17 March 2011
EMA/CHMP/SWP/739571/2010
Committee for Medicinal Products for Human Use (CHMP)

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

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

Stakeholder no.	Name of organisation or individual
1	EFPIA (European Federation of Pharmaceutical Industries and Associations)
2	Medical Products Agency, Sweden
3	Medicines evaluation Board in The Netherlands
4	Fraunhofer Institute for Molecular Biology and Applied Ecology
5	ECT Oekotoxikologie GmbH
6	LSR Associates
7	Pfizer Inc
8	F. Hoffmann La Roche –Roche Corporate Safety and Environment
9	NOTOX B.V
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The publication of a Q&A document is very much appreciated in order to give clarification on many of the specifics of the ERA guideline, and to harmonize the understanding of both, submitting industry and evaluation authorities involved in the process. However, there are some concerns with the interpretation of certain aspects of the guideline, which will be addressed below in context with the individual Q&A issues. In addition, there are some areas where the Q&A appears to place additional requirements over and above the requirements of the ERA guideline. Whilst additional advice regarding the type of data that should be submitted is welcome, these should not be written as though they are mandatory requirements. The ERA guideline states that: *"It is recognised that there are acceptable test guidelines and approaches and methods, other than those described in this section, which are capable of giving an equivalent environmental risk assessment."* It is important that this flexibility, providing such approaches can be justified, is maintained following publication of this Q&A. There are some areas which cannot be adequately addressed in the Q&A and would benefit from a formal guideline revision. For example, the positioning and use of the OECD 308 study and sediment toxicity testing, plus the use of Kow vs Dow for ionisable compounds, are key areas requiring further review. We would welcome further discussions, possibly via a workshop, to address the need for, and details of, a formal EMA Guideline revision.	The SWP acknowledges the need for a revision of the current EMA guideline. Revision is being considered for the Work Plan of the SWP in 2011. The SWP agrees that interested parties should be consulted during a revision process, e.g., via a workshop. It is outside the scope of the Q&A document to impose additional mandatory requirements. However, some tests may have limited applicability, e.g., due to compound-specific properties, which may be resolved by using other more appropriate tests. Part of the aim of this Q&A document is to give pro-active guidance for both cost-effective and scientific reasons. A discussion on the applicability of the OECD 308 study is beyond the scope of the present Q&A document. The OECD 308 can be discussed in case of a revision of the guideline. Of course, industry is welcome to organize a workshop.
3	Generally, the document is clearly written. For specific comments, see below.	The comment is acknowledged. No further action taken.

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7	Pfizer's comments to the EMA Q&A document have been provided through EFPIA and reflect those as developed by the ERA User's Network. Pfizer endorses the Q&A comments as developed by ERA User's Network in their entirety. Pfizer also believes the clarification of several issues (positioning of OECD 308 and sediment toxicity testing; and use of Kow vs. Dow) as presented in EMA's Q&A is beyond the scope of a Q&A document and requires further discussion. Pfizer would support a 1-2 day workshop where industry, the authorities and invited experts may review the latest science relevant to pharmaceuticals and ascertain where further clarification and or formal revision to ERA Guidance is needed. While the current Q&A exercise is very helpful in addressing many of the questions, we feel a more broad based scientific discussion is required to successfully bring the more challenging questions to mutual resolution. Pfizer would welcome the opportunity to participate in such a workshop.	See comment to EFPIA
9	It is very elucidating that the guideline is now elaborated in more detail. It does imply though that the approach for conducting ERAs will change.	The comment is acknowledged. No further action taken.
10	No guidance is provided on volatile drug substances such as gaseous anaesthetics which are largely excreted in exhaled air.	ERA assessment of volatile drug substances is a very specific case as investigations can be limited by the volatility of the drug. Such drugs should be assessed on a case-to-case basis. Hence, no general guidance can be given in a guideline.

2. Specific comments on text

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Q&A 1 Lines 21-22	3	Comment: The link to the Agency's pre-submission procedural Advice Q&A No 41 does not work (it leads to the homepage of the EMA instead of to the referred document). Proposed change (if any): Include correct link (not known to the assessor of this document).	Accepted. The correct link will be added: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf
Q&A 1 Lines 27-35	1	Comment: Further guidance would be helpful on what would constitute a 'significant increase' for determining the requirements for the MAA. Proposed change: After Line 30 add: 'As a general guidance, an increase in exposure <10% would not be considered to be significant, since this is within the error of evaluating PEC:PNEC ratios, which are usually given to 2 significant figures. Thus, if the predicted increase in exposure is <10% a full ERA may not be necessary.	Not accepted. The definition should also be looked at in an operational manner. For instance, the increase is also significant when the trigger value is exceeded or the PEC/PNEC ratio becomes >1. This can happen at an increase of 1, 10 or 100%. Thus, it is not possible to add a concrete figure to the increase.
Q&A 1 Lines 34-35	1	Comment: The "introduction of a new generic product in a member state" will not change the exposure assessment if the use per capita is not higher than in other European countries, ie it would not increase the PEC:PNEC ratio. Proposed change: Suggest delete this example.	Partly accepted. For a generic newly marketed in a given member state, there is a significant increase in the environmental exposure as the PEC increases from zero to X. However, it is agreed that the PEC:PNEC ratio will not change when the prevalence of the disease is not higher in the new member states. Therefore, it is acceptable to submit an ERA dossier, in which equality of the PEC with that of other Member States can be demonstrated.

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			The example is not deleted.
Q&A 2 Lines 38-47	1	Comment: As for Q&A 1, whilst it is acknowledged that "There is no unique value of what constitutes a *significant* increase" some guidance should be provided in order to avoid the extremely wide range of values previously applied during ERA reviews by different rapporteurs. Proposed change: "There is no unique value of what constitutes a *significant* increase. As a general guidance, an increase in exposure <10% would not be considered to be significant, since this is within the error of evaluating PEC:PNEC ratios, which are usually given to 2 significant figures. Thus, if the predicted increase in exposure is <10% a full ERA may not be necessary."	See comment at Q&A 1.
Lines 46-47	8	Comment: Both the EMA 2006 Guideline and the draft Q&A Document intend to give clear guidance both to the applicant and to the regulator on how to proceed and on how to assess potential environmental risks, but also on how to render the conditions for an environmental risk assessment comparable for all applicants and regulators. As "significant" is not defined in the 2006 EMA Guideline, there is uncertainty on the side of both the applicant and the regulator. This uncertainty, caused by the lack of a simple definition, may lead to a differential and substantially unequal treatment of highly comparable cases, which might constitute de facto discrimination. The intent of	See comment at Q&A 1

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		both the 2006 EMA Guideline and the Q&A Document, however, cannot be to further discrimination but, on the contrary, to eliminate it. Proposed change (if any): Therefore, in our view, a discrete value in per cent increase should be given as a definition of a "significant" increase.	
Q&A 3	4	General comment: Concerning the refinement of F_{pen} in Phase I it is considered not very likely that reliable and valid data of disease prevalence data for all member states included in the registration process can be provided. On order to avoid misunderstandings and discussions it is proposed to clearly emphasize in the text that the default F_{PEN} should only be refined in very well documented certain exceptional cases and e.g. a special treatment regime has to be documented in the SPC.	Partly accepted As stated in the Q&A document, prevalence data should be published by a reliable and independent source, e.g., a peer-reviewed scientific journal or WHO. Refinement based on the posology is indeed only possible if well-documented. Thus, this should be based on the SPC or published data, unless an increase in treatment regime is very unlikely to occur, e.g., due to severe adverse effects, and this is clearly described in the clinical dossier. The answer has been reworded.
Lines 55-61	10	Comment: No allowance has been made for second-line treatments which will apply to only a fraction of the total patient population. Proposed change (if any): For a drug substance authorised only in a second-line indication, an appropriate refinement of Fpen is permissible if based on published information.	Partly accepted. In Phase I, a worst case scenario is assumed. However, if the patient population is well-defined as based on published scientific information, the Fpen could be refined for a drug substance in a second-line indication. Rewording of the Q&A is not deemed necessary.
Q&A 3 Line 56	1	Comment: A market share of 100% is often an extreme worst case. Proposed change:	Not accepted. The market share and prevalence are two completely different things. A 100% market share is always assumed because market shares can change among companies, while the prevalence stays the same. This can in

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		A market share of 100% of the affected patient population is always assumed as a worst case.	some cases be an extreme worst case when addressing the product of a single company, but not when addressing the total sales of an active ingredient.
Lines 59-61	2	Comment: The default value should always be allowed. The applicant should not be discouraged from doing further calculations of Fpen based on the risk that this could result in higher requirements. Proposed change (if any): Delete this sentence.	Accepted. The sentence has been deleted.
Lines 69-71	10	Comment: Mandating the use of an Fpen of 0.0005 for all orphan indications would mean that a phase IIa assessment would be triggered for drug substances whose maximum daily dose is > 40 mg/day. This could be a significant disincentive for some companies in respect of developing drugs to treat orphan diseases. Moreover, the policy would mean that evidence on orphan disease prevalence released by COMP as part of positive orphan designation procedures would be ignored. Many drug substances can be developed to treat a number of orphan diseases and so if a default Fpen of 0.0005 were applied to each indication, this would result in a cumulative and significant overestimate of the true Fpen. Proposed change (if any): For orphan drugs the Fpen should be determined on the basis of prevalence data in each indication with reference to positive orphan designations by COMP.	Accepted. The answer has been reworded. The prevalence should be based on the medicinal orphan drug designation adopted by the Committee for Orphan Medicinal Product (COMP).
Lines 72-76		Comment: Some drug treatments, by the very nature of the indication, are of short duration, and so their	Not accepted. Anticancer treatments are usually administrated within a well-

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		environmental impact will be lower than that for treatments of chronic conditions. Treatments for life-threatening conditions where life expectancy is less than 5 years (by analogy with the provisions of the EU guideline on limits of genotoxic impurities) should be considered as a special case and less stringent ERA criteria applied. Proposed change (if any): For treatments for life-threatening conditions where life expectancy is less than 5 years, DOSEai should be determined as the average daily dose over this time period.	defined treatment regime as an increase in dosages and treatment duration is usually not feasible due to the development of severe adverse reactions. Thus, the Fpen value can only be refined using the approach outlined in End note 1.
Q&A 3 Lines 74-76	1	Comment: End note 1 is helpful for showing how to take into account the treatment regime. However, some pharmaceuticals are taken "as needed" and cannot be placed in either of the categories 'single use' or 'well-defined treatment regime'. For these pharmaceuticals it is still a question how Fpen could be refined.	Not accepted. Refinement of the F_{pen} for pharmaceuticals administrated "as needed" is not accepted for a Phase I assessment unless justified based on published peer-reviewed scientific literature. The answer has been reworded.
Q&A3 Lines 49-81	5	Comment: Section "General assumptions": It is stated that "market research data cannot be used for F_{pen} refinement. In Phase I F_{pen} calculations, 100% medication compliance is always assumed". Does this mean that for refinement in Phase II market research data are accepted? This should be explicitly mentioned. Section "Refinement based on prevalence data": It is stated that "If regional differences exist, F_{pen}	Section "General assumptions": Not accepted. The text explicitly states that a 100% medication compliance is assumed for a Phase I assessment. Furthermore, the current guideline (EMEA/CHMP/SWP/4447/00) explicitly states that sales forecast data can be used for a Phase II assessment (page 7/12). This means that in Phase II, a refinement can be made based on medication compliance, other (or no) treatment(s), etc. This should be well documented and from an independent source, like the information needed to refine the F_{pen} in Phase I. However, a 100% market share is always

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		should be calculated for the member state with the highest prevalence of the disease." It is considered not very likely that an applicant can provide reliable and valid prevalence data for all CMS (all member states included in the registration procedure). If such data cannot be provided for all CMS it is not possible to specify the member state with the highest prevalence of the disease. Proposed change (if any): *It could be accepted that prevalence data for the (three) member states with the largest populations will be provided by the applicant and thereof the highest prevalence will be used for the F_{pen} refinement.* section "Refinement based on treatment regime": In order to avoid misunderstandings and discussions, it should be clearly stated that this refinement can only be performed if the possible (maximum) number of treatment periods per year ($n_{treatment}$) is known. In many summary of product characteristics (SmPC) only the duration of one treatment period ($t_{treatment}$) is specified (e.g. antibiotics) but not the number of treatment periods. Therefore, it should be clearly stated that estimations of $n_{treatment}$ will not be accepted, or otherwise, at which conditions they would be accepted.	assumed for the treatment with the active compound for which the ERA is performed, also in Phase II. Section "Refinement based on prevalence data": It is not necessary to provide data for all concerned member states. But if it is clear that there are regional differences, these should be taken into account. This does not have to be reflected in the member states with the highest populations; a region can for instance also be a large city or the countryside. Section "Refinement based on treatment regime": Partly accepted. The number of treatment periods is rarely stated in the SPC. Estimations of $n_{treatment}$ should be based on clinical considerations. Such estimations are easily done for a cytotoxic anticancer drug but not justifiable for a pharmaceutical dosed "as needed". Thus, in the latter case, the refinement should be based on published peer-reviewed scientific literature. The answer has been reworded.
Q&A 4 Line 88	9	Comment: QSARs are not acceptable for PBT assessment. However, in the same paragraph reference is made to the REACH guidance documents. In these documents, QSARs are mentioned as options to	Not acceptable. The text has been reworded in Question 14 for clarification purposes.

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		determine if testing for PBT Proposed assessment is needed. Proposed change (if any): Change the statement indicating that QSARs may be used to identify substances that need testing.	A new question (now numbered Q3) is added regarding the use of REACH guidance instead of the TGD.
Q&A 4 Line 90	1	Comment: Note, REACH guidance states that "The value for the dissociated molecule determined around a pH of 7 (sometimes referred to as Dow) is considered more realistic for PBT and chemical safety assessment." (REACH Chapter 7A, p105). See also comments below re use of Kow. Proposed change: Add after Line 92: 'Note that for ionisable compounds Dow is considered more realistic for PBT and chemical safety assessment." (REACH Chapter 7A, p105).	Partly accepted. The last sentence in the first paragraph of question 5ii (now Q6ii) is deleted, and a third sub-question is added. A new question (now numbered Q3) is added regarding the use of REACH guidance instead of the TGD.
Q&A 4 Lines 88-90	1	Comment: REACH PBT assessment guidance usually provides several options for identifying P, B and T properties, rather than strictly focusing on specific laboratory testing. One example for an alternative / additional approach would be the use of known metabolism data to assess the probability for bioaccumulation. Also, the general exclusion for QSARs in order to assess potential PBT properties is not in agreement with REACh and the guidance cited in this paragraph. In particular, in the mentioned guidance document (ECHA Guidance on information requirements and chemical safety assessment Part C: PBT Assessment) table C.1-2, model data for persistence and bioaccumulation are specifically addressed as a first	Partly accepted. The PBT assessment should be conducted according to the criteria as laid down in REACH Annex XIII. With regards to your example: please note that metabolism data in humans alone is not sufficient; the rate of metabolism in fish can be slower. The text has been changed.

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		step into PBT assessment. Additionally, also the use of animals should be restricted as much as possible for the purpose of the "T" parameter. Proposed change : ~~Please note that QSARs are not accepted for PBT assessment.~~ A stepwise procedure should be employed as described in the guidance document "ECHA Guidance on information requirements and chemical safety assessment Part C: PBT Assessment ". Assessment should be performed in accordance with REACH PBT Assessment guidelines.	
Line 92	9	Comment: Here another paragraph would be expected, i.e. concerning the specific mode of action that would trigger a Phase II assessment. The guideline gives an example (endocrine disruptors), but it remains unclear what other modes of action would lead to concern and trigger a Phase II assessment. In addition, it would be desirable to give some guidance on what testing is needed for endocrine disruptors (see also next comment). Proposed change (if any): Add another paragraph (i.e. question 5), concerning mode of action that would lead to concern, triggering a phase II assessment irrespective of the PECsurfacewater.	Accepted. The topic has been expanded. Currently, the evaluation of endocrine disruptors is limited to sexual endocrine disrupting compounds. However, it is acknowledged that further clarification on endocrine effects and possible additional studies is needed. This should be considered in case of a revision of the guideline.
Lines 94-105	6	Comment: It is our current practice to use OECD 107 for logKow values up to 5 (and sometimes above), which can be done if care is taken. For ionisable substances, OECD 107 can be run at fixed	Not accepted. OECD guidelines should be used as described in these guidelines. Shake flask determinations above 4 are thus not acceptable. This is caused by microdroplet formation. As long as the K_{ow} (partitioning of neutral species by definition) is derived from the measured D_{ow} values at different pHs, the

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		pH values covering the environmentally relevant range (4 to 9). It is normally sufficient to perform tests at pH 4, 7 and 9, but additional values can be investigated if clarification of partitioning behaviour is required. This is preferred to OECD 122, which has existed as a revised draft document since November 2000. The method in OECD 122 is less specific and potentially more susceptible to influence of impurities.	method can be accepted. It is agreed that OECD 122 is not yet accepted. However, any data based on that method published in peer-reviewed literature would be accepted as well.
Q&A 5ii) Lines 100-105	1	Comment: Log Kow is generally a poor predictor of bioaccumulation for ionisable compounds. For complex ionic molecules it is more relevant to use log Dow at pH 7, This is acknowledged in the REACH guidance, Chapter 7, p105[i]. Section 5ii) implies that only the Kow should be used to predict bioaccumulation, which is not consistent with REACH. Proposed change: Replace lines 100-105 with the following text: "For ionisable compounds Dow is considered more realistic for PBT and chemical safety assessment (REACH Chapter 7A, p105)." Note; If the SWP cannot agree to this change we would propose to delete 5ii) altogether since Q&A5(ii) as written is inconsistent with REACH guidance.	Partly accepted. The last sentence in the first paragraph of question 5ii is deleted, and a third sub-question is added. A new question (now numbered Q3) is also added regarding the use of REACH guidance instead of the TGD.
Q&A 5ii)	5	Comment: According to ECB (2003), the log K_{ow} is an unsuitable indicator of the bioaccumulation potential of ionisable compounds. Similarly, the use of a K_{oc} derived from a K_{ow} value in order to assess the sludge-adsorption	Partly accepted. The REACH guidance is followed. A sub-question is added to question 5 (now Q6). A new question (now numbered Q3) is added regarding the use of REACH guidance instead of the TGD.

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		potential of ionisable compounds can be misleading (ECB, 2003). The proposed assessment using the log D_{ow} considers the neutral and ionized species of ionisable compounds. Yet, the log D_{ow} may also be a poor predictor of the bioaccumulation potential of ionisable compounds (Cunningham, 2004). Proposed change (if any): *The liposome-water distribution coefficient could be considered as an alternative or additional parameter to assess the bioaccumulation potential of ionisable compounds (Escher et al., 2000).* References: Escher et al. (2000): Environ Sci Technol. 34, 3954-3961. ECB (2003): European Chemicals Bureau. Technical Guidance Document on Risk Assessment. Cunningham (2004): Special characteristics of pharmaceuticals related to environmental fate. In: Williams RT, editor. Human Pharmaceuticals: assessing the impacts on aquatic ecosystems. Society of Environmental Toxicology and Chemistry (SETAC), Pensacola, FL, USA.	
Lines 110-111	3	Comment: The rationale behind this question is not clear. OECD 303A is not mentioned in Guideline EMEA/CHMP/SWP/4447/00. Proposed change (if any): It should be checked which test is meant in this question.	It is indeed OECD 303A that is meant in the question, because this is a question that arises regularly in procedures.

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Lines 107-120	6	Comment: Is there a way of using OECD314B which follows the degradation of the test material and the formation of metabolites under more realistic conditions instead of OECD 301?	Not accepted. This question is similar to question 6 (now Q7), and the answer is therefore also similar, i.e., this is not possible (see Q&A Q7 for rationale). The OECD 314B is added to question 6 (now Q7). An OECD 301B study shows whether a substance is **readily biodegradable**. The endpoint in this study is mineralization (CO_2 evolution). The concentration of the inoculum is low (≤ 30 mg/L). Therefore, the influence of adsorption is not determined in this test. In contrast to OECD 301B, an OECD 314B study shows whether a substance is **inherently biodegradable**. The OECD 314B guideline was developed as an alternative to OECD 303A. The endpoints are mineralization (CO_2 evolution), formation of volatile degradation products, total radioactivity, concentration of the parent and metabolites in extracts. The concentration of the inoculum is high (2500-4000 mg/L). Therefore, adsorption is additionally measured in this test. If an abiotic set up is measured in parallel, it is possible to distinguish between adsorption and biodegradation. It is true that a study following the OECD 314B guideline gives more information about a substance than a study following the OECD301 B, e.g., formation of metabolites. However, it is not possible to gather information in OECD 314B about the ready biodegradability of a substance. The conditions of this test are "best-case" conditions for biodegradation: high sludge concentration, low concentration of the substance and long incubation time. In summary, it is not possible to use the OECD 314B instead of OECD 301B, because OECD 301B gives information on the **ready biodegradability** and OECD 314B on **inherent biodegradability**.
Q&A 8 i) Lines 124-131	1	Comment: There are several biodegradation tests that simulate STPs better than a Ready Biodegradation Test (eg OECD 314, OECD 303). Hence, if significant degradation is observed in any of these studies then the OECD 308 should not be required.	Not accepted. The OECD 308 study can only be waived, if the substance is readily biodegradable (following OECD 301B). Inherent biodegradability is not mentioned in the guideline with regard to waiving the OECD 308. See also our reply to the LSR comment at lines 107-120.

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		In principle, the ERA fate testing strategy found in Phase II requires further review and discussion. A specific problem area is the blanket requirement of an OECD 308 study at Phase II Tier A. 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, and which have and a low PEC:PNEC ratio (even assuming no degradation in the environment), further understanding of persistence by conducting an OECD 308 study is arguably only of academic value since the data are not used to refine the risk assessment. In such cases we would contend that an extensive study on persistence such as an OECD 308 or OECD 307 is not needed. For PBT/vPvB substances, or when the PEC:PNEC is >1, an understanding of persistence is useful for the risk assessment, however it may also be possible to derive sufficient information from a simpler screening level assessment. There are several other studies which are acceptable for use under EU REACH guidance, and which, depending on the properties of the substance, may provide better quality information to support the risk assessment. 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 through spray drift. It was not designed to simulate	A discussion on the applicability of the OECD 308 study is beyond the scope of the present Q&A document. The OECD 308 can be discussed in case of a revision of the guideline.

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		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, the data generated from an OECD 308 study does not lend itself to the generation of independent half-lives for water and sediment and the presence of bound (unextractable/ desorption resistant) sediment residues often makes determination of half-lives in sediment impossible in practice.	
Q&A 8(i)	5	General comment: In section 5.2 (Outcome of Tier A fate and effects analysis) of the 'Guideline on the environmental risk assessment of medicinal products for humans use' the last bullet point refers to information which is drawn from the study OECD 308. This information is restricted to shifting of the drug substance to the sediment. All other valuable information determined by applying OECD 308 is not considered in the outcome of Tier A. To minimise this discrepancy between data availability and data requirement at Tier A, two options are suggested (1) to develop/apply a more appropriate test system which focuses on the required information in Tier A and to move OECD 308 to Tier B. (2) to modify the data evaluation (risk assessment) step for Tier A in a way that the information available from OECD 308 can be used in an appropriate way at Tier A. Specific comment: It is stated that OECD 308 can be waived, if a compound is shown to be readily biodegradable (OECD 301). Likewise, it should also be commented (in Q 9),	See comment above. Partly accepted. Indeed, no soil assessment has to be performed if a compound is ready biodegradable. However, a study on sorption/adsorption still needs to be performed, since this study belongs to the base-set and gives important

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		whether the adsorption/desorption study (OECD 106) could be waived if the compound is shown to be readily biodegradable. The K_{OC}, derived by OECD 106, triggers the performance of terrestrial fate and effects analysis, "unless the compound is readily biodegradable" (paragraph 5.3.3). Consequently, terrestrial fate and effect studies as well as the OECD 106 would not be necessary when the compound is shown to be readily biodegradable.	information about the physical-chemical properties of the compound.
Q&A 8(ii) Lines 128-131	1	Comment: The OECD 308 study may also (sometimes) give information on half lives and transformation products, mineralisation and bound residue formulation. Crucially, however, because the risk assessment is based on a total residue approach, these data rarely have any bearing on the conclusions. Thus, for all practical purposes, often the only use of the OECD 308 is to trigger the sediment toxicity testing. It is inappropriate to demand studies which it is known at the outset are not needed to demonstrate the safe use of a medicinal product. An 'equivalent environmental risk assessment' may often be provided (ie one which gives exactly the same risk assessment conclusions) without the need to conduct an OECD 308 study (and this is 100% predictable at the outset, based on the current ERA guideline). Proposed change: Delete these lines. Alternatively, the ERA guideline should be revised to allow proper use of the data generated in the 308 study. If the guideline is revised, we would recommend that the OECD 308 should be moved into Tier B as a 'simulation' test only if needed when PEC/PNEC > 1.0	See comment above.

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		for the sediment. In lieu of the 308 in Tier A, we would recommend a sediment toxicity test as part of the base set of ecotoxicity tests using a worst case PEC.	
Line 131	3	Comment: A test number is lacking. Proposed change (if any): "OECD" should be replaced by "OECD 308".	Accepted. Test number (308) is added.
Q&A 8 iii) Line 133-140	1	Comment: Identification of metabolites is only feasible if appropriate reference material is available, in the case of pharmaceuticals usually metabolites from DMPK studies. Given the fact, that the knowledge about metabolites does not lead to any further testing, but generally the total residue approach is applied, the technical efforts required to identify metabolites in the absence of reference material often constitutes a disproportionate effort. Proposed change : *(3) the identity and amount of significant metabolites formed, particularly where the metabolites appear to be more persistent (for example if a metabolite is present at all timepoints throughout the study), assuming analytical identification is feasible. Metabolite identification becomes more important when the results could potentially impact on the ERA conclusions, e.g. when the PEC:PNEC based on the parent compound is >1.*	Partly Agreed. The question has been expanded.
Q&A 8 iv) Lines 142-145	1	Comment: "High persistence" is not defined. Also, if the aerobic test has developed anaerobic regions, there is little to be gained from a fully anaerobic test. Proposed change :	Accepted. The sentence has been replaced.

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		The aerobic systems usually also contain or may develop anaerobic parts. Thus, the testing of completely anaerobic systems asked by OECD 308 is not necessary. ~~If the results of the aerobic system show a high persistence of a drug substance in the sediment layer, it may be advisable to perform an additional test in an anaerobic water/sediment system.~~	
Lines 143-145	9	Comment: It is stated that an additional test in an anaerobic water/sediment system may be performed if the results of the aerobic system show a high persistence of a drug substance in the sediment layer. Please add an explanation why this is recommended. What is the value of this additional test? Proposed change (if any): Please add an explanation why an additional test with an anaerobic water/sediment system should be performed in case of persistent drug substances.	See comment above.
Q&A 8	4	OECD 307: Aerobic and anaerobic transformation in soil. How many soils should be used for testing? Is the anaerobic system necessary in the OECD 307 test for the environmental risk assessment of pharmaceuticals?	Accepted. The OECD 307 guideline should be followed, and accordingly four soils which differ in characteristics should be tested. Further details can be found in the OECD guideline. An anaerobic system is not necessary; OECD 307 is added to question 8 iv (now Q9 iv).
Q&A 9 Lines 149-150	1	Comment: The EMA Guideline states that "One study is generally sufficient". However, the Q&A goes beyond this by saying "preferably with 2 types of sludge and 3 soils". The (OPPTS) guideline requires 1 sludge type to be used. Extra data generation should be optional.	Partly accepted. By using the wording 'preferably', it is already indicated that this is optional.

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		Proposed change: ~~"preferably with 2 types of sludge and 3 soils"~~	
Lines 148-156	6	Comment: The Kd is concentration dependent. Should this parameter be the K_F^{ads} the Freundlich adsorption distribution coefficient ?	Sorption is usually linear at sufficiently low concentrations. Non-linearity can not be established when only a K_d is submitted as this is a point estimate. Adsorption is preferably determined as K_F. Note however, that Simple Treat assumes linear sorption (K_d input).
Q&A 9 Lines 149-150	9	Comment: Are there circumstances when the 3 soils need not be tested? For instance, if a substance does not bind to sludge, would additional testing in 3 soils be required? Proposed change (if any): Please add an exemption if applicable.	Accepted. The OPPTS guideline is also mentioned in the guideline and it requires only one sludge type to be used. In Phase II tier B, K_d for sludge is necessary for SimpleTreat modelling and K_{oc} is needed for equilibrium partitioning calculations in sediment and soil risk assessment. In Tier B of the guideline (EMEA/CHMP/SWP/4447/00), the OECD 106 is requested with respect to sewage sludge modelling. In case K_d values determined by OPPTS are available, these can also be used at this stage (at least 2 sludge types). Adsorption constants determined using OECD 106 are needed for Tier B assessment of soil and sediment. Thus, if sediment and/or soil assessments are triggered, it is necessary to test in soils.
Q&A 9 Line 161	1	Comment: Q9 is somewhat confusing. Proposed change: In principle, only the Kd (or Koc) for sludge is used in Tier A to trigger terrestrial testing. Thus the most relevant study is the OPPTS study and the OPPTS guideline requires only 1 sludge type to be used. Extra data generation should be optional at Tier A.A measured Kd for sludge of 3700 L/kg is equivalent to a Koc trigger of 10000 L/Kg (since in the SIMPLETREAT model sludge contains 37% organic carbon).	Question 9 & 10 are combined in order to minimize possible confusion. Accepted. Text is changed.

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		In Tier B, measured Kd/Koc values for soil and sediment should be used where available wherever the risk assessment needs refinement. In such cases it is recommended that the OECD 106 or OPPTS test is used to derive specific soil and/or sediment Kd/Koc values as appropriate. The HPLC method is only suitable for indicative purposes. Thus, if the Koc determined using the HPLC method is close to the trigger value of 10000 L/Kg, or if the Koc is used in any Tier B calculations, then it is necessary to ask for another study using a batch equilibrium method.	Partly accepted. A sludge K_d is not appropriate for soil and sediment equilibrium partitioning calculations in Tier B. For these calculations, a soil K_{OC} needs to be determined. Accepted. In Tier B, specific K_{OC} or K_d values are necessary and the HPLC method is not suitable there. Only OECD106 is mentioned in the guideline with respect to sewage sludge modelling (paragraph 5.3.1).
Q&A 10	1	Comment: Q&A 10 is not needed if the above changes are made to Q&A9 Proposed change: delete Q&A 10, subject to making above changes to Q&A9	Accepted. Q9 and Q10 are combined.
Q&A 10	4	If a substance is readily biodegradable and there is no risk identified in Phase II Tier A, adsorption/desorption data is not required (see 5.3.3). Is the performance of the OECD 106 in such a case still required for completeness of Tier A?	Not accepted. The adsorption/desorption is part of the base set of Tier A and should always be performed, since this study gives important information about the physical-chemical properties of the compound.
Q&A 11 Lines 168-172	1	Comment: It is inappropriate for a single test with cyanobacteria to be the basis for representing the effects of antimicrobials on all aquatic photosynthetic organisms, including macrophytes. As has already been acknowledge by the EMEA in a Q&A document for implementation of a CVMP guideline for environmental impact (EMEA/CVMP/ERA/172074/2008-Rev.1),	Not accepted. OECD 216 is not a good replacement of the algal test. Moreover, the OECD 216 is a soil test, and is as such not representative for water systems. We will, however, add a slightly rewritten version of the text from the Veterinary Q&A as a clarification in the present Q&A.

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		"bluegreen algae" are prokaryotes and are more similar to bacteria. All other algae are eukaryotes. The CVMP Q&A goes on to say that "The implication that cyanobacteria are somehow related to algae is not correct. However, a growth inhibition study on cyanobacteria is required because these organisms are usually more sensitive than algae to compounds with antimicrobial activity." Many of the "bluegreen algae" that could be tested are nitrogen fixing microorganisms with sensitivity to antimicrobials that can be adequately represented by the results from OECD Study 216. Alternatively, cyanobacteria sensitivity could be evaluated by collecting a minimum inhibitory concentration as would be done for any other individual microbe in a normal MIC test (US FDA CVM Technical Assistance Document 4.02, 1987). Proposed change (if any): We suggest amending the text in line with the comment above.	
Q&A 11	4	Comment: It is proposed to include a comment on the relevant parameter for the assessment of the algal tests: Growth rate should be used for the evaluation of the test as currently used for Classification & Labelling and recommended by ECHA (2008). ECHA (2008): Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance, section R.7.8.4.1. Data on aquatic pelagic toxicity	Accepted. This will be added as a sub-question (Q&A Q11 iv).
Q&A 11	5	Comment:	Accepted. This will be added as a sub-question. A new question

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A fourth question could be added to this issue: Which endpoint should be used, the most sensitive of yield and growth rate or only growth rate? Recent procedures according to REACH guidance (ECHA, 2008) recommend explicitly to use growth rate as the relevant endpoint for risk assessment. References: ECHA (2008): Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance, section R.7.8.4.1. Data on aquatic pelagic toxicity.	(now numbered Q3) is also added regarding the use of REACH guidance instead of the TGD.
Q&A 12 Lines 188-194	1	Comment: The testing of hormones should be done in relationship to the mode-of-action of those compounds. The OECD is presently developing specific test guidelines for endocrine active compounds and preparing guidance on the use and interpretation of fish tests in relation to hazard and risk assessment of those substances. In essence, hormonal compounds with different modes-of-actions (e.g. agonists or antagonists to sex hormone receptors) may require a different testing strategy. In any case, it should be taken into account that life-cycle tests in fish require a large number of fish. Therefore, based also on animal welfare considerations, a case-by-case decision should be made in determining which testing strategy is the most appropriate for a particular hormonal compound with known mode-of action. Similarly, if the sensitive life stages are known, targeted tests with shorter exposure duration and requiring a lower number of fish may be	Partly accepted. Wording is changed.

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		equally informative for risk assessment as a full life-cycle test. Proposed change: ~~These endpoints can only be assessed in a fish full lifecycle study, but not in an ELS or an acute fish toxicity test.~~ These endpoints can only be addressed in a study which addresses the sensitive life stages (e.g. in a fish full or partial lifecycle study), but not in an ELS or an acute fish toxicity test.	
Q&A 12 Lines 188-194	9	Comment: What about the short-term reproduction assay in fish (OECD 229 and OECD 230)? These tests should be mentioned here. Further, other organisms should not be disregarded. Fish are not the only organisms that may be exposed or responsive to endocrine active substances. What about thyroid-like hormones? And what about cases where the Phase I PECsurfacewater is below the action limit of 0.01 µg/L but a Phase II assessment is triggered by the endocrine mode of action? Would a complete Phase II assessment be needed in such cases, or can the testing regime be tailor made? Finally, what about higher organisms such as (fish-eating or surface water inhabiting) mammals and birds? Proposed change (if any): Add a paragraph on endocrine active substances and the way they should be considered. Please refer to the REACH guidance for this purpose (ECHA, Guidance on information requirements and chemical safety assessment, Chapter R.7b:L endpoint specific guidance, 2008). Please also	See comment above. The OECD 229 and 230 are now mentioned. A new question (now numbered Q3) is added regarding the use of REACH guidance instead of the TGD. Yes, if a Phase II assessment is triggered because of the endocrine mode of action, a complete Phase II assessment is necessary. These animals are out of scope of this ERA.

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		provide some guidance on what testing to be considered in case the PECsurfacewater does not exceed the trigger value.	
Q&A 12	4	Comment: In the answer to question 12, only the Fish full cycle test is mentioned as appropriate test method to deliver relevant information for detection of sexual endocrine effects in fish. For the safe evaluation, Fish Full Life Cycle Tests (FLCT) and two-generation test represent the golden standard. However, in the meantime, a tiered testing strategy was formulated to detect a potential for endocrine disruption in vivo. As mentioned in Knacker et al. (2010), at first an in vivo screening test should be performed. Two respective technical guidelines have been validated by the OECD: the 21 day Fish assay (OECD TG 230) and the Fish Short term reproduction assay (OECD TG 229). If the short term test indicates an effect on the assessed endpoints (Vitellogenin, Secondary sex characteristics, reproduction), a Fish Full Life Cycle test should be performed. However, if precise information about the sexual endocrine mode of action is available a focus of the test design may be possible if it covers the most sensitive exposure period and the most sensitive population relevant endpoint. It was shown that the Fish Sexual Development test (FSDT) could be the adequate test for androgen	See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		receptor agonists and aromatase inhibitors. References: Knacker et al. (2010): Environmental effect assessment for sexual endocrine-disrupting chemicals: Fish testing strategy. Integr Environ Assess Manag. 6(4), 653-662	
Q&A 12	5	Comment: The answer to this question provides important information on suitable tests in case of an endocrine mode of action of a pharmaceutical. However, only one test, the full life cycle test, is mentioned that should be performed in such cases instead of the fish early life stage test (OECD 210). Proposed change (if any): *To our opinion, it would be more appropriate to follow a tiered testing strategy as adopted e.g. for chemicals (see ECHA, 2008). According to this strategy, an in vivo screening test (OECD 229 or OECD 230) should be performed if effects on the estrogen or androgen axis are expected. If effects are observed in such a test, long-term adverse effects should then be characterised in a fish sexual development test, a fish partial life cycle test or fish full life cycle test (see also Knacker et al., 2010). If effects on the thyroid axis are expected, an amphibian metamorphosis assay would be more appropriate than a fish test.* References:	See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ECHA (2008): Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance, Appendix 7.8-5, Assessment of available information on endocrine and other related effects. Knacker et al. (2010): Environmental effect assessment for sexual endocrine-disrupting chemicals: fish testing strategy. Integr Environ Assess Manag. 6(4), 653-662.	
Q&A 13 Lines 197-198	3	Comment: It is indicated that the combination product may be tested, but it is not clear when this is necessary. Proposed change: It should be indicated in what circumstances testing of a combination of active substances is necessary.	Not accepted. Testing of a combination of active substances is not required. It is always an addition to testing the individual active substances. Thus, no circumstances need to be specified.
Q&A 14 Lines 199-201	10	Comment: No evidence is provided to justify the statement that read-across is not permitted. Surely it should be possible to evaluate this principle based on environmental toxicity and fate data for closely related drug substances (such as simvastatin and lovastatin for example)? REACH guidance is cited in the Q&A document at line 86. However what is not mentioned is that reading-across data from one substance to another, where scientifically appropriate and documented, is a concept that is encouraged in the REACH legislation. Proposed change (if any): Read-across should be permitted on a similar basis to that employed in the	Not acceptable. The wording is changed.

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		REACH legislation.	
Q&A 14 Lines 199-201	1	In general, the use of QSARs and read-across for structurally related substances should be encouraged when considering action limits, interpreting data and/or designing more appropriate tests (intelligent testing). ERA Guidance specifically requests in Section 5 page 5, that "All relevant data should be taken into account, …"in Phase II of the ERA. REACH Chapter 6 Guidance on QSARS and Grouping of Substances and Chapter 7.b Endpoint Specific Guidance provide detailed discussion around how to use QSARs, under what circumstances they would be considered 'relevant' to the ERA and what additional information is required to substantiate their use. The application of 'Intelligent Testing Strategy' has also gained interest with the growing importance of minimizing animal use. Some recent advancements include: • ECETOC. 2007. Intelligent Testing Strategies in Ecotoxicology: Mode of Action Approach for Specifically Acting Chemicals. Technical Report No. 102 • Endorsement of the ECETOC guidance in the KNAPPE Final Report (http://www.knappe-eu.org/fichiers/60-D6.6%20final%20report%20final.pdf) to the European Commission on pharmaceuticals in the environment in 2008; • August 25, 2010, International Conference discussing results of an UBA (German Environment Agency) financed project on modeling approaches for hazard prediction of pharmaceuticals to aquatic organisms. Proposed Change: The use of QSARs and read-across from other structurally related substances may be used to	Partly accepted. The sentence 'all relevant data should be taken into account' is not quoted completely by the commentator; it is followed by the examples of what all relevant data are. Obviously it refers to the type of data and not to data from other compounds. The results of the UBA conference were going to be used to make a prioritization for actives to be tested; it was very clearly stated there that these methods cannot replace actual testing. The wording is changed.

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		consider the relevance of action limits, help interpret data and/or design more relevant tests (Intelligent Testing), providing that general guidance is followed as provided in REACH and that the appropriate justification for the approach is provided.	
Line 203	10	Comment: Even with the additional guidance on metabolites, it's still not clear what programme of testing would be needed for a pro-drug, particularly one that is readily hydrolysed to the active moiety. Would two separate programmes be needed on the drug substance and active moiety? Proposed change (if any): Clear guidance should be given on the environmental assessment of pro-drugs.	The environmental risk assessment should be performed with the active compound entering the environment. If a pro-drug is nearly fully metabolized to the active moiety (> 90%), only the active moiety needs to be tested. If any of the two (active moiety or pro-drug) is entering the environment in more than 10% of the administered dose, an environmental risk assessment needs to be performed for both of them. The question is added to the Q&A.
Q&A 15 (iii) Lines 224-233	1	Comment: Summing the PEC/PNEC ratios for parent and all metabolites when a full EA is conducted on each, is not necessarily justified. Quite often the receptor binding or mode of action for the metabolite is different (not present) as with the parent, and therefore should be treated separately as is done with combination products. A full rationale to the approach and whether the PEC/PNEC ratios are summed or not should be required.	Partly accepted. In the case that PECs and PNECs for parent and metabolite(s) are determined individually, summing their ratios is considered justified based on the assumption of concentration additivity. It is acknowledged that concentration addition is not the correct concept *per se* for substances that have different mode of actions (MoA). However, it has been demonstrated (also for mixtures of pharmaceuticals with widely differing MoA) that the assumption of concentration addition leads to a reasonable prediction of the effect of mixtures. Concentration addition is expected to be slightly overprotective compared to e.g. independent action, which is acceptable from a regulatory point of view. See for instance Backhaus et al. (2010), KEMI report PM 3/10 and Kortenkamp et al. (2009). (http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf) or underlying studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 225-233	9	Comment: It is stated that in case the PEC of the active ingredient is changed based on metabolism data, the risk of metabolites should be addressed by performing a complete ERA. However, would it not be possible to address the toxicity of metabolites in a qualitative approach, i.e. if data are available from the toxicological database indicating that metabolites are essentially less toxic, or less active, is it really necessary to perform toxicity testing with these metabolites? Would it not be possible to use the toxicity endpoints from the active ingredient as conservative endpoints for such metabolites? Proposed change (if any): Please further elaborate the issue of (non-)testing with metabolites.	Yes, it is possible to use the toxic endpoints from the parent compound as conservative endpoints for metabolites; this in fact is similar to the total residue approach. A metabolite being less toxic does not waive a full Phase II ERA, since the risk also depends on how much of the metabolite will be present in the environment.
Q&A 15 Line 227	5	Comment: The footnote [2] in line 227 should be explained.	Accepted. This should be footnote 1. Text is changed.
Q&A 16 Lines 238-248	1	Comment: Sediment concentrations can be adjusted for OC, but the PNEC should not. Proposed change : ***i) Should sediment concentrations be recalculated into standard sediment?*** Yes, ~~results from toxicity tests~~ $PEC_{sediment}$ should be recalculated into standard sediment with an organic carbon content of 10%, according to REACh guidance.~~:~~ ~~measuredOC,sedimentstandardOC,measuredsedimentstandard~~~~*ffNO ECNOEC*~~ $PEC_{sediment}$ ~~is~~ may be calculated from $PEC_{surface\ water}$	Not accepted. The PNEC should also be adjusted for organic carbon (OC), so the PEC and PNEC can be compared using the same amount of organic carbon. It is acknowledged that this is not specifically stated in REACH guidance for the PNEC sediment, but it is specifically stated for the PNECsoil, PECsoil and PECsediment. Moreover, it is common practice, also within the REACH framework, to use OC-normalized PNECs, since the EUSES model also only uses normalized PNECS. A new question (now numbered Q3) is added regarding the use of REACH guidance instead of the TGD.

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		using equilibrium partitioning and ~~EU TGD/~~REACH equations, if no measured $PEC_{sediment}$ is available. Please refer to REACH guidance Chapter R16.5; equation R16-41 and references (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm?time=1266832225). This results in a $PEC_{sediment}$ which is ~~also~~ expressed in standard sediment with an organic carbon content of 10%. ~~Hence, the PEC/PNEC ratio for sediment uses two concentrations based on equal characteristics.~~ This $PEC_{sediment}$ can then be used to calculate the $PEC_{sediment}/PNEC_{sediment}$, using either calculated or measured (if triggered from OECD 308 testing) $PNEC_{sediment}$.	
Q&A 16 (ii) Lines 249-254	1	Comment: Normalizing to organic content may not be appropriate for ionizable substances given the mechanisms of sorption are likely to be related to ionic interactions rather that straight partitioning into the organic matter. In these cases, normalizing to a standard pH (i.e. pH 7.0) may be more appropriate. An option to use Koc from sediment data determined in OECD 106 is preferred.	Partly accepted. In these cases, care should be taken that all testing is performed at an environmentally relevant pH. As stated in the Q&A, for these compounds a tailor-made approach may be followed, if this can be substantiated and is well reported. This will be added to the Q&A.
Lines 275-282	9	Comment: In the text, Fpen is described as being the prevalence of the disease within a population. Therefore, why need to calculate the Fpen as CONai_region / (DOSEai x n_i,region x Nd)? Why can the Fpen not be addressed simply as the fraction of the population carrying the indication? The described calculation is only useful when a drug is not	Accepted. End note 1 has been reworded.

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		administered daily, as in the example in lines 270-273. Proposed change (if any): Please indicate that the calculations in End note 1 are only useful for medicinal products with a well-defined posology. In other cases, Fpen is simply the prevalence of the disease.	
End note 1 Line 286	5	Comment: Instead of N_d the figure 365 should be used.	Partly accepted. The issue has been clarified in the text.

[i] Extract from REACH, CHAPTER R.7A, page 105:

Guidance on regulatory compliant K_{ow} determination for ionisable substances and salts
The K_{ow} is typically defined as the partition coefficient of the neutral, undissociated form of a substance. However, the relative extent to which an ionisable substance is likely to be dissociated in the environment (with pH usually in the range 5-9) can have a marked effect on its physicochemical properties, especially the octanol-water partition coefficient and water solubility, which in turn affect fate and behaviour. As log K_{ow} is routinely used to predict bioconcentration/bioaccumulation potential, this aspect is especially important in a PBT context. For substances which dissociate within an environmentally relevant pH range (pKa 5-9), values for K_{ow} shall be derived for the neutral form, and preferably also for the dissociated form. In some cases a factor 4-5 has been recorded between the log K_{ow} of both species. The value for the dissociated molecule determined around a pH of 7 (sometimes referred to as Dow) is considered more realistic for PBT and chemical safety assessment.