be made more explicit. Proposed change: Provide clear overview of higher tier (IIB) data requirements, e.g. 'perform OECD 308 (aerobic systems only) when in Phase IIA, $RQ_{gw} \geq 1$ for the exposure route via surface water.'	No change to the guideline. Rationale: OECD 308 is listed in Table 12 (previous table 9) and is marked as a required fate study for Tier B groundwater assessment.
766	27	typo DT 50 Proposed change (if any): remove space	Text edited.
766	48	Please amend DT 50 to DT50 Could you add an explanation for the propose use of DT50 at 12°C when the temperature of groundwater in Europe is usually with the range 2 to 4°C	Text edited. It is acknowledged that the temperature in groundwater/bank filtrate varies by seasons, urban influence and geographically in Europe. The temperature profile along the flow path from surface to groundwater influences the degradation. Changes of the temperature were not included in the model. For the development of SiMBaFi four bank filtration sites in Germany was investigated. Their groundwater temperature ranges between 8.0 and 14.2°C because the groundwater/bank filtrate strongly reflects the temperature conditions of the infiltrating surface water.
768	1	Please re-affirm that DT50 values from the OECD 308 are to be based on total system, not water or sediment, consistent with ECHA Guideline.	No change to the guideline. In line 768 and in table 9 the guideline explicitly explains to use DT50 values derived from total system.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Make the guideline explicit that DT50 values are for the total system.	
768 Table 9	1	Reference is made to using Kfsoil; however, this is only determined in Tier 3 testing of OECD 106, which is not required and is not listed as a necessary input parameter in Table 1. Proposed change (if any): Kfsoil should be removed from the guideline document or guideline is needed on when Tier 3 testing would be appropriate or required.	Text edited. K_D and K_{OC} have been changed to K_F and K_{FOC} throughout the GL. Explanation added to chapter 4.2.1.2
768	48	Please note that the FOCUS guidance is currently recommended for determining the half-lives of a substance for REACH and PPP. Four different first order kinetics models are currently recommended, with two more in discussion. These are Single-First Order (SFO), Double First Order Parallel (DFOP), First Order Multi Compartment (FOMC) and Hockey-Stick (HS). Further discussion and advice should be sought about how and why to justify which model should be used.	No change to the guideline.
770	27	missing word: 'the realistic worst case should be used' Presumably the realistic worst case scenario. Proposed change: 'the realistic worst case **scenario** should be used'	Text edited.
773	1	For refinement of the PECgw, the user is able to apply the SiMBaFi model to predict concentration in the groundwater at a location 5 days of travel in the groundwater from the	The groundwater flow of 5 days represents the 20 percentile "realistic worst-case scenario" of observed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		source. This value has no scientific basis and seems arbitrary. Please provide a scientific justification.	values at German bank filtration sites. This default flow times is the result of a groundwater model approach and subsequent statistical evaluation of the modelling results. For further details please refer to the report, manual or publication linked here: https://www.umweltbundesamt.de/publikationen/mathematical-transport-simulation-of-pharmaceutical
773	27	Eq. 27 uses a K_d value as input, a soil adsorption coefficient not normalised to organic carbon. This is different from the use of a (geometric mean) K_{oc} value at other places in the guidance. Groundwater models that have been derived for Dutch national purposes as well as those in international frameworks (e.g. PEARL, PELMO), have explicitly been developed such that average *DT*50 and adsorption contstant values should be put in, *in order to arrive at realistic worst case outcomes*. Input of extreme values will result in extreme outcomes, which is undesirable from a risk management perspective. Hence, we propose the model be redefined to allow input of a mean adsorption constant. Or, is the intention that Rf be calculated for three different soil types (each with their respective K_f) and the worst-case Rf be used in risk assessment? Proposed change: Develop modelling to result in realistic worst case outcomes and adapt singular K_d input to reflect this.	No change to the guideline. Rationale: This comment is not understood. K_F is an input value in Eq. 30. As for all calculations in this guideline where adsorption data is used, the realistic worst-case scenario is envisaged by recommending a geometric mean. The prerequisites for the parameter are listed in the beginning of chapter 4.2.7.2 (old 4.2.6.2).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
781	1	The guideline requires calculation of concentrations at a production well; however, it is unclear how this is relevant to an environmental risk assessment. It is likely that the terminology is being taken directly from the SiMBaFi model but in this case a refined PECgw should be calculated and not a PECproduction well. Is the ERA guideline straying towards protecting human health and drinking water?	No change to the guideline. Rationale: For the risk assessment of human medicines the entry into the groundwater is considered conservatively via bank filtration. The SiMBaFi model is a bank filtration model considering the flow from surface water to the groundwater production well. As bank filtration is a non-natural process production well is a common technical term for the end of the transport route. Therefore, and to be in line with supporting information of SiMBaFi model this terminology will not be changed. For the scope of the guideline please refer to other comments above.
784	48	Please check the equation as this could be simplified i.e. ln2/DT50 is equal to the degradation rate constant (k).	No change to the guideline. Rationale: An input of the DT50 is necessary to calculate the $PEC_{GW\text{-}REFINED}$. By simplifying the equation 26 with the degradation rate constant (k) an additional equation is needed. As DT50 values are widely known as results from simulation studies, no further simplifications are needed.
786	27	add comma after 100% for readability and delete space between 100 and % Proposed change (if any): As the percentage of bank filtrate at the production well is assumed to be **100%,** the resulting PEC_{GW} equals the calculated concentration in the production well (eq. 27).	Text edited.
792-796 and 1233	45	It is necessary to have trigger values for the different risk characterization categories (i.e. insignificant, low, moderate, high, cannot be excluded and exempt).	No change to the guideline. Rationale: There is no scientific basis for classification of risk into categories.
797	29	The new soil trigger emphasises the importance of soils and their ecological functions. It considers the present findings	Comment is noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		about active substances originated from human pharmaceuticals in sewage sludge and soil. It is scientifically sound that a trigger value should depend on substance characteristics and on the predicted environmental concentrations. The 'EU Strategic Approach to Pharmaceuticals in the Environment' points out the importance to know more about effects, accumulation and persistence of active substances in soil. The new trigger and the new approach in effect testing are fully in line with this intention.	
798	48	Please could you clarify this paragraph. We are unsure of the main message of the paragraph.	Text edited. Rationale: The word "combined trigger" is replaced with "a set of trigger values depending on a combination of chemical-physical substance properties (Kfoc) and the predicted concentration in surface water", as the latter depends on the dose and the fraction of a population receiving the active substance during a given time.
800	17	A Koc value of 10 000 L/kg is indicated as a trigger value. Please clarify that this is the value determined in sludge. Proposed change (if any): Specify that the Koc indicated as the trigger is that for sludge	No change to the guideline. Rationale: This is clear from Table 10.
800	27	indicates. the word is redundant in the sentence Proposed change (if any): delete 'indicates'	Text edited.
805-806	27	as phrased now, the wording '(not a particular sensitive group of species)' is unlucky. Moreover, the adverb 'entire'	Text edited. Species selection is outlined in Table 11.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(entire soil compartment) is not needed and should be deleted. Moreover, we wonder why both should be made explicit here. The point of departure that the soil ecosystem is the protection goal should rather be explained in an introductory section. As for water: representative species/process are selected for testing, etc. It then suffices to simply state here: the soil compartment. Proposed change: When the PEC/PNEC ratio is ≥ 1, a risk to the soil compartment is indicated. Make sure that principles of risk assessment, species selection, assessment factor scheme etc. to cover the soil ecosystem, are explained briefly in an introductory section (as for water).	
806-807change to the guideline. Rationale:	1, 25, 26, 42	Lines 806-807 state "If a risk is identified in Phase II Tier A, a refined assessment may be performed in Phase II Tier B." Is a Tier B assessment required? Proposed Change: Rephrase "may be" to "is needed in a Phase II Tier B evaluation."	No change to the guideline. Rationale: The applicant may choose whether to accept a risk (and possibly have to apply risk mitigation measures) or whether to refine the risk assessment. Thus, the term 'may be' is appropriate.
811	1	No justification is provided for the requirement for long-term accumulation PECsoil values. Is there evidence to demonstrate considerations beyond the P criteria are necessary?	Text edited. "Substances being persistent according to the PBT criteria (see section 5), may accumulate in the soil environment, as they are not rapidly degraded. In these cases, the concentration in soil

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please could EMA provide a scientific justification and the evidence base for concern over accumulation or high concentrations of pharmaceuticals in soil through multiple sewage sludge applications to soil?	after repeated sludge application should also be assessed using the approach presented in Eq. 22.
813-814 & 836-837	1	It is proposed that for substances which "accumulate and are not easily degraded", PECsoil after multiple sludge applications should be considered. These terms are not defined Proposed change (if any): Appropriate definitions and justifications should be provided for the terms "accumulate" and "not easily degraded" in respect to soil exposure.	Text edited. See previous comment.
813-814 and 838-839	17	For accumulating substances, the concentration in soil after repeated sludge application should be assessed. Please clarify how often sludge can be applied in one year. From the text (and table), it appears that it is assumed that application is conducted once per year. Is that correct? Proposed change (if any): Indicate how many times sludge is applied on soil per year.	Text edited. See previous comment.
813-814	25, 26	Accumulation into soil taken into consideration. Thumbs up!	Comment noted.
813-814	30	Tukes appreciates that accumulation into soil is taken into consideration	Comment noted.
813	48	Please clarify how to assess the soil after multiple applications of sludge. There are currently no OECD Test	No change to the guideline. Rationale: The procedure is described in eq. 22-23.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Guidelines to demonstrate how this could be assessed. In addition after sludge application soils are tilled and sludge will move from one redox environment to another. These variations may influence the degradation rate. Please reference to line 822.	The risk assessment approach presented in this guideline is based upon pragmatic and general assumptions acknowledging that there are numerous scientific details and assumptions that cannot be covered and reflected in the text, such as changing redox, pH and physical changes of soils though e.g. tilling and/or weathering. With regard to calculating PEC soil at steady state, guidance can be found in eq. 22-23, this approach is duplicated from the REACH risk assessment framework.
815	12	As it is pointed out that the temperatures should reflect environmental conditions in the OECD 307 – is the application of the test substance in the test done with sewage sludge, to reflect the relevant exposure situation? Nobody will apply the substances without sludge to soil. This will have massive influence for the DT50 determined in the test (orders of magnitude higher biological activity). Proposed change: add, how OECD 307 setup should be with regard to application	No change to the guideline. Rationale: It is correct that it cannot be ruled out that DT50 may change depending on if sewage sludge is added or not to the OECD 307. The 307 is not designed to add sewage sludge, therefore the degradation is measured in soil alone.
817-820	25, 26	Extrapolating DT50 is a good suggestion. However, 12°C may be too high a temperature for several areas within Europe. For instance in Finland annual average temperatures in soil are around 5°C (with occasional freezing). According to the Arrhenius equation the DT50 to be expected in the Finnish situation (5°C) would be twice as long as in a temperature of 12°C. Proposed change (if any):	No change to the guideline. Rationale: The risk assessment procedure described here is aiming to guide applicant towards an EU wide risk assessment. Some general approaches, compromises and uniform standards have to be applied in this context. 12°C is considered a realistic scenario covering the majority of regions where sewage sludge is applied to farmland. This value is also used in other substance frameworks as an EU average.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The 12°C extrapolation temperature should be decreased. Also regional differences could be encouraged to be taken into cosinderation.	
817	27	This footnote should be changed, it is misleading. The requirement to derive a *DT*50 for soil is part of a valid OECD 307 study, which encompasses *DT*50 values in four soils and clarification of the degradation pathway in one soil. Hence, the statement, 'in case three or more soils were tested' is absolutely wrong. Four soils should always be tested. It may be that it is not possible to derive reliable half life values from each soil (e.g. because degradation is very slow). But the study is not valid if it is not performed with four different soil types. Proposed change: Adapt footnote to reflect the data requirement (4 soils). Adapt text to reflect that (geometric mean) averaging is done with ≥3 reliable *DT*50 values and that the worst case *DT*50 is used when less than 3 reliable *DT*50 values are available.	Text edited. Footnote revised.
817	29	According to FOCUS degradation kinetics the geometric mean should be used if the degradation rates for parent are based on four or more soils (and on three or more soils for transformation products/ metabolites).	Text edited. See above comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please replace "three soils or more" by "four soils or more".	
818	22	Consider using should instead of must.	No change to the guideline.
823	27	textual: add 'calculation of the' Proposed change (if any): The **calculation of the** initial concentration of the active substance…	Text edited.
825	27	R16 should be R.16 Proposed change (if any): **R.16** (throughout the document)	Text edited.
828	25, 26	Since SimpleTreat and other calculation software are not perfect in estimating concentrations of especially ionic/anionic compounds in sludge, calculated concentrations should be compared to actual detected concentrations, when possible.	No change to the guideline. Rationale: The presented risk assessment framework is applicable also for HM products with new AS where no monitoring information can be expected. And it is beyond the scope of this ERA to demand actual analytical verification of environmental concentrations made in e.g. field studies.
828	27	Since PEC_{soil} is only calculated after running SimpleTreat, and *C*sludge is an output parameter of SimpleTreat, it is easier to use the SimpleTreat output value for *C*sludge. It need/should not be recalculated. Using the value provided already gives much less chance on errors too. The parameter is found in the Concentrations tab of SimpleTreat; it reads: **Combined sludge (C_{sludge})** In Eq. 28 PEC_{soil} should be renamed into *C*sludge$_{soil1}$ (0).Stay in line with REACH/BPR guidance here. The	Text edited. "The concentration in sewage sludge (Csludge) is calculated by the use of the SimpleTreat model."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		calculated concentration here is not PEC_{soil}, but only an intermediate step. After this initial concentration, sludge is applied for 10 consecutive years, and PEC_{soil} is only calculated after the 10^{th} sludge application. EMA guidance does already provide these equations (from line 835 onwards). Proposed change: • Rewrite section around eq. 29 to simply taking C_{sludge} as provided by SimpleTreat (see above); • rename PEC_{soil} to Csludge$_{soil1}$ (0). Keep up with source guidance (REACH or BPR) and modelling. Change the description that is now given for PEC_{soil} to the description of Csludge$_{soil1}$ (0). • If it is thought to complicated to provide all the equations and details, we suggest moving these to an Appendix. We are happy to assist in getting this section correct.	
828	27	C_{sludge} should be presented before eq. 28 as it is input for the equation to calculate $PEC_{soil\ initial}$. Proposed change: move section on $C_{lsludge}$ before that on calculation of PEC_{soil}. In other words, swap eq. 28 and 29 and their descriptions.	No change to the guideline. Rationale: The PECsoil is presented with reference to the upcoming Csludge calculation.
829 and 831 Table	29	Delete the number 1000000 in the equation 29 and change the Unit of $Elocal_{water}$ to [mg d^{-1}] in parameter table	No change to the guideline. Rationale: The difference in units is addressed by the inclusion of a conversion factor of 1,000,000.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
829 and 831	29	Please change the parameter Sludgerate for readability reasons to e.g SludgeRate, SLUDGERATE	Text edited.
831	1	Elocalwater is specified here as "kg d^{-1} (see Eq. 7)" but in Eq. 7 the resultant Elocalwater units are mg d^{-1} (as dose is in mg); clarification is required. Proposed change (if any): Clarify units more specifically and be consistent to avoid confusion	No change to the guideline. See comment above.
831 Table	27	• Error. The concentration in sludge (C_{sludge}) is a **dry weight** concentration! Its parameter description is: concentration in dry sewage sludge. Hence: mg kg_{dw}^{-1}. • the sludge application rate $APPL_{sludge}$ also contains a dry weight sludge mass. Its parameter description is: dry sludge application rate. It is agreed to leave the year out of the unit of this parameter as it does not re-appear in the calculated concentration in soil. Proposed change: Adapt table according to comments given above.	Text edited. Table has been corrected.
835-861	25, 26	The calculation methods for the long-term accumulation in soil seem to be in line with the RA TGD (EC 2003). Giving the equations in the guideline is a definite improvement to the 2006 ERA-guideline.	Comment noted.
836-854	1	There is an apparent inconsistency regarding the use of the term's dissipation, degradation and biodegradation when discussing DT50s For example, the text and table surrounding Eq. 32 discusses:	Accepted. The OECD 307/308 uses the term "Transformation", half-life and disappearance time depending on whether the transformation is following first order kinetics or not. In this document the words "transformation" and "half-life" are now used.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- k in terms of dissipation - DT50 in terms of biodegradation - the text refers to degradation These are all different and this distinction should be clarified. Proposed change (if any): Clarify the utilised terms for DT50 in terms of specifics of degradation, biodegradation and dissipation for long-term soil exposure assessment, Eq. 32 and throughout the guideline.	In the context of OECD 301/314 the word (bio)degradation is maintained as this is in line with the OECD GL.
836-861 1126-1156	1	There is little discussion on the consideration of non-extractable residues (NER) with respect to DT50 for risk assessment and exposure assessment. It should be highlighted that for risk assessment, bioavailability should be considered a pre-requisite. Thus, NERs should not be considered as part of the bioavailable fraction relevant for soil exposure in environmental risk assessment (ECETOC, 2010, 2013). Proposed change (if any): The draft Guideline should be revised to consider the diminished bioavailability of APIs as non-extractable residues (NER).	Text edited. See section 5.2.2.1.
845-850	27	Taking only the contribution of biodegradation into account to describe the overall removal rate constant in soil (excluding leaching and evaporation) influences the outcome of calculated PEC_{soil} values significantly for	Comment noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substances with K_{oc}<1000 L/kg and *DT*50 ≥300 d, because leaching then also represents part of the overall soil removal rate constant. We ask the drafting group to carefully consider whether the soil exposure modelling is appropriately performed with only $k_{biodegradation}$ for the expected combinations of K_{oc} and *DT*50. We are happy to share our modelling results. We note that evaporation generally does not play a significant role, but its mathematical inclusion is not problematic. Proposed change: To be discussed.	
855-859	27	The conversion is needed and fully correct. However, it can be displayed simpler to prevent confusion. See also comments for sediment (lines 659-662). There is one equation too many. The latter equation is redundant, the others should be slightly rewritten. The first equation should present: $CONV_{soil}$ = RHO_{soil} / (Fsolid$_{soil}$xRHO_{solid}) Of which the outcome (1.13) is now missing in the table. The 2nd equation should state: PEC_{soil_DW} = PEC_{soil} x $CONV_{soil}$ Proposed change: Change equations as stated above.	Text edited.
860	22, 29	Value for CONVsoil missing in the table.	Text edited, see comment above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Add the default CONVsoil value 1.13 in the table.	
868	29	Ionisable test substances should be tested at pH values where the test substances are present in neutral state and at an environmentally relevant pH (5-9). Please add therefore the following sentence. Proposed change: please add "For ionisable test substances, care should be taken that testing is performed at pH values where the test substances are present in neutral state and at an environmentally relevant pH (5-9)."	Text edited.
869 (table 11)	1, 13, 19	"OECD 222/ OECD" – should this include the Enchytraeid study guideline number? Proposed change (if any): "OECD 222/OECD 220"	Text edited.
869	29	Toxicity endpoint for the nitrogen transformation test OECD 216 in the table should be corrected according to corresponding text passage of the guideline. Proposed change: please correct to "≤ 25% of control**"	Text edited.
869	29, 48	Proposed change: In Table 11 please add "OECD 220" as TG number for test on enchytraeids in table column "Guideline"	Text edited.
870 (Table 11 footnote)	1	It is unclear why the N-transformation study is recommended only to be tested at 1xPEC and 10xPEC. This poses difficulties when conducting testing:	Not agreed. Rationale: The presented outline of testing and risk assessment for the soil microbial community is in line with the method and procedure used for veterinary medicinal products. Furthermore, it is within the scope presented in OECD 216 for agrochemicals as

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Usually, the PEC is not 100% clear at the time of testing and the current exposure assessments are conservative. - Often additional indications are added in subsequent applications – potentially altering the PEC - The guideline recommends a dose response study for non-agrochemicals - Is the 10x a requirement, or will this be sufficient to cover increases in PEC for ERA? Proposed change (if any): Footnote should be removed, or the possibility of a dose response study should also be permitted (see also comment below)	stated: "The tests from which this Guideline was developed were primarily designed for substances for which the amount reaching the soil can be anticipated. This is the case, for example, for crop protection products for which the application rate in the field is known. For agrochemicals, testing of two doses relevant to the anticipated or predicted application rate is sufficient." HMP entering the arable soil environment via sewage sludge used as fertilizer have the potential to influence the soil microbial communities in a similar manner to VMP and agrochemicals and the exposure concentration can be predicted (PEC).
870	17	For the nitrogen transformation test, the indicated test design is to include 1x and 10x the PEC, which is the approach adopted for agrochemicals. However, in case new indications are added later on, new Member States are added, or the prevalence of the indication increases, the PEC is likely to increase, and the study may no longer be suitable. Would it be acceptable to conduct a dose response test, as is done for industrial chemicals? Proposed change (if any): Test design should not be fixed to 1x and 10x PEC	No change to the guideline. See comment above.
870	27	The footnote * to the nitrogen transformation test (OECD 216) should be edited. Studies should not be conducted at 1x and 10x the maximum PEC. This test setup was	No change to the guideline. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		developed years ago to match the needs for the risk assessment of plant protection products. It does not result in a NOEC or EC10 and hence the result does not feed into the risk assessment as performed for human pharmaceuticals (and many other frameworks). The OECD guideline 216 provides the possibility to conduct this test using five test concentrations, which allows for determination of ECx and/or NOEC. See e.g. para 5 of TG216: '*Thus, with chemicals other than agrochemicals, the effects of a series of concentrations on nitrogen transformation are determined. The data from these tests are used to prepare a dose-response curve and calculate ECx values, where x is defined % effect*.'. This is the preferred test set up. The requirement should be altered such that a test for 'non agrochemicals' with at least five concentrations is always submitted for human pharmaceuticals, aiming to adequately determine an EC10 and/or NOEC level. The current footnote ** is applicable to the risk assessment of plant protection products ('agrochemicals'), it is not applicable to the test set up end result type needed for the risk assessment of human pharmaceuticals. The footnote should be removed. Proposed change: 1). Table 11, column two, row 1: change '<25% of control' into: EC10 or NOEC [mg kg^{-1} dry weight]	

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		2) edit footnote * into: Studies should be conducted with at least five test concentrations as per OECD 216 for 'non agrochemicals' aiming at determination of an EC10 and/or NOEC. Footnote ** becomes redundant. Delete.	
871-874 (table 11 footnote)	1	The footnote (denoted '**') is confusing, and overall, the interpretation of the N-transformation study in this guideline is confusing. Currently the footnote implies that a <25% deviation at day 7, for example, would constitute "no long-term influence" irrespective of >25% deviation at later timepoints. This is not considered to be the intention. The OECD 216 guideline states: "If, on the 28th day, differences between treated and untreated soils are equal to or greater than 25%, measurements are continued to a maximum of 100 days." The interpretation being that if less than 25% deviation this can be considered as a 'no effect concentration' at the end of the study or at any subsequent timepoint after day 28 if extended. Ideally the use of this study should allow flexibility to use either a two concentration or dose response design in the current assessment scheme. It should be possible to select a NOEC, using the same criteria, from either a dose response study or two concentration style study. Either NOECs (i.e. PNECs) can then be utilised in the current risk	No change to the guideline. See comment above.

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		assessment scheme and allow flexibility for the Applicant to use values not based on PECs (which can change). Proposed change (if any): The footnote should be revised. Suggest the following: "An assessment factor is not relevant to this endpoint – The substance can be evaluated as having no long-term influence on nitrogen transformation in soils when the difference in nitrate formation between the treatment and the control is < 25% after 28 days."	
871-873	15	The below footnote implies that results could be ≤25% at Day 14 and then >25% at Day 28 and still be classified as having no long-term influence on nitrogen transformation in soils. I believe this should as per the OECD 216 guideline (section 33). Proposed change (if any): Please add a footnote to the Table and include the text: An assessment factor is not relevant to this endpoint – when the difference in rates of nitrate formation between the lower treatment (i.e., the maximum PEC) and control is ≤25% at any sampling time from day 28, the substance can be evaluated as having no long-term influence on nitrogen transformation in soils.	No change to the guideline. See comment above.
871-873	17	The evaluation of effect is stated to be based on nitrification rate at any sampling time before day 28, which should not deviate by more than 25% from the control. Why before day 28? The study is usually conducted until day 28 or	No change to the guideline. See comment above.

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		longer in case of deviations >25% at the end of the study (for agrochemicals). Please clarify. Also, from the footnote it is not clear how the rate should be calculated: is it the overall rate from day 0 to end of study, or different rates in consecutive intervals? The latter makes more sense, otherwise intermediate samplings could be omitted. Proposed change (if any): Clarify how results should be evaluated	
873	13	Which are the consequences of the results in the set-ups with 10 x PEC? If they don't trigger any action, why is this concentration tested?	No change to the guideline. See comment above.
888	22	When would refinement based on consumption data be applicable? Define, or delete "consumption data". Proposed change (if any): See comment.	Text edited. "If a risk for soil organisms has been identified in Tier A, it is possible to refine the emission rate to influent wastewater by metabolism data as performed in Tier B for surface water (see section 4.2.3.2)."
890-891	25, 26	The aim of Tier B exposure assessment seems to be to decrease the PEC_{soil}-value. This should not be the only aim. Tier B should include e.g. analysis of potential uncertainties and their impact on the PEC_{soil} and RQ calculations. Increases in PEC_{soil} and RQ and incorporation of the precautionary principle should also be possible outcomes of the Tier B assessment. Proposed change (if any):	No change to the guideline. Rationale: The main aim of the PEC refinement is not *per se* to make it lower, but to make it more realistic.

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		"If a risk for soil organisms has been identified in Tier A, *Tier B exposure assessment is required. The aim of this assessment is to identify the most significant uncertainties in deriving both PEC_{soil} and RQ, to estimate their impact on the outcome and to* refine the emission rate to influent wastewater by using consumption data and metabolism data as performed in Tier B for surface water (see 4.2.3.2)."	
892-903	2	As with many other compartments in the scheme, the Tier B refinement options are limited. For the soil compartment specifically: - No exposure refinements in soil are proposed - No refinements suggested for species other than N-transformation Proposed change (if any): PECsoil refinement should be based on the soil+sludge or soil degradation study results + considering the usual sludge to soil application regime in line with VMP ERA PECsoil refinement base on degradation in soil.	No change to the guideline. See above for responses to comments in line 870 and l888.
892-903	1	As with many other compartments in the scheme, the Tier B refinement options are limited. For the soil compartment specifically: - No exposure refinements in soil are proposed - No refinements suggested for species other than N-transformation Proposed change (if any):	No change to the guideline. See above.

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893	1	Discussion of an RQ for soil based on nitrogen transformation is included. But the determination of such an RQ is not described above since the determination of a PNEC for nitrogen transformation is not given. Proposed change (if any): An approach utilizing the NOEC or EC25 for N-transformation as a PNEC equivalent would enable multiple, more transparent approaches to the risk assessment (i.e. PECsoil/PNECN-Trans <1) when the PEC and Study concentrations are not equivalent. This approach should be clarified.	No change to the guideline. See above.
893-895	1	Inclusion of 100d extension to the OECD 216 study is confusing to include at Tier B. The increase in the study duration is within the study, which is conducted at Tier A. Proposed change (if any): Suggest the study extension is discussed in Tier A. Also, a study extension within dose response studies can be considered as a refinement for long-term NOECs or EC25 values.	No change to the guideline. See above.
893-894	13	Which test concentration has to be considered for RQsoil (1 x PEC or 10 x PEC?). Which concentration has to be tested in Tier B?	No change to the guideline. See above.
893-895	17	It is indicated that in case a risk is calculated for the soil compartment based on the soil nitrification test, the test should be extended to 100 days in Tier B. This would not be necessary if a dose response design would be adopted (see previous comment), as in that case	No change to the guideline. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the test design is independent on the PEC value and will always deliver a NOEC. This would be in line with the text in the OECD 216 test guideline, which states that for chemicals other than agrochemicals, a dose response should be constructed. Please note that a risk may be indicated at a later stage in case the PEC has increased. Therefore, it would be more efficient to have a test delivering a NOEC rather than having an effect <25% at a certain PEC (see also previous comment). It is not desirable to have to repeat a study due to test design that no longer matches the expected environmental concentration. Proposed change (if any): Please consider previous comment on test design to avoid having to repeat a study due to risk assessment and/or changed PEC values.	
896-899	27	See our comments to Table 11 (lines 869-870). These comments equally apply to Table 12. Proposed change: Adapt as proposed in comments to Table 11 (lines 869-870).	No change to the guideline. See above.
896	29	See comment for line 869 (table 11)	Text edited.
897-899 (table 12 footnote)	1	As with Table 11 this footnote is confusing: "at any sampling time before day 100". The extension is designed to demonstrate that short-term effects >25% can be acceptable if recovery is observed within 100 days. Proposed change (if any):	No change to the guideline. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest change to: "An assessment factor is not relevant to this endpoint – when the study is extended, the substance can be evaluated as having no long-term influence on nitrogen transformation in soils when the difference in nitrate formation between the treatment and the control has returned to a level <25% within 100 days.	
897-899	15	The below footnote implies that results could be ≤25% at Day 56 and then >25% at Day 100 and still be classified as having no long-term influence on nitrogen transformation in soils. I believe this should as per the OECD 216 guideline (section 33). Proposed change (if any): * An assessment factor is not relevant to this endpoint – when the difference in rates of nitrate formation between the lower treatment (i.e., the maximum PEC) and control is ≤25% at any sampling time from day 100, the substance can be evaluated as having no long-term influence on nitrogen transformation in soils.	No change to the guideline. See above.
902-903	25, 26	The presented calculation methods do not exclude risks to the environment. They ensure they are unlikely, but do not exclude them. If the aim is to exclude risks, I propose either selecting the default values used in ERA-calculations more conservatively or decreasing the RQ-threshold from 1 to e.g. 0,1. Proposed change (if any): Please consider reselecting the default values more conservatively or decreasing the RQ-threshold.	No change to the guideline. Rationale: The threshold value of 1 is considered sufficient to assess (exclude) risks for all environments.

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904-957 (section 4.2.8)	27	Section 4.2.8. on secondary poisoning is not in accordance with the methodology in the guidance document for derivation of EQS under the WFD. We have rewritten the section and will submit this along with our comments. Proposed change: Revise section 4.2.8 according EQS guidance (WFD) as submitted in separate document.	Text edited. The methodology available under the Water Framework Directive (WFD) has been taken into account and chapter 4.2.8 has been revised, also in accordance with the comments below.
904	29	It is highly appreciated that the risk for secondary poisoning is now assessed for HMP. Scientific literature shows that there are pharmaceutical substances that accumulate in the food chain and are found in top predators. Therefore, assessment of secondary poisoning completes the prospective risk assessment and is in line with EQS requirements of the water framework directive.	Comment noted.
904-957	29	Comment: The chapter does not include the risk characterisation of secondary poisoning via the terrestrial compartment. Proposed change: **Proposal for the "general" part (lines 904-923):** Secondary poisoning is a toxic effect on predators from consumption of contaminated prey (aquatic or terrestrial) It is relevant for compounds that accumulate via the food chain (biomagnification), mainly lipophilic compounds. Biomagnification takes place via the aquatic and the terrestrial food chain, and the respective secondary poisoning has to be assessed separately. When the log Kow indicates a bioaccumulation potential, a bioconcentration factor in fish (BCFfish) should be	No change to the guideline. Rationale: The secondary poisoning assessment initially focusses on the aquatic compartment as this compartment is considered most relevant regarding the emission routes of pharmaceuticals. Therefore, the chapter focusses on the aquatic food chain. A sentence is added indicating that the terrestrial food chain is also relevant to assess when the terrestrial risk assessment is triggered. The 'input values' section has been shortened in the published guideline.

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		determined experimentally. The BCFfish is an accepted indicator for bioaccumulation in aquatic, the BSAFworm (biota to soil accumulation factor) for terrestrial species. **Proposal for the "input" values part (lines 937-945)** Inputs for the calculation of secondary poisoning potential are the BCF_{FISH}/BSAF and the most relevant mammalian toxicity data from the non-clinical part of the dossier, i.e. preferably the lowest no observed adverse effect level (NOAEL) from a chronic repeat-dose toxicity study (minimum of 28 days) in the most sensitive species. This NOAEL is converted to a no-effect-concentration in food, (NOEC). There are different methods to derive predictable no effect concentrations for predators ($PNEC_{Biota}$) available, e.g. ECHA 2017c; ECHA, 2016 and Water Framework Directive EQS (European Communities, 2018).	
904-913 and 484-486	36	In chapter 4.2.8. Secondary poisoning, the statement about the risk for secondary poisoning (on birds and mammals) gives an impression that the risk is highest for lipophilic compounds and the guideline requires evaluation of secondary poisoning when log Kw is ≥3. Although it has been shown in the scientific literature that the lipophilicity does indeed correlate with the uptake of active substances in fish, the elimination of the active substance (from fish or any species at all) is hardly dependent on the lipophilicity. A number of different enzymes (primarily cytochrome P450) in charge of the xenobiotic elimination in human are also expressed in fish, but the elimination kinetics is almost	No change to the guideline. Rationale: The current guideline is, as far as possible, in line with other regulatory frameworks in which secondary poisoning is assessed, such as REACH and WFD. OECD test guideline 319B is not considered sufficient to use as evidence to decide on further assessment of secondary poisoning.

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		impossible to predict based on molecular properties. To certain degree, the metabolism (elimination) of the active substance in fish may follow that in human, but oftentimes the elimination kinetics in fish is much slower and sometimes the critical isoenzyme forms (in charge of the active substances elimination in human) are completely lacking in fish. This may result in significant bioconcentration of the active substances in fish, even if their log Kw is <3. On the other hand, some highly lipophilic active substances may be effectively eliminated by the fish enzymes, with only very moderate risk of bioconcentration. Since the adaptation of the first ERA guideline in 2006, OECD has released The Test Guideline 319B to determine the clearance of a test chemical in vitro using sub-cellular liver fraction of rainbow trout (Oncorhynchus mykiss) as the metabolising system. Proposed change: In accordance with the 3R implementation (lines 116-117 of the revised ERA guideline), the OECD 319B test should be implemented as part of Phase II Tier A studies so that this data (clearance in fish) could serve as an additional trigger for the secondary poisoning tests. Ideally, OECD 319B should be supplementary data to the current log Kw -based decision on whether or not the fish bioconcentration test (OECD 305) should be conducted, i.e., either one (low clearance or log Kw>3) should trigger the secondary poisoning tests.	

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905	22	Proposed change (if any): Consider adding "predatory fish".	Text edited.
905-909	25, 26, 30	Secondary poisoning may also be possible through the terrestrial foodweb via earth worms -> birds, etc. Proposed change (if any): "a bioconcentration factor in fish (BCF_{FISH}) *and earth worms* should be determined experimentally"	No change to the guideline. Rationale:See response to the comment to line no. 904-957, stakeholder no. 29
905	27	Although secondary poisoning risk assessment is usually performed and modelled using birds and mammals, the phenomenon of secondary poisoning is not restricted to these two animal taxa. The sentence should be adapted as proposed. Proposed change: Secondary poisoning is a toxic effect on animals at trophic levels higher in the foodchain (e.g. predatory fish, birds and mammals) resulting from … etc.	Text edited.
907-909	7	We believe that the trigger value for secondary poisoning is overly conservative at logK ≥3. We consider that closer alignment with other legislation would be more appropriate, such as the veterinary medicines guidance (logK ≥4.0). We know of no examples of a pharmaceutical with a logK <4.0 that has proven to bioaccumulate with a kinetic BCF >2000 (Constantine et al., [attached poster]); suggesting little scientific justification not to align these triggers at logK ≥4.0. Further, both traditional (Miller et al. 2016) and machine learning models of accumulation in both fish and invertebrates support this threshold (Miller et al. 2019).	No change to the guideline. Rationale: The trigger of Log Kow ≥3 is in line with the trigger in other regulatory frameworks such as REACH and WFD. OECD test guideline 319B is not considered sufficient to use as evidence to decide on further assessment of secondary poisoning.

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		Predictions of bioaccumulation for molecules against a measure of logK are based on adsorption to lipids and do not consider metabolism. Therefore, if a trigger of 3 must be maintained, then a tiered testing strategy whereby molecules with logK between 3 and 4.0 could first be tested in the in vitro S9 and hepatocyte assay (OECD 319a/b), or more complex and physiologically competent organoid *in vitro* models such as liver spheroids (Baron et al. 2012, 2017; Uchea et al. 2013, 2015), and gill models to demonstrate both uptake and metabolism (Schnell et al. 2016; Stott et al. 2015). If a molecule was found to be readily metabolised in such an assay, then the BCF would not be required as accumulation is highly unlikely. These alternatives are established (and accepted by both the OECD and ECVAM) and therefore under ethical priorities of the EU legislation EU 2010/63/EU these must be used before testing in vertebrates outside of regulatory requirements; this is the opportunity for the legislation to move forward and use these tools. This could significantly reduce the numbers of animals used whilst maintaining appropriate levels of protection. Proposed change (if any): Amend the secondary poisoning trigger to Log K ≥4.0 to align with veterinary medicines guidance. Alternatively include a tired testing strategy for molecules between LogK of 3 and 4.0 with a focus on in vitro assays to reduce animal testing.	

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907-908	1	The trigger for secondary poisoning is said to be the Dow between pH 5 and 9. But here it says log Kow which is defined in lines 375 and 376 as the ion-corrected Dow for the neutral species. These are inconsistent. Proposed change (if any): We suggest that a footnote could be added for clarification, e.g. as log Kow for neutral APIs but log Dow determined between pH 5 and 9 for ionizable APIs.	Text edited.
908/909 and 914	1	We believe that the log Kow-trigger (≥3) for bioconcentration testing in context with secondary poisoning is too low. This will result in unnecessary fish testing. The respective trigger for secondary poisoning (BCF of 100) is also too low. Non-bioaccumulative compounds are not likely to represent a risk in the food chain. As we suggest above, there should be harmonisation with the trigger values in the veterinary medicines' (≥ 4.0) or REACH (≥ 4.5) guidelines. In the interest of transparency and scientific integrity, it would be highly desirable for EMA to conduct a retrospective analysis to evaluate whether APIs meeting the log Kow ≥3 criterion have been associated with secondary poisoning of birds and mammals. Proposed change (if any): Use the trigger of log P (or D)ow of 4 (see also guideline EMA/CVMP/ERA/52740/2012, 2015) and a BCF of 2000 as in the bioaccumulation ("B") criterion.	No change to the guideline. Rationale: The trigger of Log Kow ≥3 is in line with the trigger in other regulatory frameworks such as REACH and WFD.

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Line 908-909, 925, Table 13	1	OECD 319 A&B, for determination of intrinsic clearance values using rainbow trout hepatocytes (319A) and rainbow trout liver S9 subcellular fraction (319B) was finalized in 2018. BCF values can be estimated from intrinsic clearance values as per Nichols et al. (2013). Proposed change (if any): Estimated BCF values based on *in vitro* intrinsic clearance data (OECD 319 A&B) may be used to assess B or vB, provided that the final results will most likely not result in borderline cases of meeting either the B or vB criterion."	No change to the guideline. Rationale: OECD test guideline 319B is not considered sufficient to use as evidence to assess B/vB properties.
908	1	Does it have to be fish? Lines 1160-1161 suggest that for determining B in the PBT assessment, a species other than fish could be used. Could a non-fish species also be used for secondary poisoning? We also recommend that this guideline should be worded with such flexibility that where appropriately justified or as other techniques (e.g. *in vitro* and *in silico* approaches) become more widely accepted, they can be used. For example, OECD 319 A&B for determination of intrinsic clearance values using rainbow trout hepatocytes (319A) and rainbow trout liver S9 subcellular fraction (319B) was finalized in 2018. BCF values can be estimated from intrinsic clearance values as per Nichols et al. (2013).	No change to the guideline. Rationale. On the first: Although it is correct that bioaccumulation studies with other aquatic species may also be used to conclude on secondary poisoning, the current guideline focusses on experimental values for fish as bioaccumulation in fish is most commonly tested and to keep the guidance simple for the user. No change to the guideline. Rationale: On the second: OECD test guideline 319B is not considered sufficient to use as evidence to assess B/vB properties.
909	48	Please consider amending as follows: It should be noted that a lack of accumulation in mammals does not exclude a potential for accumulation on fish and other aquatic species and vice versa. Investigations have shown that the presumed dominant mode of lipid/adipose bioaccumulation	No change to the guideline. Rationale: The scope of the guidance is to keep it simple, therefore current text is considered sufficient.

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		may only be relevant for certain substances and potentially species. Accumulation in proteinaceous tissues has been proposed and is being explored under REACH. An example of this are the perflourinated compounds perfluorooctanoic acid (PFOA) and perfluorosulphonic acid (PFOS)	
911	27	The general, primary reason of bioaccumulation is uptake of substances in lipophilic parts of membranes; other processes may also cause or contribute to accumulation. The sentence should include 'also' at the start. Proposed change (if any): Add 'also': Accumulation may **also** occur …etc.	Text edited.
913	29	There may also be other indications of bioaccumulation, see therefore ECHA Guidance, chapter R.7c. We propose an approach that further allows taking other indications of bioaccumulation into account. Proposed change (if any): Please add following sentence: If other indications for a bioaccumulation potential exist (e.g., measured data in biota in the field data or special structural indications), it may be necessary to perform the PBT assessment even if the logKow < 4.5.	No change to the guideline. Rationale: The scope of the guidance is to keep the assessment simple, therefore current information is considered sufficient.
914-915	1	Clarify what secondary poisoning characterisation is required for: Secondary poisoning characterisation in ECHA R.10 and R16 includes the following: Risk to freshwater fish-eating predators, risk to marine fish-eating predators,	No change to the guideline. Rationale: See response to t comment to line no. 904-957, stakeholder no. 29

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		risk to marine top predators, Assessment of poisoning via the terrestrial food chain (worm eating predators). Proposed change (if any): Reflect the clarifications from above in the revised guideline.	
917-918	27	'When mammalian toxicity data are not available for further assessment (i.e. calculation of a $PNEC_{BIOTA}$) can be waived.' Understanding that mammal studies cannot be asked in case of 'old' or existing substances, we propose to use the concept of recalculating the therapeutic dose into an ADI (using an assessment factor) as a worst-case check with respect to secondary poisoning. For a pragmatic calculation method we propose the route of 'human fish consumption of the WFD guidance' (section 4.5). The result of this calculation can be presented, and in case the outcome is a potential risk, this could be flagged. Proposed change: Use the therapeutic dose (DOSEai) to perform an indicative secondary poisoning assessment in case no mammal toxicity data is available.	No change to the guideline. Rationale: The original sentence has been removed from the guideline and therefore the comment is not relevant anymore.
918	48	Could you explain why, when mammalian toxicity data are not available, further assessment (i.e. calculation of a $PNEC_{BIOTA}$) can be waived? What would justify doing so? Would it not be better to state that "at this time it is not possible to complete" rather than "waived" (which sounds like "dismissed").	See response to the comment to line no. 917-918, stakeholder no. 27

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919-923	1	This paragraph is not needed here, because all aspects of PBT are covered in the respective section. Proposed change (if any): We suggest deleting this paragraph.	Text edited. The first paragraph (line 914-918) is considered relevant for the secondary poisoning assessment, the second paragraph (line 919-923) is considered partly relevant. Text of the second paragraph is amended.
919	27	Add a unit behind 2000 Proposed change (if any): > 2000 **L/kg**	Text edited.
919	48	Please clarify whether all PBT criteria are assessed under the EMA regulations as standard. For REACH substance each endpoint is iteratively assessed as P, followed by B, followed by T. i.e. if a substance does not meet the persistence/very persistent criteria then bioaccumulation assessment will not be required to determine bioaccumulative/very bioaccumulative etc	No change to the guideline. Rationale: The requirements regarding PBT/vPVB assessment are specified in the corresponding chapter (Chapter 5).
921	27	information on (not) ready biodegradability should also be taken into account, a textual addition is proposed Proposed change: '…(Table 16) should be also assessed, **by using all available information on degradation: the study on ready biodegradability,** the study on degradation in soil…etc.'	No change to the guideline. Rationale: Text has been amended, and the proposed change is not considered relevant anymore.
923-924	27	not correct per se. If a substance meets the vB criterion, degradation should be assessed simply using the P and vP criteria, this is normal procedure. A substance may meet the vB criterion, but not the P criterion or meet the P	No change to the guideline. Rationale. The text has been amended, and the proposed change is not considered relevant anymore.

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		criterion or meet the vP criterion, resulting in either a vB, pvB or vPvB substance. Proposed change: degradation should be assessed using the P/vP criteria.	
924-934	7	Text could be added to the effect that a single concentration should be considered sufficient for establishing a reliable BCF and reduce numbers of fish required for BCF estimation. Data is available with a variety of chemical types (including ionisable) to indicate that multiple concentrations are not required for BCF estimation (e.g. Creton et al., 2013 and Burden et al., 2014) Proposed change (if any): Include text such as: It should be noted that data reviews have demonstrated that for a wide array of chemicals the estimation of BCF is unaffected by test concentration (Creton et al., 2013 and Burden et al., 2014). Therefore, in order to reduce the burden on animals, testing of a single concentration should be sufficient for estimating the BCF for the majority of medicinal products.	No change to the guideline. Rationale: The applicant is recommended to perform a test in line with the OECD 305 guideline, in the guideline information is provided on aspects such as the number of test concentrations considered to be sufficient.
926-925 and 947	17	For bioconcentration, the BCF is indicated to be preferred over the BMF, while for calculation of secondary potential, $PNEC_{BIOTA}$ is indicated to be converted into a $PNEC_{SW,SECPOIS}$ by dividing it by the BCF_{FISH} **and** BMF. This seems contradictory. Should "and" be "or"? Proposed change (if any): reconsider wording	No change to the guideline. Rationale: Both BCF_{fish} and BMF are needed to calculated $PNEC_{SW,SECPOIS}$.

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926-928	20	Please include a reference to ECHA guidance R11 for cases where dietary tests are necessary. Also, suggest rewriting the sentence, as the message is not clear. Proposed change (if any): Suggested rewrite: "Aqueous exposure is the preferred methodology when technically feasible because dietary exposure yields a biomagnification factor (BMF) rather than a BCF. A BCF can be estimated from the depuration rate constant. However, it should be noted that these calculated BCFs may be more uncertain than experimental BCFs due to the uncertainty in the k1 prediction. See further discussion in ECHA guidance document R11."	Text edited.
928-929	27	we agree that a kinetic BCF, based on uptake and elimination rates, is preferred. Besides this it should be added that also the uptake and elimination rate derived from a simultaneous kinetic fit is preferred. Proposed change: The kinetic calculation of BCF (based on simultaneously fitted uptake and elimination rates and taking dilution due to fish growth into account) is preferred over… etc.	Text edited.
930	48	The OECD has published a spreadsheet to help with calculation of BCF from BMF data. This is available in the test guideline section beneath the guidance document on the OECD website	Text edited. The OECD spreadsheet is not cited; however a table is added with default BMF values for organic substances for secondary poisoning assessment.
931-934	1	We do not agree that the minimized approach is not applicable to the BCF estimation. As per OECD 305,	No change to the guideline.

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		substances may be evaluated using the minimized test design if uptake and depuration are expected to follow first order kinetics. Based on the rationale for the minimized test design, if first order kinetics are followed, a kinetic BCF value can be obtained regardless of whether steady state is achieved. Proposed change (if any): Replace lines 931-934, to state, The OECD 305-II minimised aqueous exposure fish test may be used to estimate the BCF and assess B or vB provided the eligibility criteria as outlined in the OECD 305-II are met and that the final results are not considered borderline cases of meeting either the B or vB criterion.	Rationale: The resulting BCF estimate from a minimized test design is considered less accurate than a full BCF study. Sentence is added: 'The kinetic BCF resulting from the minimized test should be considered as less accurate as the BCF from a full BCF study.'
931-934	1	As per OECD 305, the aim of the minimised test design is to "provide BCF estimates of adequate accuracy and precision for risk assessment decisions." As long as a substance meets eligibility criteria as outlined in OECD 305-II, mainly, "be likely to exhibit approximately first order uptake and depuration kinetics" and log Kow < 6, the minimised test design may be considered appropriate. In addition, as per ECHA guideline, Chapter 11, R11.4.1.2.2, "OECD 305-II, minimised aqueous exposure fish test may also be used to assess B or vB, provided that the final results will most likely not result in borderline cases of meeting either the B or vB criterion." Proposed change (if any):	No change to the guideline. Rationale: See response to comment to line no. 931-934, stakeholder no. 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Replace lines 931-934, to state, The OECD 305-II minimised aqueous exposure fish test may be used to estimate the BCF and assess B or vB provided the eligibility criteria as outlined in the OECD 305-II are met and that the final results are not considered borderline cases of meeting either the B or vB criterion.	
935-936 Table 13	27	The trigger value is incorrectly displayed. It is >100 Proposed change: add > sign: **>100**	Text edited. It is missing, but ≥ instead of > is added.
937 ff	29	There is only little experience with the new energy normalised method according to the water framework Directive EQS. Compared to other methods, this is time consuming, especially the required detailed research in the toxicology data set (e.g. body weight or composition and energy content of the used food). We would recommend open options regarding the usable method. In addition, we would appreciate some more explanation on the methods. Proposed change: Please insert the choice of different methods and give some explanation as an overview, e.g. as following: "For the conversion from dose to the needed concentration (NOEC) in the (lab) predator, different methods exists (e.g. REACH guidances R16 2016; TGD 2003, TGD-EQS). The REACH and TGD method take empirical default values (conversion factors, CF) into account, whereas the TGD-EQS method will replace these default values. Information	No change to the guideline. Rationale: The provided method is considered state-of-the-art and should be used to determine the secondary poisoning potential.

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		on body weight, actual food consumption and the energy content of food has to be addressed."	
938-941	1	The use of a mammalian NOAEL is needed to convert to a NOEC. The document states that preferably the lowest chronic NOAEL from preclinical studies should be used. However, the preclinical testing programme varies depending on the type of API and the envisaged treatment regime. We suggest the provision of clearer directions, which type of studies and endpoints in the mammalian testing programme are suitable for deriving this NOAEL. It should be noted that the "lowest NOAEL" is not necessarily the appropriate value for determining environmental risks, endpoints chosen should be both biologically relevant and relevant at the population level. Therefore, further guideline should be provided in the guideline, which supports the selection of the preclinical toxicity endpoint and a justification in the ERA considering treatment regime used in the study and population relevance of the effects. (Other agencies have provided guidance, see EFSA, 2009; 2015). One of the inputs for the calculation of secondary poisoning potential is "the most relevant mammalian toxicity data from the non-clinical part of the dossier, i.e. preferably the lowest no observed adverse effect level (NOAEL) from a chronic repeat-dose toxicity study (minimum of 28 days) in the most sensitive species." How does one address the issue of those drugs that have only been tested and dosed via parenteral administration, for instance, due to low oral bioavailability? Proposed change:	Text edited. Based on the comment additional guidance is given on selecting the most relevant toxicity endpoint to determine secondary poisoning. Oral administration data is preferred, and relevance of data concerning other administration routes should be justified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The use of NOAEL data and adjustment factors should be at discretion of risk assessor and relevant to the ERA outcome/ testing approach. This would be consistent with best practices for establishment of permitted daily exposures (PDEs) for residual carryover of difference medicinal products in shared facilities pursuant to EMA (2014) guidelines.	
938	20	Secondary poisoning should also be considered through a terrestrial food chain with terrestrial predators as well. The suggested assessment system will not be capable of addressing substances that may accumulate in the terrestrial food chain. The use of sewage sludge as fertilizer or sewage water irrigation will lead Proposed change (if any): Consider secondary poisoning for terrestrial predators/ecosystems	No change to the guideline. Rationale: See response to the comment to line no. 904-957, stakeholder no. 29
939-941	27	One pivotal point is missing here. The NOAEL value that should be selected, should be based on a population relevant endpoint, such as e.g. growth (length, weight), reproduction, development, mortality. If more than one study with different exposure durations and/or animals is available, the lowest NOAEL for a population relevant endpoint from all relevant studies should be selected for conversion to a PNEC, using the assessment factor applicable to the study duration. It may be that a test with shorter exposure duration reports a more sensitive endpoint than the test with longest exposure duration. In such a case, the assessment factor corresponding to the longest exposure time might be applied to the most sensitive	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endpoint, even if it is from a study with a shorter exposure time. See p. 88 of WFD guidance. Both issues above (population relevant endpoints; correct PNEC derivation procedure) should be added in the guidance. Proposed change: 1) after 'the most sensitive species', add: for a population relevant endpoint, being growth (length, weight), reproduction, development, mortality. 2) add WFD text on selection of the relevant NOAEL and assessment factor. Reference may be given for full text, but the procedure should be shortly described in the EMA guidance.	
941	22	It is unclear how this NOAEL should be converted to a NOEC, especially if the route of administration is not oral. Proposed change (if any): Consider clarifying how the conversion should be done.	Text edited. The sentence is removed from the text, and text is amended to make the steps of the assessment clearer.
941	27	typo Proposed change (if any): **repeated** dose toxicity study	Text edited.
942-943	1	We do not agree to the application of the "caloric content in food" approach, as described in the Technical Guidance no. 27 (draft, 2018). This approach is against the SCHEER advice. SCHEER 15.09.2017: "However, the scientific evidence for the new methodology is very sparse compared with the documentation that is available for the diet-or	No change to the guideline. Rationale: The approach provided by the most recent WFD guidance document is currently state-of-the-art and is followed in this guidance document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dose-based methodologies that are being used by EFSA and ECHA in current risk assessments. The SCHEER concludes that uncertainties that may be introduced with the new methodology cannot yet properly be evaluated due to a lack of scientific information." We do not see a need to use this complicated approach with little scientific support. We suggest using the approach described in Technical Guidance no. 27 (2011). Proposed change (if any): Delete sentence.	
942	17	It is stated that the NOEC may be normalised to the caloric content in food. It is not clear under what circumstances this should or should not be done. Please clarify. Also, as with all other calculations in the guideline, please indicate how the normalisation should be conducted (are there any default assumptions?). Proposed change (if any): Clarify when the NOEC should be normalised to the caloric content in food and how.	Text edited. The sentence is removed from the text, and text is amended to make the steps of the assessment clearer.
942	27	The calculation method described here does not correspond with the WFD EQS 2018 guidance. If a NOAEL is available, it is not calculated to result in a NOEC and then converted to an energy normalised NOEC, but the NOAEL itself is directly normalised to the energy content of the food. In case NOAELs are not available, but diet based endpoints are (NOEC from mammal studies, expressed in mg kg_{food}^{-1}),	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		these can be energy normalised via an alternative calculation. See p. 86 of the WFD guidance. Proposed change: We will submit a text proposal for this section based on the principles for the secondary poisoning assessment according to the WFD EQS 2018 guidance.	
942-943	27	The textual reference 'according to the Water Framework Directive EQS' is not correct. Reference should be made to the guidance document for derivation of EQS under the Water Framework Directive. Proposed change: according to **the guidance document for derivation of EQS under the Water Framework Directive** (European Communities, 2018).	Text edited.
943	7	Reference is not included in the reference list Proposed change (if any): Update reference list	Text edited.
943-949	1	Clarification on required equations, their source, and AF values, should be included here. Proposed change (if any): add "see ECHA 2008 equation R.10-17 and table R.10-12 "	Text edited. Proposed change is not adopted, but instead equations are given
945	27	typo: assessment factor is applied to the derivation of the $PNEC_{BIOTA}$ Proposed change (if any):	Text edited.

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		assessment factor is applied **to derive** the $PNEC_{BIOTA}$ or: assessment factor is applied **for derivation of** the $PNEC_{BIOTA}$	
946	27	In line with the other sections in the guidance, the title of this section should be ' Risk characterisation'. In addition, clearly provide an equation how the risk characterisation ratio $RQ_{SECPOIS}$ is calculated: $RQ_{SECPOIS}$ = $PEC_{sw,\ SECPOIS}/PNEC_{SECPOIS}$ Proposed change: 1. Change title of this section into Risk characterisation 2. Add an equation showing how the risk characterisation ratio is calculated.	1. No change to the guideline. Rationale: Based on a new outline for the secondary poisoning chapter the proposed change has not been adopted. 2. Text edited.
946	48	Could you please reference the REACH R16 guidance document in this section? Please insert the relevant equation to accompany the text "$PNEC_{BIOTA}$ may be converted into a $PNEC_{SW,\ SECPOIS}$ by dividing it by the BCF_{FISH} and BMF", which needs to be defined.	Text edited. The equations to calculate $PNEC_{biota}$ are added to the guideline, with reference to the WFD EQS guidance.
947-957	1	We suggest again to state the different tables based on the ECHA guidance which has to be used to derive the default values in the various calculations of $PNEC_{BIOTA}$, BMF etc. Proposed change (if any): Add reference to "ECHA guidance table R 7.10-3, R10-11, R10-12"	Text edited. Table R 7.10-3 is added to the guidance, the other tables are not considered relevant for the guidance.
948	1	Proposed change (if any): "Lower" instead of "higher".	Text edited.
950-952	1	We suggest giving guidance, when the alternative approaches should be used. Having two approaches without	Text edited.

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		clear guidance on which to use allows for confusion, whether the risk is determined via the food chain or via water exposure.	
956-957	29	Please use the current updated version of Water Framework Directive EQS. Proposed change: cite as „European Communities, 2018"	Text edited. Proposed change accepted but as European Commission, 2018.
958-1070	2	A tailored risk assessment for antiparasiticides should be performed. But there is no proposal how to perform assessment with antiparasiticides. Proposed change (if any): Any specific approaches, studies for antiparasiticides should be defined. If no specific approach is needed (the general ERA studies – table 1), this should be also defined in the guideline.	No change to the guideline. Rationale: No tailored assessment needs to be performed for antiparasitics. For those substances, the action limit does not apply, but a regular phase II assessment has to be performed.
958 ff	29	The enhanced chapter on a tailored effect assessment is highly appreciated and reflects the state of the science for endocrine active pharmaceuticals. Especially the overview of recommended effect studies is a very helpful tool for selection in line with the respective mode of action of the pharmaceutical.	Comment noted.
958, 960, 1031 and 1037	29	As a tailored assessment is only related to the required ecotoxicity testing it is proposed to make this clearer in the following paragraphs. Proposed change:	Text edited. The term 'tailored testing strategy' is now used.

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		Replace the terms "tailored assessment" or "tailored risk assessment" by "tailored effect assessment" in the respective lines.	
958-959	36	Chapter 4.3. Tailored assessment for active substances with a specific mode of action should be supplemented with at least antineoplastic (cytostatic) compounds. Proposed change: A specific sub-chapter should be added on how to deal with antineoplastic compounds. There is a lot of scientific evidence on the existence of antineoplastic compounds in the surface waters at concentrations below the threshold of 0.01 μg/L. Although these compounds are often rapidly degraded in the aqueous environment, regional variation in environmental temperature may significantly impact the degradation and increase the apparent PEC, e.g., in Northern countries (due to low degradation kinetics). Many antineoplastic compounds, not excluding their biological transformation products, also show high potency at markedly low concentrations, which may result in severe ecotoxicity risks even at PEC < 0.01 μg/L.	No change to the guideline. Rationale: In section 3.1.1, it is explained that there may be other substances for which the action limit does not apply. Applicants are encouraged to seek Scientific Advice in such cases. The currently available information on antineoplastic substances does not show that they have effects below the action limit (see Schwarz et al., 2021 (Environ Sci Eur 33:68)). Thus, for these substances the action limit applies. For individual substances however, when available data in the public domain shows toxicity below the action limit, the action limit does not apply.
958-960	47	Line 958 and 960: In the heading and on the first line of the text it reads "tailored assessment". Since it is a special case of "risk assessment", I suppose it should read "tailored risk assessment". The same comment applies for lines 124 and 126 where "Phase II assessment" should read "Phase II risk assessment".	Text edited. Text changed into tailored testing strategy (also in the heading). The tailored testing strategy is part of the risk assessment chapter– therefore, no changes in line 124 & 126.

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958	48	Would it be possible to mention antiparasitic, antimycotic, antiviral and antifungal pharmaceuticals as well? We do not think it is very clear what makes a specific mode of action when these have been omitted from the text. Would it be possible to also add these details into earlier text?	Text edited. Until now there are no specific tests available which would address the specific mode of action of antimycotic, antiviral substances etc. It is now stated in section 3.1.1 "*though this guideline provides guidance on specific assessment strategies only for endocrine active substances, antibacterials and antiparasitics (See Table 16, there might be other substances for which a specific testing strategy is needed due to their specific toxicity profile or mode of action. In these cases, the applicant is encouraged to seek scientific advice*"
960 – 963 and 964 – 965	1, 2	Further explanation is required for Phase II assessment for products that contain APIs with a specific mode of action, for which a tailored assessment is required. Lines 960 – 963 and 964 – 965 are in contradiction regarding the ERA requirements. Firstly, it is stated that a tailored assessment is required for "… *compounds for which the action limit applies, such as antibiotics*", while in the next paragraph it is stated that "*For all APIs that require a tailored risk assessment, an ERA Phase II assessment is required for all compartments, including fate aspects*". If an ERA Phase II assessment is required for all APIs that require tailored risk assessment (in this case also antibiotics) than the action limit does in fact, not apply to this category of pharmaceuticals. Proposed change (if any):	Text edited. Text changed to reflect that for antibacterials, a tailored testing strategy is only necessary if they enter phase II. A table is added in section 3.1.1 to further explain the two types of specific assessment strategies. The trigger values for the other compartments depends on physico-chemical properties. The assessment for other compartments will not be waived based on mode of action. This is now reflected in the text in section 4.3.

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		In general, the trigger of performing the ERA phase II for all compartments should be based on the phys-chem, fate and behaviour properties of the API and not the mode of action specific. Compounds with a low Kow and Koc value will not enter the terrestrial compartment and therefore a tailored ERA should not be performed irrespective of the mode of action for EAS and antibiotic APIs. Further explanation is needed on whether the PECsw action limit of 0.01 µg/L is applicable for antibiotics or their testing in ERA Phase II is required irrespective of the action limit. Additionally, because of the specific action mode of antibiotics a tailored risk assessment based on studies performed according to table 14, is more reasonable than performing ERA phase II for all compartments.	
962-963	46	Surprisingly the action limit should apply for antibiotics. This is in contrast to the procedure illustrated e.g. in the Phase I decision tree (Figure 2) or in line 128 where the tailored assessment immediately starts with Phase II.	Text edited. Text in 3.1.1 changed to reflect that for antibacterials, a tailored testing strategy is only necessary if they enter phase II. Figure 2 also revised for clarity.
964	7	It is unclear whether the intent is for all compartments to be examined as part of a tailored assessment or only the standard or triggered compartments at Phase II? There is no reasoning why, for example, a terrestrial assessment would be required as part of a tailored ERA for a compound which fails to meet the trigger for a terrestrial assessment. Proposed change (if any): … ~~an~~ a full ERA Phase II assessment is required ~~for all compartments~~…	Text edited. *"For all active substances that require a Phase II risk assessment, a full ERA is required. The tailored testing strategy targets only the aquatic compartment. Where respective triggers for other compartments are met, a complete Phase II assessment is still required for those compartments, including fate studies"*

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969-985	19	The omission of any fish testing may seem justified in the light of the experience since 2006, but effects on the developing fish cannot generally be excluded. Proposed change: The fish embryo test (OECD TG 236) could be considered for the antibiotics assessment as these test organisms may not be considered being vertebrates.	No change to the guideline. However, the idea of tailoring an acute short-term fish embryo assay does not seem to be suitable for evaluating antibacterial mode of action. Especially as there is no strong evidence in scientific publications for higher antibacterial sensitivity of fish embryos compared to prokaryotic species or invertebrates.
969-985	20	Soil is also a very relevant compartment for antibiotic resistance, due to the use of sewage sludge as fertilizer. Proposed change (if any): This should also be reflected in the required tests in table 14.	No change to the guideline. Rationale: The European Commission has recognised, in its Action Plan against AMR (European Commission, 145 2017), that AMR cannot be successfully tackled by isolated, sectoral efforts. A holistic approach is needed taking into consideration the different sectors committed to addressing AMR, in-line with the globally recognised "One Health" approach defined as an integrative effort of multiple disciplines working locally, nationally and globally to attain optimal health for people, animals and the environment. The majority of AMR action plans and monitoring programmes currently focus on human and livestock, but there has been growing concern that the natural environment may play a substantial role in the evolution, persistence and spread of AMR. It is, nevertheless, beyond the scope of this Guideline to evaluate potential risk to human health. Furthermore, it is currently considered immature to evaluate the environmental impact of AMR development, as proper assessment frameworks and test guidelines are absent due to for example a lack of validated strategies for establishing safe levels of substances associated to the long-term development of antimicrobial resistance and suitable

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			models for quantifying antimicrobial resistant genes in the environment.
969-984	25, 26, 30	A tailored risk assessment for antibiotics should also take antibiotic resistance into consideration.	See response above.
970 (4.3.1)	22	Is there a deliberate distinction between antibiotics and antimicrobial active substances? Is there a need for further definition? There is no mentioning of antimicrobial resistance at all. Proposed change (if any): Include at least one paragraph dealing with antimicrobial resistance, and perhaps a notion of future guideline work?	No change to the guideline. Rationale: There is a distinction between "antibacterial" (section 4.3.1) and "anti-microbial", as the latter, more generic term also includes antimycotic substances, e.g. with aromatase inhibition as environmentally relevant side mechanism of action. Only for antibacterial a tailored testing strategy as described in section 4.3.1 and table 14 should be considered. Regarding antimicrobial resistance: see response above.
974	1	The stakeholder requests the CHMP conducts a thorough re-evaluation of the default phase I PECsw of 0.01 µg/L since the value is based on a flawed and potentially biased calculation and is therefore not reflective of the actual situation in the environment nor presents a value which is intended to safeguard the environment from pharmaceutical pollution. This is supported by arguments published in (1): "*… the threshold surface water concentration of 0.01 µg/L that triggered the need for environmental testing was not scientifically based…*" and "*There is no transparency (and potential bias) over the selection of the 800 drugs (out of the 2700 drugs marketed in Germany at the time) used in the calculation*" (1) Indeed as the author states, the intention of the standard PEC calculation seems "*more targeted towards 'capturing' as many drugs as possible for subsequent Phase IIA evaluation*	Text edited. The publication by Schwarz et al. (2021; doi.org/10.1186/s12302-021-00503-0) provides scientific based evaluation of the action limit used in the guideline. The investigated long-term toxicity effect data set came from studies submitted in authorisation procedures of human medicinal products. All active substances to which the PEC action limit applies were included in this assessment. The data demonstrate that the current PEC action limit of 10 ng/L is in a relevant range. In contrast to the stakeholder's statement, the discussion in Gunnarsson et al. (2019) elaborates on possible thresholds for prioritisation for testing of legacy pharmaceuticals. However, a detailed comparison between the data evaluation of Gunnarson et al. and the data evaluation of Schwarz et al. is given in the supplementary information of Schwarz et al.

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		in order to build up a database on effect assessment rather than attempting to provide the best estimate of environmental exposure " (1) It is the opinion of this stakeholder that the PECsw should not be based only on the partial data of one country; Germany, which cannot be reflective (representative) of the rest of European countries. Therefore the PECsw trigger value should be re-evaluated including data from most (if not all) European countries. Furthermore the calculation should be publicly available / published to allow for comments in order to provide a non-biased and scientifically based derivation of the PECsw action limit. The second concern of this stakeholder regarding the PECsw value of 0.01 µg/L is the fact that there is no data on which pharmaceuticals were taken for the derivation of the action limit (that is among the 800 drugs taken for the calculation). Indeed the initial Scientific Committee on Toxicity, Ecotoxicity and The Environment (CSTEE) (2) expressed concerns regarding PECsw trigger value of 0.01 µg/L in that it was not scientifically validated; "*The action limit proposed by the CPMP may be underprotective for some highly ecotoxic pharmaceuticals in the case of pseudoestrogens or genotoxic products or be very overprotective for pharmaceuticals which are harmless to the environment. Therefore, it is neither efficient not effective*" (2). This new draft guideline addresses the issue of endocrine active substances, for which an ERA Phase II assessment is	Text changed to reflect that for antibiotics, a tailored testing strategy is only necessary if they enter phase II. A table is added in chapter 3.1.1 to further explain the two types of specific assessment strategies. With regard to antiparasiticides for human use, it is referred here to e.g. Lopes et al. (2009), Garric et al. (2007), Halley et al. (1989). Note: The stakeholder's reference to "(1), (2), (3) & (4)" cannot be followed as these citations are not explained. Additionally, the content of appendix A provided by the stakeholder cannot be followed as it was empty.

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		required regardless of the PECsw calculation. This is clearly stated "…*This concerns compounds for which the action limit does not apply, such as endocrine active substances…*" and "*If there is evidence that the active substance can exert an effect on development or reproduction by directly interacting or interfering with receptors, hormone levels or activities of oestrogens, androgens or other steroid hormones, that active substance should be assessed in Phase II regardless of the predicted environmental concentration*" The problem it seems is solved in a way that no longer connects the PECsw action limit and endocrine disruptors. Therefore, it is only reasonable to assume, the calculation of the initial PECsw action limit of 0.01 µg/L should not include these (hormone disruptors) pharmaceuticals in its dataset. The stakeholder therefore proposes that the PECsw action limit should be re-calculated in a way that it no longer includes known endocrine active substances in its dataset (exclude endocrine disruptors from the 800 pharmaceuticals used to derive the initial PECsw of 0.01 µg/L). The same arguments apply for antiparasitics, which are in the new draft guideline also exempt from PECsw evaluation – they are required to be assessed in Phase II, regardless of PECsw: "…*Some substances (e.g. endocrine active substances and antiparasitics) should enter Phase II regardless of their PEC value…*". Therefore, the same proposal as above is presented for antiparasitics: the PECsw action limit should be re-calculated in a way that it no longer includes known	

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		antiparasitics in its dataset (exclude antiparasitics from the 800 pharmaceuticals used to derive the initial PECsw of 0.01 µg/L). The tailored assessment – entering the phase II ERA independent of the PECsw values is reasonable for endocrine disruptors (effect seen at ng/L range) and antibiotics (due antimicrobial resistance) but does not make sense for antiparasiticides. Prescription of antiparasiticides to EU population is much lower compared to the endocrine disrupting compounds (hormones or corticosteroids) or antibiotics. Additionally, the antiparasiticides used for human prescription are not expected to pose effects to non-target organisms (algae, daphnid or fish) below the trigger value of 0.01 mg/L (3, 4). Proposed change (if any): The PECsw action limit of 0.01 µg/L should be re-calculated using data from most European countries and not only Germany. Present the draft calculation publicly for potential stakeholders to comment. Data on which the action limit is based on, should not include endocrine active substances and antibiotics because it is not applicable to them, they have to be evaluated in ERA Phase II regardless of the PECsw calculation. Antiparasiticides should be excluded from the tailored assessment approach.	
974	1	Comment:	No change to the guideline.

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		We agree with the exclusion of fish testing for antibiotics and further recommend including the following references in the guideline document as justification: 1. Baumann, et al. (2015). 2. Brandt, et al. (2015). 3. Le Page, et al. (2017). We would additionally suggest that the Agency refers to antibiotics instead of antibacterials on line 974.	Rationale: A more extensive citation of references is not favoured within the guideline.
974	1	We appreciate the explicit statement in the guideline that fish tests are not required for antibiotics and the overall reduction of vertebrate testing. However, we would like to confirm that an AF=10 can still be used when calculating a PNECsw if only daphnia, cyanobacterial and algae studies are performed according to the guideline. If this is the intent of the guideline, we request it be explicitly written into this subsection for clarification. Proposed change (if any): Ensure that the text allows the use of an AF of 10 for the tailored ERA for antibiotics if appropriate data are available from daphnia, cyanobacterial and algae.	Text edited.
975-977	20	Table 14 described 2 times. Proposed change (if any): Delete one heading	Text edited.
975	29	Editorial issue: please include "effect" Proposed change: "Table 14 lists the required effect studies for active substances with an antibacterial mode of action in Tier A."	Text edited.
976-977	29	Editorial issue: please include "effect"	Text edited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change Table 14: Required effect tests in the tailored Tier A assessment for active substances with an antibacterial mode of action	
976 (Table 14)	46	Since antibiotics are targeted to be effective against pathogenic bacteria it is necessary to evaluate bacterial toxicity. Indeed, cyanobacteria are procaryotes but it should be recommended to conduct bacterial tests like an activated sludge test (OECD 209) or a nitrification inhibition test (ISO 9509, in most cases more sensitive). For the assessment of antibiotics their ability to provoke resistance is of utmost importance. Therefore, it is necessary to include the MSC concept of Bengtsson-Palme (Lundström S.V. et al (2016), Minimal selective concentrations of tetracycline in complex aquatic bacterial biofilms, Sci Total Environ. 553, 587-595 *and* Khan S. et al, (2017): The use of minimum selectable concentrations (MSCs) for determining the selection of antimicrobial resistant bacteria, Ecotoxicology 26, 282-293) *and* Bengtsson-Palme J, Larsson DG. (2016): Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. Environ Int. 86:140–149.	Text edited. Regarding antibiotic resistance: see response above to Stakeholder 20.
986-1070	30	For the EAS, Guidance of EFSA & ECHA (Guidance for the identification of endocrine disruptors in the context pf Regulations (EU) No 528/201 and (EC) No 1107/2009 and OECD GD 150 should be also mentioned and preferably to be followed also in this context.	No change to the guideline. Rationale: The proposed EAS identification approach is adapted to the existing CHMP ERA approach and also with consideration to the content of the non-clinical (non-ecotoxicological) dossiers that are also generated for pharmaceuticals before market authorization applications (such dossiers contain pharmacological, pharmacokinetic and toxicological studies). Reference to biocide

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			and plant protection legal frameworks are not considered relevant in this context. Although there are some differences, the combined content of the non-clinical dossier and the proposed revised CHMP ERA guideline overlaps with/covers much of the OECD GD150 levels 1 to 5. As such, the proposed section on EAS identification is considered sufficient.
986	46	This section is focused only on oestrogenic, androgenic and other steroidal hormones (lines 995/996) – pharmaceuticals that are intended to influence the endocrine system. Furthermore, the tailored risk assessment will also apply for drugs with non-intended endocrine activity (line 1001). How should these substances be identified systematically? The limitation on only sexual hormones is not justified. It is well-known that other hormones like thyroidal hormones may also trigger severe environmental effects. Interestingly thyroid hormones are mentioned in table 15. This is inconsistent with the text. It should be clarified that all drugs having an intended endocrine activity should be subject of a tailored risk assessment.	No change to the guideline: Rationale: The proposed approach is intended to focus on pharmaceuticals that have pharmacological mode of action and indications that directly affect oestrogenic (E), androgenic (A), thyroid (T) and steroidogenic (S) hormone regulation ('EATS modalities'). Such pharmaceuticals are considered established EAS (endocrine active substances) and should be assessed with a tailored assessment. Pharmaceuticals with *suspected* E, A and S modalities also require a weight of evidence approach (based on data in the non-clinical dossier and, if relevant, from academic sources). If fulfilling the criteria in a case-by-case WoE assessment, then such pharmaceuticals should also undergo a tailored assessment. Pharmaceuticals with non-EATS modalities are not considered. The text regarding this issue has been further clarified.
987-988	27	This sentence should include the notion that the concentration mentioned refers to surface water. Notably, a comparison is made with a much lower concentration level *in vivo* in the next sentence, but apart	Text edited. The text has been changed to specify that it concerns surface water.

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		from *in vivo* it is not reported to which *in vivo* medium this concentration refers (blood?, plasma? cytosol?, etc). Proposed change: Adapt text with suggestions given above.	
987	43	Section 4.3.2. Endocrine active substances often work additively (various publications by A Kortenkamp, T Backhaus and others). By basing the ERA on individual substances, it fails to meet its reality value. Addition effect of EAS, at least of the original substances and their main metabolites and other important transformation products, should be included in the ERA.	No change to the guideline. The CHMP ERA is based on a total residue approach, which is also described in section 3.2.1. Comment noted. However, mixture issue will not be addressed in the guideline due to the product-based authorization procedures at EU.
987-988	27	[Regarding "*Some drug substances may affect the reproduction or development of vertebrate or lower animals at 987 concentrations < 0.01 µg/L.*":] this sentence should include the notion that the concentration mentioned refers to surface water. Notably, a comparison is made with a much lower concentration level in vivo in the next sentence, but apart from in vivo it is not reported to which in vivo medium this concentration refers (blood?, plasma? cytosol?, etc). Proposed change: Adapt text with suggestions given above.	Text edited. The text has been changed to specify that it concerns surface water.
988	48	Please could you clarify this paragraph. We are unsure of the main message of the paragraph. Is it to justify the specific criteria outside of the main T section?	Text edited. The 0.01 ug/L value refers to that most classes of pharmaceuticals are considered non-problematic if Phase I PECsw is below that value and do not require a risk assessment. EAS pharmaceuticals

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			with very high affinity for steroid receptors etc. are considered to need a tailored risk assessment even if PECsw < 0.01ug/L. GL text has been updated.
994	1	There is a lack of clarity about substances where the mode of action is designed to be a direct effect on non-reproductive hormonal systems (e.g. corticosteroids). The term Endocrine Active Substance (EAS) needs to be explicitly defined in the context of this guideline, to help clarify. Proposed change (if any): We suggest the EMA consider acknowledging the extensive work by other authorities on definitions and guidance available in this area to justify their definition (Bergman, Heindel, Jobling, Kidd, & Zoeller, 2013; European Commission, 2018; IPCS, 2002; Kortenkamp et al., 2011; OECD, 2018).	Text edited. The technical term "EAS – Endocrine Active Substances" has been sufficiently defined in the draft GL. It also covers corticosteroids. In the chapter commented (lines 994 ff), text has been updated and details on how to manage the identification of EAS can be found. Text edited. The text has been modified to also include thyroid hormone agonists and antagonists (i.e. pharmaceuticals whose disease indications concern direct effects on the thyroid endocrine system).
994	48	Comment: It is stated in this paragraph that any substance for which there is evidence that is it an EAS should be assessed in a Phase II tailored risk assessment regardless of PEC. However, line 1027 states that the evidence from published data must show endocrine related effects below 0.01 µg/L to be considered EAS. Line 1037 further states that a tailored risk assessment should be performed if published data shows effects near or above the PECSW. These instructions are inconsistent. If any substance for which there is evidence that it is EAS requires a Phase II tailored risk assessment lines 1027 and 1037 are not required.	Text edited.

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994	48	Comment: Is a substance that has a thyroid acting endocrine mode of action not considered an EAS under this guideline? Thyroid acting substances would be considered endocrine disruptors under REACH and the biocides and PPP regulations. & line 1064: Comment: Please see earlier comment on line 994 and add some detail on the note to the main text to explain why thyroid acting substances are not included in the definition of EAS but may still require testing.	Text edited. The text has been changed to clarify the issue. Pharmaceuticals whose disease indications concern direct effects on the thyroid endocrine system are now also listed as a class that require a tailored risk assessment, making the text consistent with table 17. Note that the WoE approach for suspected EAS pharmaceuticals does not include thyroid assessment, as thyroid hormone level, synthesis changes etc. are very common findings in toxicological tests in non-clinical dossiers and it would be very difficult to draw conclusions from such data.
994-997	45	"If there is evidence that the active substance can exert an effect on development or reproduction by directly interacting or interfering with receptors, hormone levels or activities of oestrogens, androgens or other steroid hormones …". It should be clearly stated in the guideline what kind of evidence is required.	No change to the guideline. Rationale: The types of relevant evidence are discussed in the updated text under the heading Identification of EAS (4.3.2).
994 and 1025	22	It is unclear when the efforts to identify an EAS for substances not intended to target the endocrine system should be performed. Should an EAS-statement always be included in the ERA? It is also unclear when identified signals in the scientific literature are adequate to classify a substance as an EAS needing a tailored testing strategy. Scientific literature referred to will have to be of acceptable quality and the signal be of adequate strength before fish data is triggered. Proposed change (if any): Please clarify as far as possible. Cross-refer to section 6.2?	No change to the guideline. Rationale: There are two levels of EAS identification. The first level is for pharmaceuticals that are established EAS – i.e. substances that have a pharmacological mode of action and disease indication that directly affect oestrogenic (E), androgenic (A), thyroid (T) and steroidogenic (S) hormone regulation ('EATS modalities'). EATS-based endocrine systems – and go directly to tailored risk assessment. On a second level, there is a case-by-case weight of evidence (WoE) approach for pharmaceuticals with suspected oestrogenic, androgenic or steroidogenesis mode of actions (thyroid modality not included in the WoE approach, see earlier comments) that determines the EAS classification and need for tailored risk assessment. Types of relevant endpoints is described in section 4.3.2. Regarding academic data quality, this is covered in section 6.1 and 6.2. Pharmaceuticals with known or suspected

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			non-EATS modalities are not considered. The text regarding this issue has been further clarified in the text. An EAS-statement does not need to be included always in the ERA (see also section 4.1 and Figure 2).
994-997	45	"If there is evidence that the active substance can exert an effect on development or reproduction by directly interacting or interfering with receptors, hormone levels or activities of oestrogens, androgens or other steroid hormones …". It should be clearly stated in the guideline what kind of evidence is required.	Text edited. The types of relevant evidence are discussed in the updated text under the heading Identification of EAS (4.3.2).
1000	27	a tailored risk assessment should be *followed*, not used. Proposed change (if any): change used into **followed**	Text edited.
1001	48	You note that information on potential non-intended endocrine activity should be obtained from respective parts of the dossier. Which *in vitro* tests would be included in the dossier as standard, and would these appropriately cover all the estrogenic, androgenic and steroidogenic (and thyroid) modes of action?	No change to the guideline. Rationale: "Respective part of the dossier" refers to the non-clinical part of an application and not ERA dossier requirements for application for marketing authorization. For extra guidance how to interpret results from in vitro tests, please see e.g. OECD GD150 or OECD DRP178 [ENV/JM/MONO(2012)23].
1004	1	Suggest that further clarity or guidance is given on statements around information on "changes in steroidogenic tissues (adrenals and gonads)" will be classed as EAS – this information comes from the non-clinical toxicity database, but there is no clarification on what is classed as a "change"; this needs to be considered carefully as often effects on the gonads can be recorded but may not	No change to the guideline. Rationale: It is outside the scope of this guideline to cover all possible degrees of changes for different endpoint relevant for endocrine disruption. It should be noted that the EAS assessment will not focus on individual endpoints (e.g. changes in steroidogenic tissues) but a case-by-case weight of evidence (WoE) approach on all the data.

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		be due to endocrine activity and such changes may not result in population relevant effects.	
1005	27	Typo, agonism, antagonism, should be changed into agonist, antagonist Proposed change (if any): agonism, antagonism should be changed into agonist, antagonist	No change to the guideline. Rationale: Agonism, antagonism is considered correct.
1006	1	A Weight of Evidence (WoE) approach is suggested to assess whether a substance is classed as an EAS – is this required for all compounds or just those that have a known pharmacological MoA which is endocrine acting? Proposed change (if any): Clarify whether a WoE analysis is necessary to assess whether any substance is classified as an EAS, or only those with a known pharmacological MoA with a primary endocrine effect. More importantly, please specify which definition of an EAS the EMA wants applicants to use and given the complexity and diversity of WoE approaches for ecological assessments (especially for EAS), please specify the WoE approach EMA wants applicants to follow (e.g. EFSA, 2017; Hall et al., 2017; Stevenson & Chapman, 2017).	No change to the guideline. Rationale: These considerations are part of phase I assessment; for details, please see section 4.1 and figure 2. Consequently, an EAS-statement does not always need to be included in the ERA. The WoE approach is primarily for pharmaceutical substances that are not indicated for direct oestrogenic, androgenic or steroidogenesis-based treatments of diseases but still are suspected to have oestrogenic, androgenic or steroidogenesis modes of actions/modalities. It is outside the guideline to provide specific recommendation on particular WoE approaches
1006-1014	1	It is unclear how *in vitro* and *in vivo* data will be evaluated by a regulator. We are concerned about evaluating information without context, specifically the *in vivo* data. For example, endocrine-related adverse effects at the LOAEL could be due to a high dose level/toxicity.	Text edited.

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		Proposed change (if any): We suggest revising line 1006 to: Preclinical data should be evaluated using a weight of evidence approach to decide if the substance should be considered an EAS and assessed in Phase II using a tailored risk assessment. Data for evaluation could include…	
1009-1011	27	On in vitro data. The cut-off value of 1 µM should not be used because it may lead to false negatives for many EAS (e.g EC50 for the transactivation of bisphenol A is higher than 1 µM). See e.g. Dang 2010, Toxicol Lett 192: 298–315 and Dang et al. 2011 Toxicol Lett 201:152–175. Proposed change: The way of triggering may need to be revised, consider changing the cut-off value for in vitro data to 1 mM.	Text edited. It is agreed that species differences in receptor/enzyme affinities noted in the referred articles, and bioaccumulation, may be of relevance. At the same time, established EAS pharmaceuticals, which by definition are direct-acting on such systems - tend to have affinities in the lower nanomolar range, IC50 and EC50 affinity tests tend to at maximum be in the lower uM-range (in the primary and secondary pharmacology sections of the dossier) and a shift from 1uM to 1mM is considered too great. The in-vitro values have been changed to 10 uM for receptors and enzymes as they are more in line with the conditions of the tests commonly reported in the non-clinical dossier.
1009	27	editorial; propose to change the following: to decide if the substance should be considered ~~to be~~ an EAS and assessed … Proposed change (if any): to decide if the substance should be considered an EAS and **be** assessed …	Text edited.

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1012-1013	27	typo's; add space between value and unit: 1 µM, change agonist and antagonic mode into agonistic and antagnonistic mode Proposed change (if any): <1 µM agonistic and antagonistic mode	Text edited.
1015	1	Concern again with interpretation. Changes in adrenal tissues (i.e., changes in weight) can occur without endocrine modes of action. Proposed change (if any): Changes in adrenal tissues should be considered endocrine-related when supported by other temporally concordant responses.	No change to the guideline. Rationale: A general WoE approach is recommended in which changes in adrenal tissue is only one possibility of several.
1022-1023	34	Assessment of endocrine disrupting effects: We were surprised that only estrogenic, androgenic and thyroidic activities were considered. In fact, several recent publications have highlighted that glucocorticoids and progestagens are prescribed and released in higher amount than estrogenic or androgenic or even thyroidic drugs [Runnals et al. 2010, Hum. Ecol. Risk Assess.; Besse and Garric, 2009, Environ Pollut.]. This is not only reported in Europe but also in Asia and North America [Chang et al. 2017, Environ. Sci. Technol., Daniels et al. 2018, Chemosphere]. This environmental occurrence should be considered in the selection of the assays. For instance, detection of chemicals with thyroidic activity is scarce. Thus, even though the HPG axis is of particular concern,	Text edited. Text of section changed slightly to make it clear that a case-by-case decision based on expert judgement allows to include several endocrine modes of action into the specified assessment. Furthermore, e.g. glucocorticoids are considered as "other steroidal hormones" for tailored test strategy (see draft column 996). Regarding the thyroid activity: agreed, text changed to include thyroid activity.

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		other endocrine pathways involved in crucial physiological processed should also be considered. Also, since some drugs can modulate the clearance rate of endogenous hormones (and so homeostasis) by increasing/decreasing gene expression of detoxification enzyme activity (PXR, CYP3A4) through activation of specific nuclear receptors, such targets should also be investigated. Therefore, it is surprising that the guideline specifically mentions that this should not be considered as a mechanism that would warrant evaluation as an endocrine active substance.	
1025	48	It is stated that evidence from published literature may also be used to determine if a substance is an EAS, including effects on invertebrates. The endocrine system in invertebrates is not well understood and at present there are no internationally validated *in vitro* or *in vivo* mechanistic tests for endocrine disruption in invertebrates. Although we agree that data from invertebrates could be used as part of a weight of evidence approach together with vertebrate data, if endocrine related effects are seen in vertebrates this should be sufficient on its own. If the only data showing potential endocrine effects are for vertebrate and invertebrates, we would not consider this sufficient to trigger further testing.	No change to the guideline. Rationale: This kind of scientific discussion is considered the subject of case-by-case expert judgement. As such, this ERA revision does not intend to give more specific recommendations on relevant taxonomic classes.
1026	1	The endpoints intersex, sex ratio, and feminisation or masculinisation are related to both development and reproduction. Proposed change: 'effects on reproduction' into:	Text edited.

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		'effects on development and reproduction '. Add 'and' before 'developmental effects on.'.	
1027	48	When identifying a substance as an EAS *in vitro* and *in vivo* data from the dossier can be used or published data showing effects below 0.01 µg/L can be used. Does this cut-off apply to the dossier data too, or just to any published data?	0.01ug/L is a cut-off value for going from Phase I to Phase II for 'common' pharmaceuticals (uncommon ones needing more consideration being EAS and antimicrobials). EAS-substances are stipulated to be relevant to the environment also at concentrations <0.01 ug/L, as they tend to have very high affinities for biotargets that in turn are important for the functionality of certain endocrine systems (i.e. with EA(T)S modalities) underlying reproduction, behaviour etc. Many EASs tends to have relative low max-doses, which in turn tends to reduce the calculated Phase I PECsw to low values unless the patient population is very large. That being said, the action trigger value in itself has very little impact on the actual EAS identification. Many pharmaceuticals have a PECsw < 0.01g/L and are not considered or suspected to be EAS simply based on their PECsw. The identification of EAS substances applies for both the dossier (toxicological and ecotoxicological part) and published data.
1028-1029	1	It is specified that substances only need be treated as an EAS (i.e. tailored RA) where effects occur below the trigger of 0.01 µg/L. Proposed change (if any): We suggest clarifying this statement to: Where the evidence demonstrates that endocrine adverse effects	Text edited. See also revised chapter 3.1.1.

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		would be expected, even if below the trigger of 0.01 µg/L, the API should be...	
1030	27	endocrine adverse effects we propose to write endocrine related adverse effects Proposed change (if any): endocrine related adverse effects	Text edited.
1030 ff	34	**Methods to assess endocrine disrupting effect:** Most of the described assays are *in vivo* based whereas some *in vitro* screening methods are available and validated for screening for at least estrogenic activity (guideline 455). Thus, we were surprised that the 3Rs regulation was not better taken into account. In addition, although not standardized yet as OECD guidelines, further robust methods to screen for the transactivation of a panel of relevant nuclear receptors including the human AR, GR, MR, PR, PXR, PPAR, RXR receptors are described in the literature [Seimandi et al 2005, Bellet et al. 2012, Wat Res ; Creusot et al. 2010, ABC]. Such tools are also available with the zebrafish receptor, in vitro [Cosnefroy et al. 2010, Tox Sci ; Riu et al. 2011, Tox Sci] or in vivo at the embryogenic stages [Brion et al. 2012, PLOSone] and so raising less ethic concern. Also, we were surprised that the reference guidance document from the OECD (guidance document N150) was not taken into account in the tiered strategy to characterize endocrine disrupting properties. In fact, *in vitro* screening as a first step prior to confirmation of the effect at the embryogenic and/or adult level appears relevant in the frame of the 3Rs regulation.	No change to the guideline. Rationale: Since pharmaceuticals are neither biocidal nor plant protection products an identification as "endocrine disruptor" (for hazard evaluation) is not necessary. The assessment of risks is appropriate for pharmaceuticals and these methods are based on scientific derivations of the intrinsic mechanisms of action of the active substances.

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1030-1070	36	The testing of EAS should be in accordance with the EFSA and ECHA guidance (Guidance for the identification of endocrine disruptors in the context pf Regulations (EU) No 528/201 and (EC) No 1107/2009) and the OECD 150 guidance Proposed change: The above-mentioned guidance(s) should be followed as far as possible also in the context of human medicinal products.	No change to the guideline. Rationale: Since for pharmaceuticals with endocrine mechanisms of action these mechanisms are well known and described, an additional in-vitro screening for these endocrine mechanisms seems superfluous and a waste of resources. In individual cases where this information is not available it might be appropriate to use additional in-vitro screening methods and guidance like the OECD GD 150. This is a case-by-case decision and is enabled by the relevant chapters of the ERA guideline. Consideration of 3R principles is mentioned in section 3.1 and 3.2.3.
1035	1	We appreciate the explicit statement in the guideline that for EAS, tests can be waived according to the MoA. However, we would like to confirm that an AF=10 can still be used when calculating a PNECsw and request clarification if an RQmicroorganism would still be required as part of the ERA. If this is the intent of the guideline, we request it be explicitly written into this subsection for clarification. Proposed change (if any): Make it clearer that an AF of 10 can be applied to tailored ERAs for EASs. Remove the need for the evaluation of a RQmicroorganism for EAS with a PEC below the action limit.	Text edited. Sentence added (waiving of OECD 209 and appropriate AF of 10).
1037-1041	22	This paragraph includes some repetitions already mentioned in paragraph 1025-1029. Proposed change (if any): Consider revising.	No change to the guideline. Rationale: The lines 1025-1029 describe evidence for EAS identification and lines 1037-1041 contain information for selecting the most appropriate chronic ecotoxicity study within tailored testing.

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1039	7	Typographical error. Tailored assessments are required where effects are observed below the PEC not above. Proposed change (if any): …near or ~~above~~ below the ~~predicted~~ PECsw…	Text edited.
1039-1040	27	See comment to line nr. 1026. Proposed change: Update according to updates in line 1026.	Text edited.
1039	48	Please add a definition of 'near' so that it is clear when a tailored risk assessment is required.	Test edited.
1047	1	We disagree with the OECD 229 study being considered only a screening test and not suitable for a quantitative risk assessment. This test can be modified to include endpoints of concern based on mode of action and/or include additional concentrations to reduce the uncertainty with wide concentrations spacing. We consider it is feasible to consider such studies in a conservative risk assessment. Proposed change (if any): Please see the following reference for example considerations for inclusion of such studies in risk assessment: Wheeler et al. (2014).	No change to the guideline. Rationale: Modifying a test differently from the technical guideline protocol should be based on expert judgement and is a case-by-case decision. There may be justified cases for doing so, but it is not the intention of the guideline to cover every single and specific case.
1047-1058	27	On the tiered testing strategy for fish toxicity tests. TG229, 230 and 234 are all partial life cycle tests. TG234 should not be considered as a higher tier test since it is also a screening test when 3 concentrations are tested. It is suggested that TG229 and TG234 should be treated equally when 5 or more test concentrations are used. This is	Text edited. Please see answer above. In addition, a downgrading of OECD 234 might be possible as a case-by-case decision, but the test then no longer corresponds to the OECD TG. Regarding OECD GD 148 with stickleback: text adapted.

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		especially important for reproductive toxic chemicals to which TG234 may be less sensitive than TG229. In addition, if TG230 is added here, GD148 should be added too. Proposed change: Add text to this section: Results from TG 229 and 234 can only be used for quantitative risk assessment if at least 5 concentrations have been tested. Add OECD GD 148 to the text.	
1047	44	We agree that a tiered testing strategy should be employed. In particular: • It is important that all non-animal approaches (e.g. a literature, CLP inventory and REACH database review as well as QSAR, *in vitro* assays, read-across) are fully explored, prior to commencement of any new *in vivo* fish testing, in order to a) determine if endocrine disruption concerns are an issue at all; b) identify what the likely endocrine disrupting mode of action is, and c) inform the best overall toxicity and endocrine effect testing strategy. • The overall goal should be to minimise the extent of the total testing on vertebrates (i.e. fish), both in terms of the overall number individuals as well as	No change to the guideline. Rationale: Considerations of 3R principles and weight of evidence approach are mentioned in sections 3.1, 3.2.3 and 4.3.2 of the ERA guideline. However, it is not always possible to dispense with fish tests for accurate risk derivation, even if endocrine activity has been demonstrated in the preclinical part of the dossier.

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		the extent of the exposure (length of the study) i.e. the degree of suffering expected. • Depending on the information already available, the optimum testing strategy may or may not include an endocrine disruption screening test i.e. there may be high confidence regarding whether the substance is an endocrine disruptor or not, and what the likely mode of action is (and so a screening test may not be worthwhile), or conversely, little may be known about the substance in which case a screening study may help in wisely choosing the next full assay to perform. • The most appropriate strategy may be to perform an endocrine test (such as TG 234) directly and omit the chronic fish toxicity test TG 210 (i.e. if, from the outset, you have a strong indication that the substance is an endocrine disruptor and what the likely mode of action is). • Note that if endocrine disrupting effects are considered to be a likely possibility, and there is information available indicating a particular mode of action is likely, then in order to minimise the *in vivo* testing, care should be taken so that the most appropriate test should be selected, noting that different assays such as TG234, the Fish Short Term Reproduction Assay (TG 229) or the Medaka	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Extended One Generation Reproduction test (TG 240) are available. The assay selection should be based on indications gained elsewhere of the likely mode of action, noting that there is currently no single assay that can conclusively determine endocrine disrupting activity *via* each currently known mode of action. For instance, assay TG 234 is able to detect some endocrine disrupting modes of action, but not all and so a negative result may trigger further vertebrate testing, particularly if there are concerns raised elsewhere.	
1053	1	We propose to modify line 1053 to clarify the triggering of longer-term fish testing and what is meant by "…in such a test…": Proposed change (if any): Please state "If effects are observed, determine if they are expected at environmentally relevant concentrations and then characterise in a fish sexual development test or a fish full life cycle test if required." It should also be clarified that the OECD screening studies available may not be the most appropriate use of animals depending on the MoA or sensitive endpoints, in which case careful consideration should be given to the testing strategy.	Text edited. Text changed to reflect that effects in screening tests are meant. Reference to environmentally relevant concentrations is not relevant here. Information on the limitations of screening tests can already be found in the corresponding chapter 4.3.2.
1054	48	When deciding between a FSDT and FFLCT consideration should also be given to the minimisation of the number of animals required for testing to provide the necessary data.	No change to the guideline. Rationale: Considerations regarding 3R are of general importance and can be found in the sections 3.1 and 3.2.3.

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1055-1067	22	The request for a fish full life cycle test, or a fish sexual development test even in a situation where an endocrine active mode of action is known, and a risk already is identified (for instance for substances affecting sex hormones in Table 15), is not supported. It is not understood what such study can help in risk assessment, particularly within the current legislation, for a known endocrine active substance of those types. Unnecessary studies, for the purpose of the ERA, particularly involving animals should be avoided. Proposed change (if any): Revise wording to a more open recommendation, where such study(ies) should primarily be asked for in cases where there is uncertainty in relation to endocrine activity.	Text edited. Agreed, unnecessary studies, particularly involving animals, should be avoided. But the proposed change is not considered as it seems to be based on a misunderstanding by the stakeholder; fish full life-cycle test has not to be performed if not necessary for deduction of the appropriate NOEC/ECx value. However, text is tightened for clarification.
1057	1	If the mode of action is not known, the compound can be further characterised (e.g. through *in vitro* work) before a fish full life cycle study is required in order to reduce unnecessary vertebrate testing.	Text edited. This can be found already in the guideline text in section 4.3.2, and considerations regarding 3R can be found in the sections 3.1 and 3.2.3.
1062/Table 15	24	It might be a good idea to offer also in vitro EDC tests as options for fish full life cycle tests because 1) 3Rs 2) Tedious and expensive 3) Current literature has efficient in vitro tests for detecting EDC properties 4) There is a suggested $PNEC_{SW}$ for EDCs in the EU (0,4 ng/L) 5) OECD 455 could be applied	No change to the guideline. Rationale: Guideline text allows for expert judgement in relation to screening methods and use of information from literature to assess the mode of action of active substances. Additionally, please see answers above regarding 3R and screening.

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		At least those could be used as screening options (optional for OECD 229/230)	
1062-1064 (Table 15)	27	Table 15 can be replaced by text. All listed tests (234, 240, FFLC, DRP no. 95) can be asked and used for all estrogenic, androgenic and steroidogenic modalities, except thyroidal. TG229 with five concentrations should be added to the text. The information in table cells over ER/AR/Steroidogenisis should include the same tests, i.e. TG229 with five concentrations/TG 234/Fish full life cycle test Aromatase should be changed into steroidogenesis Agonistic should be changed into agonist Antagonistic should be changed into antagonist Proposed change: Replace Table 15 by text. TG229 with five concentrations/TG 234/Fish full life cycle test Aromatase should be changed into steroidogenisis Agonistic should be changed into agonist Antagonistic should be changed into antagonist	No change to the guideline. Rationale: Table 15 is retained for clarity and scientific reasons. The OECD 234 does not cover the fish reproductive life stage and therefore substances suspected to affect reproduction endpoints at lower concentrations than sexual development should be examined in a test that covers reproduction, i.e. FFLC. In the case of ER agonists, the fertilization rate, growth and time to first spawn are more or equally sensitive as sex ratio shifts toward females. In the case of AR antagonists, the spawning and fecundity are affected more or equally sensitive as sex ratio shifts toward females / intersexes. Please see literature: Knacker et al. (2010, Integr Environ Assess Manag 6, 653-662). Regarding OECD TG 229: please see answer above. Text edited. Aromatase inhibition instead of steroidogenesis is correct: please see literature Knacker et al. (2010, Integr Environ Assess Manag 6, 653-662). Text edited. Agonistic and antagonistic will be changed in the guideline text to agonist and antagonist, respectively.
1062	27	Add to the text of this section that in the risk assessment, only population relevant endpoints are taken into consideration, not results based on biomarker endpoints.	Text edited.

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1062 (Table 15)	48	Comment: The FSDT (OECD 234) is also suitable for determining oestrogen agonistic and androgen antagonistic effects.	No change to the guideline. Rationale: The OECD 234 does not cover the fish reproductive life stage and therefore substances suspected to affect reproduction endpoints at lower concentrations than sexual development should be examined in a test that covers reproduction, i.e. FFLC. In case of ER agonists, the fertilization rate, growth and time to first spawn are more or equally sensitive as sex ratio shift toward females. In the case of AR antagonists, the spawning and fecundity are affected more or equally sensitive as sex ratio shift toward females / intersexes. Please see literature: Knacker et al. (2010, Integr Environ Assess Manag 6, 653-662).
1063	1	The first mention of a thyroid hormone agonist and antagonist being considered an EAS is in the title of Table 15. Inclusion criteria need to be provided in text and also include the ability to develop a testing strategy based on the Adverse Outcomes Pathway and mode of action of the drug. Additionally, we disagree with the initial use of the larval amphibian growth and development assay (OECD 241) for this class of compounds, as this test is associated with a high occurrence of false positives. It may be more relevant to run *in vitro* or *in vivo* screening assays (e.g. OECD 231) to first identify if we expect relevant effects at environmental concentrations and then performing OECD 241 if necessary.	Text edited. Text in section 4.3 changed to consider also thyroid acting substances earlier in the GL text. Table 15 does not list initial but apical test protocols. However, the text of the section has been slightly changed to make it clearer. Please see also above – answers to comments regarding weight of evidence and expert judgement.
1063	7	The bottom comment suggests that the study suggestions are not subject to expert judgement. All studies for endocrine active substances will likely require expert judgement to establish to correct test to perform.	No change to the guideline. Rationale: The purpose of the guideline is to provide guidance on the evaluation of medicinal products regarding their environmental risks as detailed as possible. So, table 15 provides an overview of

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		Proposed change (if any): Suggest removal of statement and replacement with: The above are intended as a guide; other studies may be appropriate subject to expert judgement and existing knowledge and data.	the currently recommended aquatic effect tests for apical endpoints with vertebrates.
1064	48	Please see earlier comment on line 994 and add some detail on the note to the main text to explain why thyroid acting substances are not included in the definition of EAS but may still require testing.	Text edited. Note on table 15 deleted to take into account thyroid acting substances.
1068-1070	22	This paragraph is superfluous, and not needed in this guideline. Proposed change (if any): Consider deleting this paragraph.	No change to the guideline. Rationale: It might be appropriate to seek scientific advice on case-by-case basis.
1070	48	Is the purpose of the EAS testing to provide sufficient data to be able to conclude on whether a substance is an endocrine disruptor or to derive a NOEC for endocrine effects that can be used to calculate the PNEC for use in the risk assessment? If it is the latter, it would be helpful to include some guidance on which reported endpoints would be suitable for PNEC derivation. For example, would a change in biomarker (e.g. Vtg) be used or would the endpoint need to be population relevant (e.g. change in sex ratio)?	Text edited. Sentence added to clarify that biomarkers are not usable as apical endpoints for PNEC derivation. Information about appropriate endpoints to derive PNEC for risk assessment can also be found in section 4.2.1.3. Please see also answers above.
1089-1092	17	It is stated that for substances for which a Phase II assessment including the soil compartment is performed, no additional testing is required for the PBT assessment. However, the currently proposed Phase II does not include an OECD 308 study or an OECD 309 study, but is limited to	Text edited. Two new figures are added to the document, one with a step-by-step approach for the risk assessment (RA), and one with a step-by-step approach for PBT/vPvB assessment. It is specified in which order studies need to be conducted. Data from the RA can be used

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		a ready biodegradation study (OECD 301) and possibly an OECD 307 study. If no further testing would be needed, and a substance is not readily biodegradable, this statement implies that the PBT assessment is restricted to the soil compartment, which is not in line with the ECHA guidance on PBT assessment. Only in case the P or vP criterion has been met based on the data from the soil compartment, further testing for persistence should not be required. In other cases, however, other compartments will also have to be studied. Proposed change (if any): Consider rewording	for the PBT/vPvB assessment. Additional text is added next to the PBT/vPvB figure, which will be included in this chapter.
1090-1094	14	The text is a bit confusing regarding demands for further assessment (or not) if you have a compound with a very low PECsw (<0.01 µg/L). If the substance has a very low log Kow, no phase II risk assessment or definitive PBT assessment are required. If log Kow >4.5, a definitive PBT assessment is required. What are the requirements if you have a compound (PECsw <0.01 µg/L) with a log Kow between 3 and 4.5? Do you need to perform a simulation degradation study (line 1090-1092), and do you need to study bioaccumulation in fish (line 1093-1094)? Proposed change (if any): Clarify if these two subsections are applicable for the PBT screening or for the definitive PBT assessment only.	Text edited. For further changes, see the response to comment to line no. 1089-1092, stakeholder no. 17.

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1093	1	In keeping with the EMA CVMP/VICH Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (Nov 2004), Section 3.3.2, a Phase II BCF trigger of log Kow ≥ 4.0 is appropriate for human medicinal products. OECD 319 A&B, for determination of intrinsic clearance values using rainbow trout hepatocytes (319A) and rainbow trout liver S9 subcellular fraction (319B) were finalized in 2018. BCF values can be estimated from intrinsic clearance values as per Nichols et al. (2013). Proposed change (if any): Revise and harmonise the log Kow trigger for a fish BCF from ≥ 3 to ≥ 4.0. Estimated BCF values based on *in vitro* intrinsic clearance data (OECD 319 A&B) may be used to assess B or vB, provided that the final results will most likely not result in borderline cases of meeting either the B or vB criterion."	No change to the guideline. Rationale: The trigger value is in line with the secondary poisoning assessment under the WFD.
1093-1098	17	This section states that when a substance meets the B criterion and the T criterion, the P criterion should be investigated. This is not in line with the ECHA guidance on PBT assessment, which indicates that the assessment should start with the P criterion. Probably, this section aims at those substances for which a bioconcentration study was triggered in Phase II and an OECD 307 was not conducted or did not indicate the substance to meet the P criterion. This should be clarified.	Text edited. See the response to comment to line no. 1089-1092, stakeholder no. 17

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		Proposed change (if any): Please consider describing the different approaches for PBT assessment for substances remaining in Phase I (starting with the P criterion) and for substances that enter Phase II (starting with the B criterion).	
1093	20	To minimize animal suffering, B criteria should not be assessed experimentally before the P criteria is concluded. Bioaccumulation testing on readily biodegradable substances is not informative and may be very difficult to interpret. Substances with high persistency and strong toxic effects are still problematic, and the information is still very relevant for risk assessment if the substance is demonstrated to not be PBT. Proposed change (if any): Require persistency testing to be performed before testing on bioaccumulation. The tiered approach to test the persistency of the substance using screening tests should still be followed, but with an option to go directly to simulation testing if the applicant prefers.	Text edited. See the response to comment to line no. 1089-1092, stakeholder no. 17
1099	1	API ingredient is considered environmentally relevant for risk assessment and/or PBT assessment, revise for consistency. Proposed change (if any): Change "environmentally relevant compound" to API ingredient.	No change to the guideline. Rationale: The environmentally relevant compound may be the AS but could also be a transformation product (in case of a prodrug).
1101-1186	30	Thank you for including the PBT assessment to the GL.	Comment noted.

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1101	33	The definition of a PBT screening criterion based on KOW is highly problematic. Presumably the underlying logic is that a chemical with a log KOW < 4.5 is unlikely to fulfil the B criterion and therefore will not be PBT. This approach to chemical hazard regulation is outdated. The PBT regulations in e.g. REACh and the Stockholm Convention are based on a chemical application domain that was considered relevant in the 1990s, namely hydrophobic, semivolatile chlorinated and brominated hydrocarbons. The EMEA regulation has a completely different chemical application domain, and it is essential that the guidance builds on scientific understanding that is relevant for this domain. Research during the last 20 years has clearly demonstrated that "B" is not a prerequisite for a chemical to be an environmental hazard. Persistent, hydrophilic (non-B) chemicals can be hazardous. The most obvious example is the perfluorinated alkyl acids, which are incurring remediation costs in the hundreds of million Euros. The need to update hazard regulation has been recognized in some regulatory circles, for instance in the initiative spearheaded by the German Environment Agency to include PMT (Persistent, Mobile and Toxic) compounds under hazard regulation in REACh. As a consequence, the KOW trigger should be removed from the guidance. If a screening step is to be used in hazard assessment, then it must include a reliable evaluation of persistence. Otherwise, the regulation will not protect against hazardous substances.	No change to the guideline. Rationale: Due to overlap of the current guideline revision, the regulation of the new hazard classes PMT/vPvM under CLP and the revision of the pharmaceutical legislation, the guideline does not address the assessment of PMT/vPvM.

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		For further reading see McLachlan, *Environ. Sci.: Processes Impacts*, **2018**, *20*, 32-37.	
1108	34	"log Dow for the neutral molecule". This is a contradiction in terms, because the log Dow is defined as the "observed" octanol-water partition coefficient that might include partitioning of both the neutral molecule and the ionic species. Proposed change (if any): Change to "log Dow should be determined"	No change to the guideline. Rationale: For PBT/vPvB screening a log ion-corrected logarithmic octanol-water distribution coefficient for ionisable compounds (log D_{ow}) for the neutral molecule is needed.
1109	14	This comment relates to our previous comment (line 1090-1094). Are there any requirements triggered if log Kow is between 3 and 4.5? Proposed change (if any): See previous comments on line 1090-1094. Depending on that answer, this subsection might need editing.	Text edited. See response to comment to line no. 1089-1092, stakeholder no. 17.
1113	1	Table 16, clarify applicable test guidelines Proposed change (if any): Table 16, include relevant OECD protocols Persistence criteria: (a) and (b) OECD 309, (c) and (d) OECD 308 aerobic, (e) OECD 307 Bioaccumulation criteria: OECD 319 A&B OECD 305	Text edited. A table is included with relevant study to conclude on PBT/vPvB properties. This is not an exhaustive list of all possibilities as there are additional tests which may be used dependent on physio-chemical properties of substance. In addition, other information may be used as supportive information to conclude on these properties. ECHA guidance should be followed.

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		Add Toxicity footnote to Table 16, stating: Substance is not considered toxic if NOEC (or EC10) is < 0.01 mg/L and no effects were observed up to the limit of solubility.	
1114 (Table 16)	22	Typo: Persistence, vPvB c "the degradation half-life in soil…"	Text edited.
1117	27	We propose that the 'most recent' REACH guidance on PBT assessment be followed, hence taking care of future updates. Proposed change (if any): add 'most recent' and add R.11 The **most recent** REACH guidance on PBT assessment (**R.11)** …	Text edited.
1120 – 1121	1, 2	It should be noted that proposed use of 3R "whenever possible" and the sentence "QSARs (Quantitative Structure-Activity Relationships) and read-across cannot replace the studies requested in this guideline" are in fact, mutually exclusive. It is not clear how to use the principles of 3R when the alternative to experimental testing (in vitro, in silico, read-across or QSAR) – which (for the purpose of risk assessment, encouraged by all other major institutions such as ECHA, EFSA, FDA etc…) are not allowed. For example, even if it could be argued that ecotoxicity QSARs are not applicable to human pharmaceuticals because of the specific modes of action (line 1120 – 1121), their physico – chemical and environmental fate properties (biodegradation, adsorption to soil, partition coefficient etc..) are independent of their mode of action and should	No change to the guideline. Rationale: There is a need to further develop and validate alternative methods to animal testing, as these methods are currently not suitable to replace experimental studies. For some type of active substances tailored testing strategies are provided to avoid unnecessary testing. In addition, data sharing is encouraged between MAHs when relevant studies were performed with the same active substance as is being applied for marketing authorisation.

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		be made possible to be assessed by specific QSAR programs. Furthermore, with regard to the principles of 3R it is not clear, how the repetition of ERA Phase II studies by several applicants is benefiting the animal welfare. This draft guideline clearly states that generic medicinal products are not exempt from providing an ERA and cannot cross reference to the ERA dossier of the reference. In turn this leads several repetitions on ERA Phase II studies, since every subsequent applicant (beside the originator) is compelled to assess the environmental risk by performing his own studies. Proposed change (if any): Please present some examples where the use of 3R is applicable. Present alternative testing strategy in order to avoid testing on fish (OECD 210 and OECD 305, as requested by (1)). Additionally, we propose the use of validated QSAR programs for the prediction of animal toxicity endpoints should be allowed – especially for physico – chemical and environmental fate properties. In the interest of animal welfare the repetition of animal studies by several applicants should be restricted.	
1121	44	Suggest rewording to: "In order to avoid unnecessary animal testing, testing for the PBT criteria is conducted sequentially and in the order of P, then B and lastly T. For medicinal products for which Phase II of the risk assessment is performed, it is expected	Text edited.

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		that the required data for the PBT assessment will already be available (with the exception of persistence data, should a soil assessment not have been required). However, if there are any data gaps a stepwise approach should be taken whereby any new *in vivo* data is generated last."	
1126-1128	13	It is explained when OECD 307 and 309 have to be performed. An explanation for OECD 308 is missing. Proposed change (if any): Addition of an explanation regarding the use of OECD 308.	Text edited.
1126	27	"Is not P" is too stringent (see Reach R11. Explanatory Notes to Figure R11-3, page 42). Proposed change: If the active substance is readily biodegradable (OECD301) it is generally considered not persistent, and no further testing is required.	Text edited.
1127	48	Please carefully consider recommending the OECD 309 for derivation of the environmental half-life (DT50). As noted further into the text (line 1143) for the most persistent substances removal from the aqueous phase is determined by dissipation due to partitioning to the sediment rather than true degradation. Data from a hydrolysis study could be used to determine the 'worst-case' water phase half-life. Natural waters have the lowest microbial population of all environmental compartments that are examined. The reduced probability of a competent degrader being present	See response to comment to line no. 1128, stakeholder no. 20 and response to comment to lines no. 1128-1129, stakeholder no. 29).

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		to initiated biodegradation may unrealistically bias the persistence assessment.	
1128	20	Comment: The text is easily misunderstood to be a contradiction. Proposed change (if any): suggest rewriting to make clear that a PBT assessment is still relevant at this point. "If a Phase II PBT assessment is required, but not a Phase II risk assessment ~~is not required~~, a surface water simulation study (OECD 309) may be preferable."	Agreed. Sentence is removed and text is amended.
1128-1129	29	Using OECD 309 is not harmonized between the regulations. As there are pros and cons for using this test for pharmaceuticals (conservative approach for assessing persistence but less information about transformation as in other simulation tests as OECD 308 / 307). It is preferred to waive such a specific recommendation. This should be open to the applicants. Proposed change: Delete the sentence "If a Phase II risk assessment is not required, a surface water simulation study (OECD 309) may be preferable."	Agreed. Sentence is removed and text is amended.
1131-1132	25, 26	Same comments as for lines 817-820.	See response to comment to line no. 817-820, stakeholder no. 25-26.
1133	1	Extrapolation of degradation half-life values to 12°C to assess P and vP are only relevant when B or vB is fulfilled. It should also be clear that these DT50 values are for the total system.	No change to the guideline. Rationale: Although it is so specified in the REACH guidance as stated by the comment of the stakeholder, extrapolation to 12 °C is always needed when the degradation test is performed at a

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Extrapolation of degradation half-lives to 12°C in assessing P and vP is only relevant when B or vB is fulfilled. ECHA states in R7B that "Consequently, for persistence assessments where the B and T criterion have been met, and simulation data exist for degradation at 20°C, consideration should be given whether temperature correction should be applied. This will be particularly important where the measured half-life is close to the persistence criteria. This correction, if applied, should be based on the Arrhenius equation and extrapolate from 20°C to the temperature of the environmental media at the point of sampling". The guideline should also be clear that the DT50 values are for the total system.	different temperature. In addition, degradation is assessed per compartment.
1133	12	The persistency criteria as shown in Table 16 are established most likely under the assumption of 20°C (Matthies, M., Beulke, S. 2017 : Considerations of temperature in the context of the persistence classification in the EU, Environ Sci Eur, 29:15: DOI 10.1186/s12302-017-0113-1). ECHA changed its mind and currently all DT50 (DegT50) values have to be calculated to 12°C with the Arrhenius equation. But the triggers stay the same. This doesn´t make sense scientifically. We simply continue the mistake here for harmonisation rules?	No change to the guideline. Rationale: The criteria specified in the guideline are in line with the criteria under REACH.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: are we allowed to think scientifically? Or we have to follow the ECHA guidance 1:1? Than the chapter is unnecessary and should simply refer to ECHA 2017.	
1136	1, 13	Factor is missing in Arrhenius equation Proposed change (if any): Change 1/- to 1/T1	Agreed. Proposed change accepted.
1136-1137	22	The Eq is not labelled.	Agreed. Equation number (45) is added.
1136, Eq	27	Comment: • the equation misses T_1 in the denominator of the first term in the exponent • the equation is not numbered Proposed change: add equation number and add T_1 as indicated above.	Agreed. Proposed changes accepted.
1136	27	throughout document uniformise the correct UK, plural form of half-life. This may be half-lives but seems not correct to us. Therefore, half-life values may be correct (used in line 1138). Proposed change (if any): use correct plural form of half-life. Or uniformise the use of half-life value which already occurs multiple times.	Agreed. Proposed change implemented throughout document.
1137	48	There appear to be a unit missing from the parentheses. Please double check?	Agreed. Unit is added.
1140-1142	19	It keeps unclear, how the experimental determination of a value for EA for degradation of the active compound should	Agreed but not with proposed change. Text is amended, to reflect the use of the default value as no guidance is available on how to experimentally determine EA.

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		be conducted. The default value may lead to unrealistic temperature corrections. Proposed change: An acceptable way for the determination of a specific EA should be provided.	
1141	22	The footnote 8 should e.g. be put in parenthesis, to be separated from 18.	Agreed. Proposed change implemented.
1144	27	typographical: a power of -1 and footnote nr 8 combined now give mol^{-18} which reads a bit unlucky. Please adapt. Proposed change (if any):	Agreed. Proposed change implemented.
1149-1150	29	The sentence does not make it clear how to deal with non-extractable residues (NER). Currently there is no harmonised procedure to differentiate between irreversibly bound NER (e.g. biogenically bound) and potentially reversible NER (heavily sorbed, physical inclusion) that are released in the environment and should be considered for the assessment of persistence. Proposed change: Replace the sentence by 'The formation of non-extractable residues should not per se be considered as degradation. While irreversibly bound NER (e.g. biogenic bound NER) can be seen as safe sink, potentially reversible NER (heavily sorbed, physically entrapped) pose a potential risk for the environment and should be considered in the assessment of persistence. Currently there is no harmonised approach to	Agreed. Text is amended.

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		differentiate between the different NER types and to consider the reversible part of NER in the assessment of persistence Scientific work is on-going and should be considered when providing an assessment.	
1150-1154	2	Regarding the definition of API being persistent after conducting the OECD 307 or 308 studies. According to the Reflection paper on poorly extractable and/or non-radiolabelled substances three definitions of residues are stated: - Extractable residues (ER) available with "mild" extraction methods with aqueous and organic solvents - Non-extractable residues (NER) are extractable using harsher extraction methods (refluxing, microwaves or pressurized liquid extraction) - Bound residues (BR) can only be released under extreme conditions where the integrity of the substance and/or matrix is likely to be affected Proposed change (if any): In order to define the persistency of the tested API (OECD 307, 308 and 309) the following criteria have to be considered: - API degrades slowly and fulfils the P criteria according to the guideline (DT50 > 120 days) - API degrades into a predominate (> 30%) compound that degrades slowly and fulfils the P criteria according to the guideline (DT50 > 120 days)	No change to the guideline. Rationale: Proposed change is not considered relevant. The definitions in the reflection paper are different than the definitions under REACH. Currently guidance on NERs is updated under REACH. Terminology used in this document is the terminology used under REACH, with differentiation between irreversibly bound NER and potentially reversible NER.

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		- API degrades into several compounds, cumulatively they represent > 30% applied API that degrade slowly and fulfil the P criteria according to the guideline (DT50 > 120 days) Any other study outcome results in no persistency of the parent compound, this also applies to formation of NER or BR that are formed during the OECD 307, 308 and 309 studies. It is important to emphasise that both NER and BR are mobilised only at conditions not existing in the environment, therefore they will not become available to the surrounding organisms in a form or quantity that may pose a risk for the environment.	
1150	12	Why not? NER CAN be assessed as degradation. It requires a specific characterisation, which is described in Kästner, M., Trapp, S., Schäffer, A. (2018): Consultancy services to support ECHA in improving the interpretation of Non-Extractable Residues (NER) in degradation assessment. Discussion paper - final report. ECHA, June 2018 Proposed change: add link to the paper	Agreed. See response to comment to line no. 1050-1054, stakeholder no. 2
1157 (and 924)	46	The assessment of bioaccumulation in sections 4.2.8 and 5.2.2.2 is only based on the bioconcentration by uptake via the gills aiming at an equilibrium between water and fish. This test is not adequate for sparingly soluble substances (like most vPvB substances) and nanomaterials where in many cases the test results may not be reproducible, and	Agreed. However, aqueous exposure is the preferred methodology. A dietary test can be used, but a BCF should then be determined (calculated) and not a BMF.

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		equilibrium will not be achieved). OECD added in test guideline 305 the option to determine a biomagnification factor via dietary uptake. Oral uptake is the dominant pathway for uptake of such substances. The corresponding paragraphs should be revised and supplemented.	
1162-1166	22	Repeat of text in 4.2.8, possible to refer to 4.2.8 to reduce text.	Agreed. Text amended.
1162	48	Please add some text to note that lack of bioaccumulation in aquatic species does not indicate lack of accumulation in mammals e.g. perflourinated compounds. Please see previous comment made to line 909	See response to comment to line no 909, stakeholder no. 48.
1176	22	CLP inventory is not described or in the abbreviation list.	Agreed. Definition is added.
1176	27	The CLP inventory is a very useful source. Two things should be added: • the URL to ECHAs CLP inventory database • if an API is listed in the inventory with a *harmonised classification*, the resulting classification for C, M, R and STOT RE can be used to conclude on the T assessment. This may be added to EMA guidance. Proposed change: Add URL and some text on potential use of notified and harmonised classifications contained in the CLP inventory.	Agreed. URL is included and text is amended.
1178-1186	2	PBT assessment: If the compound is classified as carcinogenic (category 1A2 or 1B3), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A4, 1B5 or 26), then, according to the guideline no toxicity studies are necessary to perform? What is in this case the outcome of the assessment – possibility of RQ calculation?	For PBT/vPvB no toxicity studies are needed, however for risk assessment toxicity studies may still be needed.

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1181	27	'for welfare reasons' should read 'for animal welfare reasons' Proposed change (if any): add 'animal'.	Agreed. No change made as sentence is removed.
1188	27	Data search. Section 3.2.3 (line 191) states a complete literature review, refers to section 6.1, but this is not further guided in this section (6.1). Proposed change: Clarify what 'the complete literature review' constitutes. Take note that a review that is too wide puts an unnecessary burden on both applicants and assessors. Be precise.	Further guidance regarding the targeted literature review has been included in section 6.1.
1189-1193	25, 26, 42	Published data should also be used as reference for calculated concentrations in waters, sludges and soils. Proposed change (if any): "If of acceptable quality, data from published literature on the active substance may be employed in the ERA as (…) - *screening/monitoring results may be used as reference results in estimating evaluating the uncertainties related to PEC-calculations*"	Monitoring data is not included in the ERA; the assessment is based on calculated PECs. Reference to monitoring data is deleted in section 3.2.3.
1189	44	The information that can be gathered from a literature review can be very useful and may serve to avoid further *in vivo* testing; for this reason, please can a recommendation for performing a literature review be emphasised in the earlier parts of this guideline.	This is already explicitly stated in section 3.2.3.

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1189-1190	45	For increased transparency, it is necessary to specify what is an acceptable quality.	Agreed. Acceptable quality is reliability 1 (reliable) and 2 (reliable with restrictions) according to the CRED method (Moermond et al). A reference to section 6.2 where this is further elaborated is added.
1192	29	Proposed change - please include "of ecotoxicological effect tests" to clarify the point: • a support for a proposed tailored approach of ecotoxicological effect tests	No change to the guideline. Rationale: A tailored assessment strategy can include other aspects than the ecotoxicological effects test. The GL text has been updated with a reference to section 4.3.
1193-1199	7	It is stated here that published literature or other data can be useful to "help with the interpretation of experimental data" there is little discussion on the use of data in an interpretative way. For example, the use of measured environmental concentrations (MECs) in risk assessment, labelling or mitigation discussions. For established products it is possible that a number of measured environmental concentrations (MECs) may be available. There are many factors which may influence to reduce the actual concentrations of APIs observed in the environment, these are not always incorporated into the predictions of environmental concentrations. MECs may help contextualise this conservatism in-built into the predicted environmental concentrations (PECs). It should be highlighted as a possible option to refine risk assessments, label text and/or mitigation requirements if, for example, the 90th%ile of available MECs are below the PNEC (an indication of insignificant 'real-world' risk). Proposed change (if any):	It is recognised that use of published literature data or other data is not sufficiently discussed in the revised draft GL. However, given all uncertainties attached to use of MECs for risk assessment (e.g., sites for sampling, methods for analysis, representative values etc.), use of MECs is not introduced in the GL as an option for consideration. To avoid confusion, the text 'to help with interpretation of experimental data' has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Include some discussion around the potential for the use of MECs in risk refinement strategies, labelling and/or risk mitigation discussions.	
1194	44	Suggest amended wording as follows: "To be acceptable for use in risk and/or PBT assessment, literature studies should be of sufficient **relevance and** reliability…"	Agreed. Text in section 6.1 has been revised.
1200-1201	10	This statement basically contradicts the principles of 3Rs and the principle that studies which bring no further knowledge should not be repeated.	Regarding endpoints published in (E)PARs or other regulatory summaries (e.g., in the biocide or PPP framework): these are not acceptable because of legal reasons: Endpoints are owned by the company who submitted them in the original procedure and cannot be used by other applicants without a letter of access. If the applicant has a letter of access, the applicant also should have the study reports available and submit those. Besides this, (1) endpoints may have been evaluated using older standards or in different frameworks and not meet current standards. (2) EPARs have not always been updated with new data or changed assessments during former procedures. Some more text on this is added in section 3.2.3 and section 6.1.
1200-1201	22	A letter of access is asked for in case reference is made to a public assessment reports (EPAR; PAR). This seems appropriate. However, if the company makes reference to *'reviews of summary data from other regulatory frameworks'*, it is really sufficient with a letter of access? Would it not be needed that the studies are submitted also to the medicine agencies to enable full review of the data within our system?	For summary data from other regulatory frameworks, the same applies as for EPARs. The applicant should show ownership or a letter of access. The applicant automatically should then have access to the underlying studies and submit those. This is now further specified in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Consider revising.	
1202-1208	1	The guidelines recommend Klimisch or CRED for evaluation of studies which sets up a potential conflict where each method supports different conclusions. Proposed change (if any): Recommend a preferred method for evaluating study reliability and relevance, suggest which kind of study might benefit most from each method, or present a decision tree to arbitrate conflicting conclusions.	Text changed, CRED is recommended, and it is further elaborated that only studies which are Reliable (R1) or Reliable with restrictions (R2) may be used.
1202-1208	1	Our experience with the Water Framework Directive is that non-standard studies with non-standard endpoints that are not linked to adverse outcome at the population level are used in regulator decision making. The guideline is not clear how disputes in the interpretation of reliability and relevance between the registrant and the reviewer will be resolved. Proposed change (if any): The EMA needs to establish procedures to resolve disputes over non-standard data where agreement cannot be reached on its reliability and relevance. Options for definitive studies to GLP should be allowed and this should be able to replace or overwrite any nonstandard studies it is designed to resolve.	Reference is now made to population-relevant endpoints and the WFD guidance where this is further specified. Disputes may arise concerning every part of the guidance. Regular procedures are in place to solve these.
1202-1208	22	Who should present the evaluation described in this paragraph? The company, to be assessed by authorities, or should it be undertaken by the assessment team ? If the	Agreed and revised. The Company submits the literature review.

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		company should present such review, it may be good to clarify this. Proposed change (if any): Consider revising.	
1204	29	6.2. Evaluation of studies It should be considered that in cases of inappropriate study quality, this study has to be repeated. Proposed change: Please include additional sentence after "…in the same manner.": It might be necessary to repeat studies (standard studies or from literature) with non-reliable results although the OECD validity criteria were met.	Studies of good quality are expected. If relevant and reliable data are missing, the assessment can likely not be concluded and consequently requests to the applicant are triggered. The text in section 6.2 has been changed to explain more specifically the requirements for acceptable studies. Repetition of studies can in some cases be necessary, but it is not considered necessary to specify this in the GL.
1209-1224	1	Precautionary measures must be appropriate. Any measure unnecessarily imposed will lead to patients getting tired of reading such "warnings" and patients will eventually disregard them. If measures are truly necessary, they must be clear and provide directions instead of pointing to other sources of information. Proposed change to the guideline (if any):	Agreed. No change of the guideline required.
1209-1236	2	The ERA phase II studies are performed with API and not with the finished product. According to this, the ERA report does not differ between MAHs (innovator and/or generics) and its products consisting of the same API, having the same indications, MDD and pharmaceutical form, consequently SPC and risk mitigations are identical between the products. These findings additionally support the idea of public availability of the ERA data published by the innovator in form of PAR, to which the generics may refer,	Agreed. Please refer to Q2b of the Phase I decision tree for further guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		which is also in the public interest being aware of the environmental consequences by using the product. On the other side, it does not make sense to repeat the ERA studies with the same API, since difference in ERA outcome may follow between the MAHs, consequently a revision/unification of SPC and risk mitigations between the MAHs must follow since ERA is API specific. Proposed change (if any): Unification of SPC and risk mitigation measures between the innovator and generic products is mandatory. The ERA phase II studies performed with API, reflect the risk for the environment of the API and not of the product. If a risk for a particular product, based on its own ERA phase II data, exists, a unification of SPC and risk mitigation measures for all MAHs must follow.	
1209	43	Section 7. The risks are still too much projected onto the environment, while these substances (and the micro-organisms that have become resistant) return to humans via the environment (soil, food, water, air). The measures should therefore be aimed at preventing this medicinal environmental cycle, e.g. with treatment specific measures (waste separation and processing).	Comment noted. However, the measures mentioned are beyond the scope of the ERA (waste separation etc.)
1211-1213	4	Comment: Proposed change (if any): The applicant should propose and discuss a strategy for risk mitigation. Appropriate mitigation	Unclear as this is the same text as in the GL (line 1211-1213). Removed the excess 'to'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		measures should generally aim at minimising the quantity discharged into the environment.	
1217-1220	1	Appropriate measures regarding the use of the medicinal product (e.g. to avoid the discharge of formulations such as patches and other devices into the sewage) are recommended. It would useful to provide an EMA recommended wording to ensure harmonisation across companies for similar product forms. Proposed change (if any): Please add proposed wording for appropriate discharge of formulations such as patches and other devices into the sewage.	Agreed. Wording in guideline has been changed.
1225	20	Applicants should be encouraged to make reference standards available to labs involved in environmental monitoring activities	No change to the guideline. Rationale: This idea was discussed but it was concluded that it will not be taken up in the guideline as the feasibility is seen to be very low. Furthermore, this is outside of the scope of the guideline.
1225-1232	22	This paragraph is very unclear. How, where, when? Should it be reported somewhere? The placing of this paragraph in the section 7. Labelling and risk mitigation is questioned.	Agreed. The wording of this section has been revised and the specific paragraph has been removed.
1233 (Table 17)	1	In case the ERA has identified a potential risk to the environment, new SmPC wording is recommended in sections 5.3 and 6.6 but for the label (packaging) and PIL, the wording should be considered on a case-by-case basis depending on the specific risk. It would be useful to provide an EMA recommended wording for the label and the PIL to ensure consistencies across companies/products.	No change to the guideline. Rationale: the proposal is out of scope of the guideline revision.

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		Proposed change (if any): Replace "no statement*" by some proposed wording appropriate for patients.	
1233 (Table 17)	1	Appropriate product storage and disposal is recommended. Information with regards to disposal will be provided in section 6.6 but what about information with regards to storage (SmPC section 6.4)? Proposed change (if any): Please add proposed labelling statement for SmPC section 6.4	No change to the guideline. Rationale: Not necessary, as storage requirements do not differ from regular storage conditions.
1233 (tab. 17)	1	Table 17. If the PL directs a patient to the pharmacist to find out the proper way a medicine should be disposed, there should be a system in place such that pharmacists know that they may get that question and know how to find the answer, that is they must know local requirements as well as drug product specific information. In many countries, there may be a governmental website with disposal information following local requirements that patients could be directed to on the PL (e.g. in Germany: https://arzneimittelentsorgung.de/home/) If environmental protection is to be seriously addressed, then clear advice needs to be given and parties involved in waste handling must be reimbursed for this. If nobody pays for it, it will not happen and patients and HCPs will seek the "simple" solution (i.e. toilet or household waste). Proposed change (if any): **Table 17.** **Current ERA data do not suggest a potential risk to the environment**	No change to the guideline. Rationale: The guideline cannot propose generally applicable disposal advice for all Member States. This must be solved on national level.

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		SmPC: "Any unused medicinal product or waste material should be disposed of in accordance with local requirements available at <www. >" (e.g. www.arzneimittelentsorgung.de/home/) PL: "Do not throw away any medicines via wastewater. Ask your pharmacist for advice on disposal of unused medicines or visit your governmental website at <www. ….>" (e.g. www.arzneimittelentsorgung.de/home/) **ERA has identified a potential risk to the environment.** SmPC: "Any unused medicinal product or waste material should be disposed of in accordance with local requirements available at <www. >" (e.g. www.arzneimittelentsorgung.de/home/ PIL: "Do not throw away any medicines via wastewater. Ask your pharmacist for advice on disposal of unused medicines or visit your governmental website at <www. ….>" (e.g. www.arzneimittelentsorgung.de/home/	
1233	10	Negative impact of statements in the labeling such as "Environmental risk assessment studies have shown that <act.subst> may pose a risk for <environmental compartment(s)> " or "<Environmental risk assessment studies have shown that <act.subst> has the potential to be persistent, bioaccumulative and toxic to the environment.>" on the patient compliance should be considered. This statement should only be used for SmPC in order to sensitise medical personnel to the proper handling of harmful waste of unused medicine.	No change to the guideline. Rationale: Unclear as this statement is included in SmPC.
1233	17	The columns for SmPC 5.3 and SmPC 6.6 refer to sections (6.6 and 5.3) that do not appear within the document. They likely refer to sections within the SmPCs? Please clarify. Proposed change (if any): Check references to sections in the table.	No change to the guideline. Rationale: SmPC 5.3 and SmPC 6.6 refer to the sections in the SmPC document and not to sections in the draft guideline.

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		Please consider adding further abbreviations, like Kow and Dow, SiMBaFi, and possibly the abbreviations used in the equations. Proposed change (if any): Consider extending the list of abbreviations.	Agreed. List of abbreviations has been updated.
1233	25	Currently PBT-properties are instructed to be highlighted only if an environmental risk has been identified. However, PBT-properties are inherent properties and as such they are independent of the outcome of the risk assessment. Therefore, PBT-substances should always be highlighted and instructions on e.g. proper disposal of unused pharmaceuticals should be given. Also, it should be highlighted if there is high uncertainty in the outcome of the risk assessment. For instance, in situations where the calculation method is highly sensitive to certain variables within the realistic range of those variables, it should be highlighted that the result may underestimate risks. E.g. if a normalization temperature of 12°C is used, the ERA does not necessarily exclude risks to soil environment in northern areas. Proposed change (if any): Please include two new rows with appropriate instructions & statements: - New row 1: "Substance has been identified to have PBT-properties" - New row 2: "Risk assessment uncertain"	No change to the guideline. Rationale: the proposal is out of scope of the guideline revision.

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1233, Table 17	29	There should be a revision of the table and further discussion on how to communicate concerns referred to the PBT classification of a substance. A PBT classification is related to the characteristics of an active substance therefore if all required tests are available and the criteria were met, the substance is a definitely a PBT substance. The word 'potential' is misleading. Furthermore it is proposed to include information about environmental risks or hazards in the package leaflet for maintaining the proper use and disposal of such products. Proposed change: See attached Document Proposal-labelling_PBTsubstnaces.doc	No change to the guideline. Rationale: The proposal has been acknowledged and discussed after thorough consideration it has been agreed to keep the wording in the table.
1233	40	Table 17: Proposed labelling aimed at minimising discharge of unused medicine into the environment Within the PL (5) column it is written "Do not throw away any medicines via wastewater **<or household waste>** for both ERA categories. The recommendation to not throw away any medicines via household waste is a **contradictory to existing recommendations in Germany**. The German Federal Ministry of Health recommends that drugs count as "municipal waste" and can therefore be disposed of with household waste since household waste is incinerated in waste incineration plants or pre-treated mechanically-biologically before it is stored in landfills.	No change to the guideline. Rationale: The table includes proposed wording which can be adjusted. In the case of Germany, the part of the sentence including 'or household waste' can be removed but it is necessary to keep it for other member states with a different disposal system.

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		In some areas of Germany different recommendations/disposal routes are available/advised, please find the overview here. Proposed change (if any): **Remove "<or household waste>"** for both ERA categories in column PL (5).	
1233	48	First use of PL. Please define and add to the "definitions" section. Proposed change (if any): Proposed labelling (PL)	PL is abbreviation for Package Leaflet. Definitions have been updated.
1239 (Section 8)	22	This section is superfluous. Proposed change (if any): Consider deleting this section.	No change to the guideline. It is necessary to mention the possibility to seek scientific advice at EMA or NCAs.
1254	24	Some references are missing	Agreed. List of references has been updated.
1255-1257	29	Please refer to the current updated version of Water Framework Directive EQS. Proposed change of reference: EC (European Communities) (2018), Technical Guidance for Deriving Environmental Quality Standards. Guidance Document No. 27, Updated version 2018.	Agreed. List of references has been updated.