EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 May 2016
EMA/CHMP/SWP/96156/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev 1*)

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

Stakeholder no.	Name of organisation or individual
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2	Bayer Pharma AG
3	Dr François HUBERT
4	ECT Oekotoxikologie GmbH
5	Sini Eskola, EFPIA
6	Dr. Ulrich Memmert, Eurofins Regulatory AG
7	Dr Jürg Oliver Straub, F.Hoffmann-La Roche Ltd
8	R. Arno Wess, Harlan Laboratories Ltd.
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	This Q&A update is helpful in many respects in terms of clarifying what is required under the existing guideline, however we think that more fundamental changes should be considered for the actual ERA guideline, in particular for the fate testing strategy found in Phase II. A specific problem area is the blanket requirement of an OECD 308 study at Phase II Tier A which, for a complex study, often adds little value to the overall assessment. We would propose that the most appropriate persistence study, focused on the most relevant environmental compartment, should be considered at Tier B, if needed. For pharmaceuticals which have a low Kow (or Dow), and hence clearly will not fulfil the PBT or vPvB criteria, the OECD 308 study is only of academic value since the data are not used to refine the risk assessment. In such cases, provided the PEC:PNEC is low, we would contend that an extensive study on persistence such as an OECD 308 or OECD 307 is not needed, and that sediment effects testing should be an option at Tier A, instead of conducting an OECD 308 study. This would also be much more consistent with structured testing approaches found elsewhere (e.g. in the REACH technical guidance). As for the OECD 308 Guideline itself, it should be recognized that this Guideline was developed to assess the fate of pesticides (not human medicines) predominantly in irrigation/drainage ditches exposed	Comment is noted. However, the scope of this public consultation phase was changes to the ERA Q&A list. Therefore, any general comments to the ERA guideline being more in the scope of a revision of the guideline than a refinement of the Q&A will not be considered in this procedure. Nevertheless, these comments will be collected, compiled and addressed in the scientific discussion of the SWP on an ERA guideline revision.

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	through spray drift. It was not designed to simulate the fate of chemicals in surface waters such as rivers and lakes and the guideline clearly states that "It is not suitable to simulate conditions in flowing water (e.g. rivers) or the open sea". Furthermore, as highlighted in the specific comments below, the data generated from an OECD 308 study often does not lend itself to the generation of independent half-lives for water and sediment and the presence of bound (unextractable) sediment residues often makes determination of half-lives in sediment impossible in practice. In terms of generating data on biodegradation that would be more relevant to the ERA we propose that alternative studies should be considered (eg OECD 314B method for activated sludge). STP simulation studies (eg OECD 303, CAS, etc) may be suitable for further follow-up in Tier B if needed (ie if PEC/PNEC > 1). The recommended studies should focus on methods that provide meaningful biodegradation rates that can be used in the risk assessment. This is not achieved with the OECD 308 study.	
2	The Q&A document 2015 clarifies and details some of the questions which were addressed in the earlier Q&A document EMA/CHMP/SWP/44609/2010 and updates references to assessment guidance following most recent publications under the REACH legislation. It is appreciated that some un-clarities from the previous Q&A could be solved by the new document. Some specific aspects of the draft Q&A are addressed in the following. We would like to emphasize that, though we consider the Q&A very	Comment is noted.

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	helpful in the preparation of regulatory Environmental Risk Assessments for human medicines (ERAs), this Q&A should not replace a pending review of the existing ERA guideline CHMP/SWP/4447/00 dated 2006.	
3	As REACH guidance replaces TGD guidances, may we use the ecotoxicological data published and reviewed by the ECHA to drawn the ERA report of a medicinal product which is not PBT/vPvB, even if the PECsw is higher than 0.01 µg/L? For instance "benzoate benzyl" used as the positive reference in OECD 107 test and as additive in feed, was evaluated by the ECHA as not PBT/vPvB. Ref. ECHA (European Chemicals Agency) 2013 – Benzyl benzoate - PBT assessment.001 - PBT assessment: overall result. *apps.**echa**.europa.eu/.../DISS-dffb4072-e2c2-47ae-e0...*	Comment is noted. In accordance with Article 8(3) of Directive 2001/83/EC, as amended, a new marketing authorization application shall be accompanied by the evaluation of the potential environmental risks posed by the medicinal product. A cross reference to data and assessments performed under other legislations like REACH or the EU Plant Protection Products Regulation is not foreseen. Availability of such data may be supportive for the assessment but cannot replace actual data in the dossier.
4	The questions and answers document (EMA/CHMP/SWP/44609/2010 Rev. 1) provides additional, specific information supplementing EMEA/CHMP/SWP/4447/00 corr 2 that is very useful for applicants and risk assessors. We appreciate that this document has been revised to include updated / more specific information.	Comment is noted.
5	EFPIA are currently assessing on how ERA could be refined to include post approval refinement of environmental risks e,g, where multiple products with the same active substance have entered the market and environmental exposure may be higher than that captured within a product specific risk assessment. We wish to continue this dialogue with EMA in the near future.	Comment is noted. However, the scope of this public consultation phase was changes to the ERA Q&A list. Therefore, any general comments to the ERA guideline being more in the scope of a revision of the guideline than a refinement of the Q&A will not be considered in this procedure. Nevertheless, these comments will be collected, compiled

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	This remainder of the response to this consultation concentrates on the revised Q&A sections and areas where the current ERA guidance could be improved. This Q&A update is helpful in many respects in terms of clarifying what is required under the existing guideline. However EFPIA recommend that EMA consider more fundamental revisions to the ERA guideline. One aspect of the ERA guidance that requires particular attention is the environmental fate and exposure guidance described within Phase II. Our specific concerns are focused on the requirement of an OECD 308 study at Phase II Tier A and the lack of robust data describing removal in a sewage treatment plant. The OECD 308 test is a complex study that adds little value to the overall environmental exposure and persistence assessment. An assessment of the OECD 308 has recently been published by Ericson et al (2014) titled "Experiences with the OECD 308 Transformation Test: A Human Pharmaceutical Perspective" (Integrated Environmental Assessment and Management; 10 (1) 114–124). With regard to improving the scientific and environmental relevance of the exposure assessment of human medicinal products we would propose that: An activated sludge dieaway test (e.g. OECD 314B or OECD 303) is conducted at Phase II Tier A. This reflects the down the drain nature of environmental exposure via the sewage treatment plant, and The most appropriate persistence study, focused on the most relevant environmental compartment, should be considered at Phase II Tier B, for compounds that have a high Kow.	and addressed in the scientific discussion of the SWP on an ERA guideline revision.

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	For pharmaceuticals which have a low Kow (or Dow), and hence clearly will not fulfil the PBT or vPvB criteria, the OECD 308 study is only of academic value since the data are not used to refine the risk assessment. EMA should also consider removing the trigger for a sediment effects assessment (OECD 218/219) from the OECD 308 study and include the sediments effect study at Phase II Tier A. These approaches would also be much more consistent with structured testing approaches found elsewhere (e.g. in the REACH technical guidance). It would be helpful to include revisions to ERA guideline (2006 EMA ERA Guideline corr 2) and changes in EMA Pre-meeting requirements (addition of the review of draft ERA) in the ERA 'Q&A' update. Both are pivotal for the applicant in developing the appropriate ERA strategy for marketing authorisations and in the preparation for EMA meetings. Efpia recommend that all new corrected versions to the ERA guidance are shown with a front page that clearly describes and dates the specific corrections that have been made. The PBT assessment for products below the Phase I action limit, that have a high log Kow (>4.5), and the PBT assessment for products that trigger a Phase II assessment under the ERA guidance are fundamentally different. Low PEC products (< 10 ng/l) with a high Log Kow conduct a PBT assessment according to REACH guidance. This is far more intelligent and flexible that the guidance currently	

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	provided within the EMA Phase II guidance. For reasons of consistency for (i) human medicinal product assessment and (ii) harmonisation across chemical guidelines we recommend that all PBT assessments of human medicinal products assessed by the EMA are conducted according to the REACH Guidance.	
6	The further refinement of this helpful Q & A document is highly appreciated.	Comment is noted.
7	An additional Q&A supplement to the EMA 'Guideline on the environmental risk assessment of medicinal products for human use' is overall welcome, as it will bring clarification and detail to questions and uncertainties regarding the interpretation of the Guideline. However, there is one proposed amendment to the existing Q&A document that may be highly debatable in view of extending a required testing range while not adding substantially to knowledge and interpretation of data. This point will be addressed in the Specific Comments section.	Comment is noted.
11	APIC has no specific comments to the proposed text in the ERA 'Q&A' update. EMA has provided additional clarity in several sections that is helpful in interpreting the guidance. It would be helpful to include revisions to ERA guidance (2006 EMA ERA Guidance corr 2) and changes in EMA Pre-meeting requirements (addition of the review of draft ERA) in the ERA 'Q&A' update. Both are pivotal for the applicant in developing the appropriate ERA strategy for marketing authorisations and in the preparation for EMA meetings.	Comment is noted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
60 - 80	12	Comment: In question 1 the need for an ERA is discussed. It is stated that regardless the legal basis, an ERA is needed, including those under art 10 of Directive 2001/83/EC (lines 62-70). However, the ERA may consist of a justification for the absence of data. We have several comments concerning the answer provided in this Q&A. <u>Generics replacing the marketed reference product or other generics</u> In many situations it can be anticipated that the introduction of generic products to the market will only lead to replacement of other products (reference product or other generics) and thus would not lead to an increase of the environmental exposure. Furthermore, even when the introduction of a generic could be anticipated to lead to an increase in use (e.g. for economic reasons the uptake of a generic could be higher than of the reference product), this still is not expected to cause an excess of the environmental risk previously calculated for the reference product. As clearly stated in the ERA guideline, the calculation is based on a default uptake (F_{PEN}) of 1% of the total population or (in case of a refined F_{PEN}) on the	Comment noted The need for ERA data for generic applications continues to be a matter of debate. On one side it is noted that an ERA data waiver in marketing authorization applications is done often on the assumption that no significant increase of the active compound in the environment will take place. In this view, actual consumption data, if available, are considered as a reasonable possibility to demonstrate whether an increase is expected or not. On the other side it can be argued that generics will in most cases only lead to substitution and thus would not change the exposure to the environment, nor would the anticipated risk to the environment be any different in other member states when a generic is introduced. For clarification, wording of question 1 was slightly amended. Further review on how to consider consumption data and the consequences of an increase of the geographical area for the anticipated risks will be considered in the discussion on the revision of the ERA guideline.

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		assumption that 100% of the diseased population is treated. <u>Relevance of consumption data</u> In lines 73-74 consumption data are mentioned as a source of suitable information. It is not clear how to use consumption data for a justification not providing study data. Consumption data are not part of the Predicted Environmental Concentration (PEC) calculation. Nevertheless, there could be situations where consumption data could be helpful is assessing the prevalence of a certain indication. E.g., when a medicinal product is not replacing a marketed product, but products prepared in pharmacies, used as last resort therapy, it is not obvious what the prevalence of the last resort indication is. Instead of assuming the total prevalence of the disease, consumption data of the drug substance may shed light on the prevalence of last resort indication. <u>Introduction to the market in a member state where the reference product is not marketed</u> In lines 79-80 the example is given that the introduction of a new generic medicinal product in a member state where the reference product is not marketed would lead to an increase of the treated population and consequently an increase of environmental exposure.	

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		In our view this example is in conflict with the ERA guideline. Calculation of the PEC is based on the Maximum daily dose consumed per inhabitant (mg.inh^{-1}.day^{-1}), Fraction of market penetration (by default 1% of the total population or, alternatively, 100% of the target population), amount of wastewater per inhabitant per day (200 L.inh^{-1}.day^{-1}) and dilution factor (10). In this calculation the number of inhabitants and the size of the geographic area or the size of the water surfaces is irrelevant. By applying a dilution factor of only 10, even the most extreme ratio of population density/water surface area should be covered. Consequently the introduction of a product in an additional member state does not change the calculated PEC value and thus also not the previously calculated environmental risk. Proposed change (if any): We suggest that the answer to question 1 should be clarified and aligned with the guidance provided in the ERA guideline	
65	1	Comment: Should Q&A No 41 actually be Q&A No 53 "When do I have to submit an Environmental Risk Assessment (ERA)? *Rev. Oct 14*"? Proposed change: replace 41 with 53.	Accepted. Wording is changed accordingly.
65	5	Comment: Should Q&A No 41 actually be Q&A No 53 "When do I	Accepted.

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		have to submit an Environmental Risk Assessment (ERA)? *Rev. Oct 14*"? Proposed change: replace 41 with 53.	Wording is changed accordingly.
71-75	5	Comment: It would be helpful if the Q&A document could clarify whether it is permissible to use market forecast data to justify an insignificant increase in the extent of use in comparison to recent overall consumption data.	Not accepted. In general, market forecast data should not be used as outlined in question4 of the Q&A.
77-75	2	Comment: Compared to the previous version, this paragraph has been amended by the term "(e.g. consumption data of the active ingredient in kg/year, preferably for at least the last 4 years in several involved Member states)". However, there is still un-clarity, how the absence or presence of a significant increase can be determined. In case of an extended indication of an existing product, the question remains, if prevalence data should be used assuming 100% use of the new product, or if predictions of market shares can be used to adjust the increase for the new product. A clarification would be appreciated.	Partially accepted. Basically we agree that more details how to define a "significant increase" in exposure would be helpful. However, since this can also be regarded as a case by case evaluation we see the responsibility of the applicant to incorporate convincing arguments for expected "significant" or "non-significant" increase of the active compound in the respective application. In this view there might be cases where the use of prevalence data could be reasonable.
85	4	Comment: The abbreviation 'MAH' should be explained. Proposed change (if any): see above	Accepted. MAH will be amended by 'marketing authorization holder'.

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166-172	5	Comment: It is currently unclear which log Kow value will trigger a persistent, bioaccumulative and toxic (PBT) assessment and/or bioaccumulation study e.g. will the log Kow of the neutral molecule trigger a PBT assessment or a bioaccumulation study when it exceeds the value of 4.5 or 3, respectively, even if the neutral species occurs outside the environmentally relevant pH range. Efpia believe that a PBT assessment or a bioconcentration study should only be triggered if a logD (or logKow) determined in the environmentally relevant pH range exceeds the trigger value of 4.5 or 3, respectively.	Not accepted. In Q6 ii) it is clearly stated that an ion-corrected log Dow for the neutral molecule should be reported together with the respective pKa value(s). The ion-corrected Dow is assumed to be equal to Kow. Furthermore, this log Dow value should be determined as a function of pH covering an environmentally relevant pH-range. The ion-corrected log Dow value determined in the environmentally relevant pH range should then be compared with the trigger of >4.5.
169-172	2	Comment: The authors specified the environmentally relevant pH range as pH 4 to pH 10. We object that this is an environmentally relevant pH range. If log P(D)ow is used as a surrogate for bioaccumulation, the environmental conditions should be considered. Typically, the pH range used for environmentally relevant fate and effects assessment is pH 5 to pH 9. Experimentally derived accumulation factors will never be obtained in acidic or basic regions such as pH 4 or pH 10. Proposed change (if any): …environmentally relevant pH range (pH 5 to pH 9).	Accepted. The revised ECHA Guidance "Chapter R.7a: Endpoint specific guidance" from July 2015 (Version 4.0) recommends a pH-range of 5-9. Wording is changed accordingly.

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169-172	5	Comment: Most previous studies have typically been undertaken across the pH range 5-9. This pH range is consistent with the guidance on regulatory Kow determination for ionisable substances in the 2014 ECHA Guidance "Chapter R.7a: Endpoint specific guidance". It is impossible to test many chemicals in biotic tests at pH 4 or pH 10; a degree of pragmatism is required within the guidance. Proposed change: replace (pH 4-10) with (pH 5-9).	Accepted. Wording is changed accordingly.
169-172	7	Current proposed text: Log Dow values should be determined as described above (and then ion-corrected) or log Dow should be determined as a function of pH covering an environmentally relevant pH-range (pH 4 to 10) e.g. Draft Guideline OECD 122: Partition Coefficient (n-Octanol/Water), pH-Metric Method for Ionisable Substances. Comment: Many pharmaceuticals are ionic substances that will be charged over some part of the pH scale, e.g., bases, acids or zwitterions. The proposed new environmentally relevant pH range of aquatic compartments is clearly too wide for an initial assessment, however. While it is acknowledged that extreme environmental pH values from pH 2 to pH 10 or higher are being observed in rare instances, a range	Accepted. Wording is changed accordingly.

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		of pH 4 to 10 covers too many exceptional situations. Generally, receiving waters for wastewater treatment effluents in Europe do not lie in the wide pH range indicated. The range of pH 4 to pH 10 indicated in the current proposed text refers to OECD test guideline 122. In that guideline, this particular range is defined by the necessity of using titration with standardised strong bases or acids at pH values outside of this range (OECD TG 122, § 6, p. 2), i.e., by a technical chemical necessity rather than an environmentally relevant pH range. It is therefore proposed to narrow the environmentally relevant pH range to pH 5 to 9, which covers most rivers and lakes as well as coastal waters receiving effluent. Proposed change (if any): Log Dow values should be determined as described above (and then ion-corrected) or log Dow should be determined as a function of pH covering an environmentally relevant pH-range (pH 5 to 9) ~~4 to 10) e.g. Draft Guideline OECD 122: Partition Coefficient (n-Octanol/Water), pH-Metric Method for Ionisable Substances.~~	
170	1	Comment:	Accepted.

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		Most previous studies have typically been undertaken across the pH range 5-9. This pH range is consistent with the guidance on regulatory Kow determination for ionisable substances in the 2014 ECHA Guidance "Chapter R.7a: Endpoint specific guidance". Proposed change : replace (pH 4-10) with (pH 5-9).	Wording is changed accordingly.
170	4	Comment: A range of pH 4 to 10 is proposed. This is beyond the environmentally relevant pH range. Proposed change (if any): The text should rather read 'at least at 3 pH values ranging from 5 to 9'.	Accepted. Wording is changed accordingly.
170	6	Comment: Is the lower level of the pH-range (pH 4) environmentally relevant for human pharmaceuticals? The pH in small to large rivers receiving effluents from sewage treatment plants is normally above pH 6 and below pH 10. Note that a pH range of 5 - 9 is defined as relevant for a bioaccumulation potential in section 2.4.3.1 of EC Guidance document No. 27 (2011). Proposed change (if any): pH 5 to pH 9	Accepted. Wording is changed accordingly.
171-172	8	Comment: "Draft Guideline OECD 122: Partition Coefficient (n-	Accepted.

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		Octanol/Water), pH-Metric Method for Ionisable Substances." is erroneous. The OECD Guideline Document No. 122 is not any longer in the draft status, but gives advice for "Determination of pH, Acidity and Alkalinity" URL:http://www.oecd-ilibrary.org/environment/test-no-122-determination-of-ph-acidity-and-alkalinity_9789264203686-en;jsessionid=iom0bqru1kb8.x-oecd-live-02 Proposed change (if any): Give appropriate information for guidance.	Wording is changed accordingly.
200-201	4	Comment: There are other test systems available to study the fate of substances in the environment, e.g. OECD 309 (Aerobic mineralisation in surface water). This test can be performed as 'pelagic test' (surface water only) or as 'suspended sediment test' (water body with suspended solids or re-suspended sediment). Thus, OECD 309 might be suitable for assessing the environmental fate of APIs in the aquatic compartment. Proposed change (if any): Include OECD 309 in the Q&A document.	Not accepted. Currently, there is no alternative test system which can completely replace the information on the fate of substances in aquatic sediment systems provided by OECD 308. Therefore, OECD 308 cannot be waived. However, we agree that performance of a study according to OECD 309 may provide valuable additional information on the fate and behaviour of substances especially in the water phase. Nevertheless, the suitability of the results of a study according to OECD 309 for use in the ERA as an alternative to OECD 308 data still needs to be scientifically demonstrated.
209	2	Comment: The EMA issued a draft Q&A on the performance and treatment of data of OECD 307 for veterinary medicines (EMA/CVMP/ERA/349254/2014) recently,	Not accepted. We agree that the draft reflection paper on poorly extractable substances (EMA/CVMP/ERA/349254/2014) may provide

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		which is also applicable to OECD 308. We think it is helpful, if the guidance given in that Q&A for veterinary medicines would also be considered for the present Q&A. In particular, we miss an explanation, how the formed NERs are interpreted with respect to half-lives. Additionally, although not a new issue in the present Q&A draft, we question whether the identification of metabolites >10% (structures, chemical specification) will add any important information to the ERA in sediments. Present practice shows that commonly an identification requires very complex methods for structure determinations like high precision analytical detection techniques. Those techniques are a tremendously burdensome without relevance for the risk evaluation. Currently, to our knowledge, they are not applied routinely, even if the range of metabolites exceed the level specified in the Q&A.	helpful information on the interpretation of data from OECD 308 tests as well. However, since this paper is still a draft version currently it will not be incorporated into this ERA Q&A list. The identification of relevant transformation products >10% (structures, chemical specification, half-lives if possible) is mandatory because basic information on these substances, which potentially may prove to be hazardous (e.g. PBT substances), and their position within the degradation pathway is needed. We want to point out that the requirement for identification is part of the OECD 308 test guideline rather than the guideline on the ERA of medicinal products for human use. The reasoning for waiving the information requirements on transformation products >10% is therefore not accepted.
210	5	Comment: Could you please clarify in how far non-extractable residues are still bioavailable and why they should be included in the trigger for the sediment risk assessment? The trigger for sediment risk assessment should only include the extractable compounds (at or after 14 days, >10% of applied either parent or metabolite) Proposed change (if any): "Results from the OECD 308 test should be (1) the	Not accepted. Non-extractable residues might consist of active compounds and can be released into the environment over time or might being taken up by sediment organisms.

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		amount of compound ~~***(including Non - Extractable 209 Residues = NER)***~~ that has shifted to sediment at any time point at or after 14 days – if this is more than 10%, a sediment toxicity test is triggered; (2) half-life values in water, sediment and total system; (3) kinetic model, chi2 error level of fitting……"	
215	1	Comment: The sentence 'Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life' requires further elaboration and more pragmatism. Whilst ideally this may be 'preferred' the presence of bound (unextractable) residues often makes determination of degradation half-lives impossible in practice. Consequently the concept of a 'total system' half-life has proved useful and is used routinely for agrochemicals and veterinary medicines. This should be acknowledged in this guidance. Proposed change : Replace 'Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life' with 'Ideally, a degradation half-life is preferred over a dissipation (disappearance) half-life, however it is recognised that this may not be possible if there are	Accepted. Wording is changed accordingly.

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		significant bound or unextractable residues, in which case the Total System half-life should be reported.'	
215	5	Comment: The sentence 'Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life' requires further elaboration and more pragmatism. Whilst ideally this may be 'preferred' the presence of bound (non-extractable) residues often makes determination of degradation half-lives impossible in practice. Consequently the concept of a 'total system' half-life has proved useful and is used routinely for agrochemicals and veterinary medicines. This should be acknowledged in this guidance. Other regulatory guidance compares the total system half-life values obtained from the study to the sediment persistence criterion of 120 days. Proposed change : Replace 'Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life' with 'Ideally, a degradation half-life is preferred over a dissipation (disappearance) half-life, however it is recognised that this may not be possible if there are significant bound or non-extractable residues, in which case the Total System half-life should be reported.'	Accepted. Wording is changed accordingly.

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215-216	6	Comment: In OECD 308 studies many pharmaceuticals show a fast dissipation from the water column to the sediment phase within some days. A separate calculation of a degradation half-life and a disappearance half-life in the water phase is not possible in these cases. Proposed change (if any): Add "if possible"	Accepted. Wording is changed accordingly.
217-220	10	Comment: The proposed guidance on the requirements for identification of metabolites in the water-sediment study is not completely clear (it is states that identification of metabolites is needed for metabolites occurring at levels >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). Proposed change (if any): Could you please clarify the following: - According to the test guideline (OECD 308), the criterion of exceeding the level of 10% of the dosed radioactivity applies to the whole system. Is this meant here as well? The whole system as such is not considered in the risk assessment (i.e. differentiation is made between water and sediment compartments), therefore it would make sense applying the criterion to the water and sediment phases	Not accepted. The ERA guideline exactly follows the definition given in the OECD 308 test guideline. Identification of transformation products occurring at levels >10% of the mass balance is required. The additional criterion (2 x 5%) as it is used for pesticides is not applicable for pharmaceuticals. The determination of relevant transformation products for the water and sediment phases separately is not supported, as there is no requirement for a separate risk assessment for transformation products.

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		separately. - Is there a minimum level of presence for the persistence criterion, such as used for agrochemicals (i.e. at least 2 consecutive occurrences at >5%, or once >5% but still increasing at the end of the study, as indicated in Commission Regulation 283/2013)?	
237-241	2	This section has not been changed significantly from the previous version. However, we question that the OECD 121 is not an acceptable method for determining the Koc. In the description of the OECD 121, as cited in annex 2, a study for comparison of results from OECD 106 (batch equilibrium method) to OECD 121 came to the conclusion that there is a good agreement of the values. The guideline OECD 121 states that "Normally, the adsorption coefficient of a test substance can be estimated to be within +/- 0.5 log units of the value determined by the batch equilibrium method" (paragraph 15). Therefore, we propose to consider results from OECD 121 sufficient for the determination of the Koc at least for those cases, where the determined Koc is at least 2 orders of magnitude below the threshold for the terrestrial study programme (i.e. 10 000), because the study according to OECD 121 is much easier to perform and less dependent on variable matrix properties.	Not accepted. The fate of pharmaceuticals should be determined for the ERA under conditions reflecting the diversity of the environment being as near as possible to reality. Therefore, adsorption/desorption studies should be performed on "real" soils. Considering the wide range of Koc – values, influenced by several soil parameters it is reasonable to prefer OECD 106 batch equilibrium method against the HPLC – method (OECD 121).The OECD 121 test should only be used for indicative purposes as described in Q10.
242	1	Comment:	Accepted.

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		The revised document requires adsorption data "for at least 2 sludges". We request that clarification is provided on how these sludges should differ, i.e. should their origin be from two different locations within the same sewage treatment plant or from two different sewage treatments Proposed change (if any):	Wording is changed accordingly.
242	5	Comment: The revised document requires adsorption data "for at least 2 sludges". We request that clarification is provided on if and how these sludges might be required to differ.	Accepted. Wording is changed accordingly.
244-245	6	Comment: Are adsorption data for 3 different sediments needed for equilibrium partitioning calculations in sediment in cases where no adsorption data to soil are available? Note that in a OECD 308 study two different sediment types are normally sufficient to assess degradation and adsorption processes in water-sediment systems. Proposed change (if any): Adsorption data for at least 3 soils or 2 sediments are needed …	Not accepted. Calculation of PECsediment represents a higher tier assessment. Therefore, the calculations should be based on 3 adsorption values, irrespectively whether they are determined on soil or on sediment.
245-246, 262-263	9	Comment: At both places, it is stated that adsorption data (i.e. adsorption coefficients or *K*oc values) for soil are not needed when a risk assessment for soil is performed. This is however, not true. In the case that a risk	Accepted. Wording is changed accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessment for soil is triggered, EMA guidance EMEA/CHMP/SWP/4447/00 corr 2 refers to STP modelling to obtain PECsludge (using the SimpleTreat model, the latter being incorporated in EUSES, which may also be used) and subsequently TGD methodology to calculate PECsoil. When following this methodology, *K*oc values for soil are needed. We do not think it is necessary to cite these calculations in detail here, but we refer to pages 78-85 of the TGD1 (2003, part II) or REACH guidance R16 (2012), p. 69-76, where the employed PECsoil model is explained. Proposed change lines 244-246: Adsorption data for at least 3 soils/sediments (no preference to soil or sediment) are needed for equilibrium partitioning calculations in sediment **and soil** risk assessment ~~assessment, whereas for the risk assessment of soil no soil/sediment adsorption data are required~~ (cf. Q. 10iii). Proposed change lines 261-264: Adsorption constants used in the risk assessment of the sediment **and soil** compartment should not be determined using sludge (see answer to Q. 10i). **For the calculation of PEC_{soil} and $PEC_{sediment}$, a K_{oc} value is needed. This value is determined from the three K_{oc} values for soil that have been determined in the OECD 106 study.** ~~For the soil compartment no soil adsorption data are required for the~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~initial calculation, because the release to soil is determined by sludge from the STP, when no volatility and leaching is considered.~~	
252	4	Comment: Please replace ' **"> 10%'** by '**> 10%'**. Proposed change (if any): see above	Accepted. Wording is changed accordingly.
304	4	Comment: Why are proteins and peptides no longer exempt from an EDC assessment? They have been exempt in the past presumably based on their biodegradability, which would still be a good reason. Proposed change (if any):	Not accepted. This seems to be a misunderstanding: Proteins and peptides are still exempted from ERA, independent of their potential ED properties. Wording of question 12 was adapted accordingly.
312-314	4	Comment: It is stated that the OECD 229 and 230 tests are not suitable to detect anti-androgenic effects. However, please note that both guidelines include endpoints that enable detecting anti-androgenic effects (see ENV/JM/MONO(2012) 22, p. 47-48). Proposed change (if any): Lines 313-314 might e.g. read 'note that these tests are only suitable to detect anti-androgenic effects, if secondary sexual characteristics in fathead minnow or medaka (OECD 229 and 230) or gonad histopathology (OECD 229) are evaluated'.	Partially accepted. Wording is changed as proposed with two additional sentences for more clarification.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
314-317	4	Comment: It is stated that 'in case it is already known from e.g. mammalian toxicity studies that estrogenic or androgenic receptors are targeted, the screening assay may become redundant' and 'long-term adverse effects should then be characterised in a fish sexual development test or a fish full life cycle test'. However, with regard to the fish full life-cycle test it should be kept in mind that this test has a long duration and that a very high number of fish is used in this test. Hence, for animal welfare reasons a fish full life-cycle test should only be performed if there is justified concern of endocrine / reproductive effects in fish. Preferably, a fish screening test should be performed before considering a fish full life-cycle test. Such a screening test would e.g. provide information on the concentration range expected to lead to endocrine effects and on the type of effects to be expected. This information is relevant for selecting the appropriate concentrations to be tested in the fish full life-cycle test and to supplement the test with specific endpoints for detecting endocrine effects (cf. ENV/JM/MONO(2012), p. 229 ff.). Proposed change (if any): Since ENV/JM/MONO(2012) includes detailed considerations for selecting appropriate tests, tests for potential sexual endocrine disrupting APIs should preferably be selected as outlined in this document.	Not accepted. This seems to be a misunderstanding. Here with screening assay it is meant OECD 229 and OECD 230, respectively. It is not meant that a screening or "range finding test" to confirm the correct dosing and other details is becoming redundant. Wording is clarified accordingly to avoid further misunderstandings.

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394-395	6	Comment: Please check the conversion factor of 4.6 from wet to dry sediment. Based on the default values of ECHA R.16 (2012) the conversion factor should be 2.6: RHO_{sed} wet = 1300 g/L wet sediment Volume fraction water in sediment = 0.8 (= 0.8 L water in 1.0 L wet sediment) → RHO_{sed} dry = 500 g dry sediment pro L wet sediment → ratio RHO_{sed} wet / RHO_{sed} dry = 1300 / 500 = 2.6	Not accepted. The concentration in freshly deposited sediment is taken as the PEC for sediment. Therefore, the properties of suspended matter are used (REACH R.16.6.6.3, Calculation of PEClocal for the sediment compartment). RHOsusp = 1150 g/L, RHOsolid = 2500 g/L, Fsolid-susp= 0.1 RHOsusp/RHOsoildxFsolid-susp = 1150 / 250 = 4.6.
409	5	A non-extractable residue is as such non-bioavailable (otherwise it would be extractable) and should therefore not be relevant for the PEC calculation. The PEC is meant to be the predicted environmental concentration which is likely to cause adverse effects, which means that the compound needs to be bioavailable and not irreversibly bound to soil/sediment. EFPIA recommend that the current EMA guidance refers to the recent ECETOC guidance for the interpretation and characterization of non-extractable residues. ECETOC (2013). Understanding the relationship between extraction technique and bioavailability. Technical report 117. Brussels. ECETOC (2013). Development of interim guidance for	Not accepted. The term NER has a purely operational definition. Therefore, actual extractability depends on the extraction techniques applied. We would like to point out that the terms bioavailability and extractability cannot be used equivalently.

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		the inclusion of non-extractable residues (NER) in the risk assessment of chemicals. Technical Report 118. Brussels.	