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Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'

Draft

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Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

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The aim of the current question-and-answer document is to provide clarification and to harmonise the use of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00).

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Questions and answers

Question 1. When do I have to submit an environmental risk assessment (ERA) as part of my initial application for a marketing authorisation?

An ERA is required for all new marketing authorisation applications (MAA) for a medicinal product through a centralised, mutual recognition, decentralised and national procedure regardless of its legal basis.

For further details, please refer to the Agency's pre-submission procedural Advice, Q&A No 41 (http://www.ema.europa.eu/htms/human/presub/q41.htm).

Please note that according to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under Art 10-generic medicinal products, Art 10(3)-hybrid, Art 10a-well established use/bibliographical, Art 10b fixed combinations, Art 10c informed consent and Art 10(4) similar biological applications.

However, the ERA dossier may consist of an adequate justification for the absence of specific study data. The justification of the absence of significant increase of the environmental exposure, demonstrated by suitable information, can be accepted as a justification for the absence of a complete ERA.

On the basis of the above, generics are not exempted from providing an ERA and cross reference to the ERA dossier of the originator is not possible. Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the introduction of a new generic medicinal product in a member state where the reference product is not marketed.

Question 2. What is required for an ERA for a type II variation or an extension application?

The submission of a new ERA is needed for a type II variation or a line extension if an increase in environmental exposure is expected. For these types of applications, the environmental data previously submitted in the original dossier of the same MAH can be used. Nevertheless, the ERA dossier may need to be updated. An increase in environmental exposure is generally expected when the patient population is increased. Examples are: the addition of a new indication, the inclusion of a new patient population or an increase of the maximum recommended therapeutic dose. An extension application for the inclusion of new formulations such as a dermal patch may also constitute a significant increase in the environmental exposure if significant residual drug substance is present in the used patch. There is no unique value of what constitutes a *significant* increase. This will be assessed on a case-by-case basis.

Phase I assessment

Question 3. The Guideline states that "The Applicant may use the default value or refine the F_{pen} by providing reasonably justified market data, e.g. based on published epidemiological data". How may F_{pen} be refined in Phase I and what supporting data should be provided?

F_{pen} represents the fraction of a population receiving the drug substance during a given time. The default value is 0.01 of the population of interest, i.e. Europe or the specific member state(s).

General assumptions

A market share of 100% is always assumed. Market research data cannot be used for the refinement of Fpen as they take into account competitive products and therefore do not assume treatment of 100% of the patients in the relevant disease(s).

In Phase I F_{pen} calculations, 100% medication compliance is always assumed. In case the applicant performs an F_{pen} refinement in Phase I and the resulting value is higher than the default value (0.01), the higher value is to be used in the ERA.

Refinement based on prevalence data

The F_{pen} can be refined by submitting European disease prevalence data for the sought indication(s). Such data should be published by a reliable and independent source, e.g., a peer-reviewed scientific journal or the World Health Organization (WHO) (e.g., the International Agency for Research on Cancer (IARC)). It is assumed that 100% of the patient population is daily taking the medicinal product for the relevant disease(s), i.e., F_{pen} = prevalence of the disease. If regional differences exist, F_{pen} should be calculated for the member state with the highest prevalence of the disease. This member state should be one of the member states included in the registration procedure. For orphan drug submissions, an F_{pen} value which corresponds to the default prevalence data of 5 in 10,000 according to the EU definition of orphan drugs may be used. This yields an F_{pen} for orphan drugs of 0.0005.

Refinement based on treatment regime

In phase I, the F_{pen} may be refined taking the worst-case treatment regime and worst-case number of treatment repetitions into consideration (see end note 1). This only applies to products intended for single use (e.g. during surgery, diagnostics, etc.) and products with a well-defined fixed treatment regime. The posology should be well defined in the SPC.

Multiple indications

If the product can be prescribed for the treatment of more than one indication, the F_{pen} values for all the sought indications should be calculated. The $PEC_{surface\ water}$ values for the various indications should be calculated using the maximum prescribed dose for each indication and then summed to reach the $PEC_{surface\ water}$ that will be used in the ERA.

Question 4. A compound remains in Phase I because $PEC_{surface\ water}$ is below the action limit, but its log K_{ow} is >4.5. Should the assessment be continued and if yes, how?

Yes, the assessment should continue but instead of applying strictly the phase II of the guideline, a specific PBT assessment should be performed. REACH guidance is recommended for technical guidance (ECHA, 2008, Chapter R11, Guidance on information requirements and chemical safety assessment, Part C: PBT Assessment). Please note that QSARs are not accepted for PBT assessment. In general, the tests outlined in Phase II Tier A will have to be performed, in the order: persistence – bioaccumulation – toxicity. Use the REACH documents for further guidance: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_c_en.pdf?vers=20_08_08.

Question 5. Screening for persistence, bioaccumulation and toxicity

i) How should log K_{ow} be determined?

Log K_{ow} should be determined experimentally. A calculated value is generally not acceptable. The shake-flask method or the slow-stirring method is preferred over the HPLC method. Please note that for compounds with log K_{ow} > 4, the shake-flask method cannot be used and only the slow-stirring method is acceptable. This range of applicability is based on OECD guidelines 123 and 107.

ii) How should log Kow be determined for ionisable compounds?

In such cases, an ion-corrected log D_{ow} for the neutral molecule should be reported together with the respective pK_a value(s). The ion-corrected D_{ow} is equal to K_{ow}. K_{ow} is used in the PBT screening and to determine whether bioaccumulation is triggered.

Log D_{ow} values should be determined as described above (and then ion-corrected) or log D_{ow} should be determined as a function of pH covering an environmentally relevant pH-range (e.g. Draft Guideline OECD 122: Partition Coefficient (n-Octanol/Water), pH-Metric Method for Ionisable Substances).

Phase II

Phase II Tier A - Fate: Degradation tests

Question 6. Can the base data set according to Phase II Tier A be omitted if OECD 303A shows degradation in sewage treatment plants?

No. The base data set is not waived based on results of an OECD 303A test as the availability of sewage treatment plants varies across Europe and removal efficiencies for pharmaceuticals vary considerably. Information from this test can be used for $PEC_{surface\ water}$ refinement, but only in Phase II Tier B. Expert judgement is then needed on how to use the results.

Question 7. Is it necessary to perform a ready biodegradability test (OECD 301)?

No. OECD 301 can be waived if OECD 308 is performed. However, for a SimpleTreat modelling exercise in Phase II Tier B, it may be necessary to perform the OECD 301 test. In addition, only if the OECD 301 shows the compound to be readily biodegradable, it is possible for the applicant to waive the OECD 308 test. Please note that the microbial community should not be pre-exposed to the test compound in this test, and that the addition of more inoculum is not allowed.

Question 8. Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)

i) Can OECD 308 be waived by presenting other degradation tests?

No. Currently, no other test providing information on fate of the substance in the environment is available. Thus, the use of modified tests (e.g., shorter test duration) is not accepted. The only exception is the OECD 301 test, where paragraph 5.1.1. implies that if a compound is readily biodegradable, OECD 308 is not necessary.

ii) Can OECD 308 be waived by directly testing toxicity to sediment organisms?

No. OECD cannot be waived, since the test does not only give information on shifting of substances to the sediment, but also on half-life values, transformation products formed, mineralisation, and bound residue formation.

iii) Which kind of results should be reported for the OECD 308 test?

Results from the OECD 308 test should be (1) the amount of compound 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 system; (3) the identity and amount of metabolites formed; (4) the amount of CO2 evolution; (5) a total mass balance, including distribution in the test system at any time point and bound (non-extractable) residues. Please note that mostly a dissipation (disappearance) half life is calculated, but if it is possible to calculate a degradation half life this should also be done. Furthermore, the half life should be calculated for both the parent drug substance and for the metabolites (>10%) if possible.

iv) Are the anaerobic systems necessary in the OECD 308 test?

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 for pharmaceuticals. 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.

Phase II Tier A - Fate: Adsorption and use of K_{oc}

Question 9. Which study is preferred to determine adsorption/desorption? Is a batch equilibrium method necessary?

A batch equilibrium method is asked for (OECD 106 or OPPTS 835.1110), preferably with 2 types of sludge and 3 soils. Although in principle the HPLC method should be accepted because it is mentioned in the guideline, this method is only suitable for indicative purposes. Please note that in Phase II tier B, 'real' K_{oc} values are necessary; a K_d for sludge is necessary for SimpleTreat modelling, a K_{oc} is needed for equilibrium partitioning calculations and a K_{oc} from soils is necessary as a trigger for soil/groundwater assessment. Thus, if the K_{oc} determined using the HPLC method is close to the trigger value (10.000 L/kg) or the SimpleTreat model is used in Tier B, it is necessary to ask for another study using the batch equilibrium method.

Question 10. Should sludge be used to determine sorption? If sludge is used, what is the trigger for K_d?

Sludge is preferred to determine adsorption coefficients, since sorption in wastewater treatment plants occur primarily to sludge and the resulting values are used in Phase II Tier B SimpleTreat modelling. It is highly recommended that the OECD 106 is performed with 2 types of sludge and 3 types of soil. K_{oc} is not a good trigger if sludge is used. The correct trigger should then be K_d with a trigger value of 3700 L/kg. This trigger value is based on the SimpleTreat model, where the sludge in the relevant compartment contains 37% organic carbon.

Phase II Tier A – Ecotoxicity

Question 11. Algae

i) Which kind of algae should be used for the growth inhibition test (OECD 201)?

For the OECD 201 test the use of a green alga is recommended. However, when antimicrobials are tested, this test should be performed with a cyanobacterium (Cyanophyta; also called blue-green algae). Annex 2 of the OECD 201 guideline lists examples of species to be tested, for both algae and Cyanobacteria as well as appropriate test media. Other species of cyanobacteria are also acceptable as long as guideline criteria comparable to OECD 201 are still met.

ii) Which guidance should be used for cyanobacterium testing, since cyanobacteria behave differently from green algae? What criteria of validity need to be met, when testing algae and Cyanobacteria?

The OECD 201 test should be used, but care should be taken that the right medium and light conditions are chosen. Please refer to the answer to the previous question. The criteria of validity for controls are described in the OECD 201 test guideline § 11. If these criteria are not met, the test needs to be repeated.

iii) Is recovery within algal tests a point to consider?

No, because of the high growth rate of algal cells it may be possible that the algal population will recover if the test substance disappears within 72 h test duration (e.g. hydrolysis, photolysis). In the environmental risk assessment, algae act as a model organism for all aquatic photoautotrophic organisms, including aquatic macrophytes with a much longer generation time. So, the population of aquatic macrophytes might not be able to recover within an adequate time-frame (e.g. just one generation per year).

Question 12. Which chronic fish study should be performed for hormones?

This depends on the compound. For some hormones, it may be necessary to perform a full life cycle test because effects on reproduction parameters are anticipated due to their mode of action. An early life stage (ELS) test (OECD 210) may then not represent the most suitable life-stage and/or may not provide the most relevant endpoints. Thus, the exposure design of a study needs to include the appropriate time and life-stage of exposure necessary to elicit an effect. For example, relevant endpoints for an oestrogen receptor agonist would be fertilisation and sex ratio. These endpoints can only be assessed in a fish full life cycle study, but not in an ELS test or an acute fish toxicity test.

Question 13. Do combination effects need to be tested for fixed combination medicinal products?

The ERA is performed separately for each compound within the product. The combination product may be tested, but only as an addition to the individual tests for the compounds.

Question 14. Is read-across from other, structurally similar compounds, allowed?

No. However, it might be helpful for the design of a more substance tailored test strategy.

Phase II Tier B

Question 15. Metabolites

i) When should metabolites also be tested? Which tests should be performed on metabolites?

The current guidance does not require testing of metabolites. EMEA guidance follows a 'total residue approach', in which environmental fate and toxicity of metabolites are assumed to be covered by that of the parent compound (drug substance). However, there is an option for further refinement of the ERA based on risk quotients for separate metabolite fractions when, based on the total residue approach, a risk is still identified. In that case metabolite testing could be considered in Phase II B; see answer to Q15iii for details.

If refinement by metabolite testing is not performed, the ERA should be concluded with the statement that the use of the product is expected to result in a risk to the environmental compartment(s) concerned. Testing would only concern metabolites constituting ≥10% of the administered dose[1]. For metabolites, the same tests should be performed as for the parent. Please note that EMEA/CHMP/SWP/4447/00 designates a relevant metabolite as those being present in ≥ 10% of the amount excreted. This is corrected in this Q&A document to "relevant metabolites are those that are excreted in ≥ 10% of the administered dose".

ii) Should the toxicity of a metabolite be tested in case it constitutes ≥10% of the initial parent compound concentration in the sediment?

At the moment this is not a requirement. If it is deemed desirable by a company to continue testing (e.g. to reduce a risk quotient), expert judgement is needed to decide what tests are needed, which may then also need to include data for the aquatic species besides the sediment toxicity test.

iii) How to account for metabolism in Phase II Tier B?

The total residue approach may be abandoned in Tier II B if there is evidence of metabolism of the drug substance in humans. But please note that if the total residue approach is abandoned, a full ERA is required for each metabolites constituting ≥10% of the administered dose[2]. The PEC is then calculated separately for the parent compound and these metabolites and all resulting PEC/PNEC ratios are summed for the evaluation of environmental risk of the product. If it is not possible to perform the ERA for the metabolites excreted in fractions ≥10% of the dose, the total residue approach must not be abandoned. Only if it is certain that a portion of the parent compound never leaves the patient or metabolises into CO_2, this can be used to refine PEC for the parent. This refinement is only to be applied in Phase II Tier B.

iv) Are all metabolites measured as <10% relative to the total dose administered, subtracted from the dose to calculate $F_{excreta}$ in Phase II Tier B?

Yes, please note that this is only allowed in Phase II Tier B, not in Phase I or Phase II A.

[1] This can only be determined appropriately when the metabolism and excretion study shows a complete mass balance.

Question 16. Sediment

i) Should sediment concentrations be recalculated into standard sediment?

Yes, results from toxicity tests should be recalculated into standard sediment with an organic carbon content of 10%, according to:

$$NOEC_{\text{standard sediment}} = NOEC_{\text{measured}} \times \frac{f_{\text{OC, standard sediment}}}{f_{\text{OC, measured}}}$$

$PEC_{sediment}$ is calculated from $PEC_{surface\ water}$ using equilibrium partitioning and EU-TGD/REACH equations. 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.

ii) Should this also be done for ionisable compounds?

If the K_{oc} values from OECD 106 for different soils are comparable, it can be assumed that equilibrium partitioning theory is applicable to this compound and the normalisation approach should be followed. If the K_{oc} values are orders of magnitude apart, consult an environmental chemistry expert to decide which K_{oc} to use, or to discuss if the K_{oc} and/or normalisation of toxicity results to organic carbon should be applied. The decision should then be well reported.

iii) Can the fraction of bound residue be subtracted from the $PEC_{sediment}$?

No, the fraction of bound residue can not be subtracted from the $PEC_{sediment}$

iv) Which assessment factor should be used for sediment?

According to REACH guidance Chapter R.10.5.2.2, an assessment factor of 100 should be applied to the NOEC from a chronic sediment toxicity test when one chronic sediment test is available.

Question 17. Is it necessary to test the rate and route of transformation in soil under anaerobic conditions?

No, it is not necessary to test the rate and route of transformation in soil under anaerobic conditions.

End note 1

The following approach may then be used for the estimation of F_{pen}:

1. select a well documented worst-case estimate for the prevalence of the disease;
2. identify the maximum recommended dose and the number of treatment days per year;
3. calculate the total amount of drug used in a given region:

$$CONai_{region} = DOSEai \times t_{treatment} \times n_{treatment} \times P_{region} \times n_{i,\,region}$$

with:

Parameter	Description	Unit
$CONai_{region}$	periodical consumption of active ingredient in a particular region per year	[mg region^{-1} yr^{-1}]
$DOSEai$	maximum daily dose consumed per patient	[mg patient^{-1} d^{-1}]
$t_{treatment}$	duration of one treatment period	[d]
$n_{treatment,}$	number of treatment periods per year	[yr^{-1}]
P_{region}	prevalence for particular region	[patients inhab^{-1}]
$n_{i,\,region}$	number of inhabitants in a particular region	[inhab region^{-1}]

For products with a well-defined posology, the treatment period ($t_{treatment}$) and the number of treatment periods per year ($n_{treatment}$) should be calculated assuming the worst case treatment scenario. Such treatment regimes must be clearly stated in the SPC. For example, an anti-cancer drug administrated for five days in monthly cycles, $t_{treatment}$ equals 5 days and $n_{treatment}$ would be 12 year^{-1}.

The region concerned should be the member state with the highest prevalence of the disease.

Calculate the refined F_{pen}

With respect to assessing the market penetration for a single product, the *DOSE*ai should be used instead of the *DDD*. Hence, the default F_{pen} calculation given in the notes of the EMEA guideline can be rewritten:

$$F_{pen} = \frac{CONai_{region}}{DOSEai \times n_{i,\,region} \times N_d}$$

with:

Parameter	Description	Unit
F_{pen}	fraction of market penetration	[patients.inhab^{-1}][2]
N_d	number of days per year	[d yr^{-1}]

It follows that when F_{pen} is refined in Phase I, a reliable estimate of the disease prevalence and the number of treatment days per patient per year is essential.

[2] Note that the unit of P_{region} (prevalence) and F_{pen} (fraction of market penetration) are given in [patients inhab^{-1}] for reasons of clarity. Since *DOSE*ai is usually represented in [mg patient^{-1} d^{-1}], redundant units like 'patients', 'inhab', 'region' were introduced to provide insight during the derivation. Mathematically, both parameters (P_{region} and F_{pen}) are fractions and are thus unitless.