4 February 2026

European Medicines Agency

Second industry stakeholder webinar on the revised guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.)

Summary on main topics discussed

Guideline document: Link

1. General Information

The second stakeholder webinar on the revised Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.; hereinafter the "EMA ERA-guideline") was held on 6 October 2025 from 2.30 until 5 pm via Webex. This webinar was held to evaluate the one-year experience with the EMA ERA guideline. The webinar was hosted by EMA and input was provided by members of the Non-Clinical Working Party (NcWP) temporary drafting group for the ERA guideline hereinafter 'the ERA drafting group'. Represented as speakers were Éadaoin Griffin (Chair of the ERA drafting group), Susanne Brendler-Schwaab (Chair of NcWP), Birger Scholz and Arne Hein. EMA was represented by Rhys Whomsley, Annika Buck, Heloise Mignot and Alexandra Deaconeasa.
During this webinar a list of 20 consolidated questions which were provided by the industry trade associations prior to the meeting were addressed orally. After the questions were answered a discussion was held with the industry trade-association key lead speakers.
In the following an indicative summary on the main topics discussed during the webinar is provided. The summary was prepared by the ERA drafting group in collaboration with the Regulatory Affairs Department and the Legal Department of the EMA. The provided summary should be read in conjunction with the applicable legal provisions as well as relevant EMA guidance.

2. Procedural Topics Discussed

2.1. Data Sharing

Questions from the industry trade associations related to data sharing focused on the following topics:

a) generic applications where data sharing is not agreed, including PEC refinement with prevalence data and the need for data sharing

b) what information can EMA provide in relation to ERA and how to request it

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c) use of other data sources in the absence of data sharing agreements

d) clarification around letters of access

e) incentives for data sharing

f) data generation for legacy products

A summary of the responses to the above points is provided below (references to specific questions from the Phase I Decision tree (Figure 2 of the EMA ERA guideline) are included in brackets):

a) It was clarified that for generics, when there is an earlier ERA for the same active substance (Q2b – Yes), for which an increase in environmental exposure is not anticipated (Q2d – No), and data sharing is not agreed, if the relevant ERA was considered satisfactory by an EU National Competent Authority and the applicant is able to justify that the scientific conclusions reached for the relevant ERA remain applicable to their generic product, repetition of ERA studies will generally not be required. However, an ERA report is required to be submitted in Module 1.6 of the eCTD dossier that outlines the approach, including the path followed through the Phase I Decision tree and the appropriate justification to conclude on the ERA. Additionally, if the relevant ERA is not considered complete in accordance with the current EMA ERA guideline, it is expected that the applicant would conduct any missing studies.
It was also noted that Q2b of the Phase I Decision tree captures the possibility to avoid repetition of studies even where data sharing is not agreed. However, for generics where Q2b of the Phase I Decision tree is answered in the negative (for example, where it is not known whether the relevant ERA is satisfactory, or where it cannot be justified that the conclusions remain applicable), the risk assessment then progresses down to the next steps in the Phase I Decision tree.
In relation to PEC refinement with prevalence data and the need for data sharing, it was noted that for active substances for which the action limit is applicable (see Q4), PEC refinement with prevalence data is always a possibility (see Q6). Where a prevalence-refined PEC is below the action limit, the risk assessment concludes in Phase I and no further data are required (although the PBT/vPvB assessment must still be completed).

b) It is the responsibility of the new applicant to check existing ERAs for products containing the same active substance, if they intend to request data-sharing in lieu of generating their own ERA studies. Some high-level information about ERA may be obtained from the European Public Assessment Report (EPAR) of the concerned medicinal product. Applicants can consider other available legal avenues to obtain access to documents held by EMA. Not all assessment reports are published on the EMA website, and applicants may consider submitting an access to documents request (cf. European Medicines Agency policy on access to documents POLICY/0043). Please note that whilst it is possible to check the information from an assessment report, it is not possible to refer to an EPAR in lieu of submitting the actual data. Where consent for data-sharing has been obtained from the originator MAH, the data should be integrated into the ERA of the new product. Where consent for data-sharing has not been obtained from the originator MAH, a justification should be included.
Applicants are advised to consult the available guidance at the links below:

https://www.ema.europa.eu/en/about-us/how-we-work/access-documents

https://www.ema.europa.eu/en/about-us/contacts-european-medicines-agency/send-question-european-medicines-agency

c) EPARs or study summaries from other MAH websites are not considered sufficient to replace required studies without the underlying study data.
Other agency databases (e.g. janusinfo.se, Fass.se, premier.marionegri.it, EPA or ECHA and its registration dossier database) can inform on the availability of data. However, it is noted that e.g. FASS, PREMIER and ECHA databases are industry-based /include input from industry and do not necessarily reflect regulatory accepted data.

Some information from European Environmental Quality Standard (EQS) dossiers can directly be used by applicants in an ERA, i.e. data that has been assessed for reliability (e.g. QSs can be used as PNECs). For instance, the ibuprofen and diclofenac EQS dossiers can be used to conclude on the possible risks to the surface water compartment.
It was also noted that for active substances for which the action limit is applicable (see Q4), it is recommended that generic applicants calculate the PEC_{SW} for their product (see Q5) as a first step. If the action limit is not triggered, data sharing may not be required to complete the risk assessment as the risk assessment stops in Phase I (although the PBT/vPvB assessment must still be completed).

d) It is the responsibility of the applicant relying on data from another MAH to provide an accurate letter of access. The applicant declares that the contents of an application are accurate and obtained legally. Providing false declarations exposes the applicant to a risk of legal challenge. The legal requirement is to provide a complete and satisfactory ERA for each application. The Agency encourages sharing of data in order to avoid the unnecessary repetition of ERA studies. Without a data sharing agreement, the applicant is expected to fulfil the ERA requirement using their own data or publicly available (and not protected) data from the literature, unless it can be agreed with regulators that the scientific conclusion of a relevant ERA remains applicable to this generic product.

e) Data sharing is encouraged throughout the EMA ERA guideline, but there is currently no legal framework in place that would foresee specific incentives for such data sharing.

f) Applicants are reminded of their obligations to submit a complete and satisfactory ERA at the time of application. The commitment to perform ERA studies post-authorisation is considered a non-compliance with the applicable requirements at time of approval. Postponing agreed post-authorisation ERA studies without a valid justification (to be transmitted proactively to the Competent Authority) is also considered a lack of compliance with the applicable EU requirements. The prioritization of legacy APIs foreseen with the upcoming legislation is planned to address a bottleneck and not to suggest that some data are no longer needed. If a post-authorisation measure was agreed, it means the data are required to inform on the potential environmental risk associated with the active substance.

2.2. Literature Review

Regarding literature review, clarification was provided on the extent of the search to be performed by applicants. It was highlighted again that only literature data of sufficient quality, reliability and relevance should be used e.g., based on the CRED method. Furthermore, it is necessary to outline how the literature search was performed, e.g., declaring which search engine was used and which search terms were applied.
Industry trade associations proposed again to outline a 'guidance document' which would include further details on the literature review, in order to standardise and harmonise the process for applicants. EMA highlighted that although such guidance has not been considered necessary by EMA so far, since the same standards of methodology would apply as for other parts of the MAA application (e.g. literature review for non-clinical or clinical modules), the industry could provide their suggestions on how to conduct the literature review. Such suggestions could be brought to the attention of the Non-clinical Working Party.

2.3. Use of Consumption Data

Under the revised EMA ERA guideline, the use of sales data or consumption data to refine the exposure (meaning the PEC_{sw} in the Phase II risk assessment) is no longer possible. A level of flexibility was requested by industry e.g., with regard to long-existing treatments. In line with the guidance provided during the first stakeholder webinar on the revised EMA ERA guideline held in June 2024, and the

response to comments document published together with the revised EMA ERA guideline, EMA reiterated the following explanations.

With coming into force of the revised EMA ERA guideline using sales data or monitoring data to refine the exposure (meaning the PEC_{sw} in the Phase II risk assessment) is no longer possible as there are uncertainties related to these data, and these are also difficult to verify. In Phase I, a market share of 100% is always assumed. Sales data cannot be used for the refinement of Fpen as this will not take into account competitor products with the same API. Additionally, market shares may change quickly, so 100% market share must always be assumed. Prescription data and sales data are subject to annual fluctuations and do not consider 100% market share (compare EMA/CHMP/SWP/44609/2010 Rev. 1, Q4.). Additionally, for new active substances only prevalence data gives a reliable forecast for a realistic worst case environmental exposure scenario. For newly launched medicinal products it may take some years until maximum uptake is achieved so monitoring/sales data immediately post approval would underestimate exposure.

For the risk assessment further refinements are available in Phase II e.g., refinement of PECsw with sewage treatment plant modelling using the SimpleTreat model.

3. Technical Topics Discussed

3.1. The Acceptance of EC_{10}s and NOECs

Principles stated in the OECD guidance document 54 (Current Approaches in the Statistical Analysis of Ecotoxicity Data) should be duly considered. The EC_{10} is generally preferred as it is less dependent on the test concentrations, although both the value itself and the confidence_interval surrounding the EC_{10} may be significantly influenced by the number and span of test concentrations. EC_{10} values should always be interpolated, i.e. an extrapolated value below or above the lowest and highest test concentration, respectively, is typically less accurate and should hence not be used or be used with caution, including a comparison to the established NOEC.

3.2. Calculation of Log K_{ow} for Ionisable Substances

For dissociating molecules, a log D_{ow} is determined at (a) pH value(s) where the molecule is partly dissociated and a log K_{ow} is determined at (a) pH value(s) where the molecule is completely neutral. Neutral compounds are more likely to accumulate in organisms than ionised compounds, therefore a log K_{ow} is needed for the PBT/vPvB screening. In case a molecule is (partly) dissociated at environmentally relevant pH (pH 5-9) and the octanol:water partitioning coefficient is determined at pH values within this range; no log K_{ow} becomes available. For monoprotic acids, an equation is given in the EMA ERA guideline to recalculate the log D_{ow} to log K_{ow}. To recalculate a log D_{ow} to log K_{ow} value for monoprotic bases, the following equation is indicatively proposed (but not included in the current EMA ERA guideline):

$$K_{\mathrm{OW}} = D_{\mathrm{OW}} \cdot (1 + 10^{(\mathrm{p}K_a - pH)})$$

It is noted that also here, the pK_a should be used as input, that is the value for the acid dissociation of the conjugate base.

In case a log K_{ow} is estimated from a D_{ow}, using this equation, only the log D_{ow} determined at the pH at which the undissociated fraction is the highest should be recalculated to a log K_{ow}. Since the EMA ERA-guideline requires testing at pH 5, 7, and 9, there will generally be a log D_{ow} value for which the undissociated fraction is sufficiently high to allow for an acceptable estimation of the log K_{ow}. This applies mainly to monoprotic acids or bases. For more complex cases, such as polyprotic acids/bases and zwitterions, additional considerations are necessary. These cases require consideration of multiple pK_a values, and in the case of zwitterions, a neutral form might not exist at all in aqueous solution. Therefore, such cases are more complex and require a case-by-case assessment.

It should however be noted that an experimentally determined log K_{ow} for the neutral molecule appears generally more reliable than an estimation based on an ion-corrected log D_{ow}. Applicants are recommended to experimentally determine log K_{ow} for dissociating compounds, even if the molecule is neutral at pH values that fall outside the environmentally relevant range, for example pH 2 for acids and pH 10 for bases. While applicants have sometimes argued that these pH values fall outside the environmentally relevant range, it should be emphasized that the ionized and neutral forms are in equilibrium, and the fraction that is not charged will be available for uptake by the organism.
In case the log K_{ow} (or log D_{ow}) of a molecule is ≥3 (secondary poisoning) or >4.5 (B assessment in PBT), further testing may be needed to assess the bioaccumulation potential. The EMA ERA guideline indicates that BCF values need to be determined for fish following OECD test guideline 305. Following the 3R principles however, vertebrate testing should be avoided where this is feasible. Since 2024, the validated OECD test guideline 321 (OECD 321) is available to determine BCF values for *Hyallela azteca*, an invertebrate (amphipod crustacean). OECD 321 may be considered as alternative to OECD 305. It should, however, be noted that for the PBT/vPvB assessment, further testing with fish (meaning OECD 305) may need to be considered if uncertainties remain about the bioaccumulation potential in the aquatic organisms (see ECHA, Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.11: PBT/vPvB assessment. Version 4.0, 2023).

3.3. Secondary Poisoning Assessment

The current approach provided in the EMA ERA guideline to assess risks for secondary poisoning is acceptable. Alternative approaches cannot be accepted without further investigation. Currently, there are a number of developments. For example, the OECD 305 study to determine bioaccumulation in fish can be replaced by the OECD 321 study with *Hyallela azteca* to avoid vertebrate testing. Another development is that ECHA currently has a working group investigating the validity of calculated BCF values derived from in vitro metabolism studies. Relying solely on in vitro tests seems premature at this point in time, particularly since the trigger value for secondary poisoning is a BCF of 100 L·kg-1, and it is generally easier to demonstrate that a value is below 2000 L·kg-1 than below 100 L·kg-1. Additionally, in vitro metabolism studies only provide information on bioaccumulation in fish, and not in other relevant organisms such as mussels and crustaceans. However, it is important to note that this limitation also applies to in vivo fish tests.
For secondary poisoning via the terrestrial food chain, the EMA ERA guideline gives limited guidance, and it refers to the Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1- Corr.1) (hereinafter: "EMA ERA guideline on veterinary medicinal products"). It should be noted that in general the methodology of the latter EMA ERA guideline on veterinary medicinal products is based on, and should be in line with, the methodology set out in the ECHA Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.16: Environmental exposure assessment Version 3.0 (2016). The following technical aspects are, however, neither specified in the current EMA ERA guideline nor in the EMA ERA-guideline on veterinary medicinal products:

- $C_{POREWATER}$ is equivalent to $PEC_{POREWATER}$
- C_{SOIL} is equivalent to $PEC_{SOIL,SS}$ (i.e. taking into account degradation when DT_{50} is available for soil, Eq. 22)
- $BCF_{EARTHWORM}$ can be determined experimentally following OECD Test No. 317, which is particularly useful as a refinement.

3.4. New Requirements for OECD 106 (Tier 3 Requirement)

For adsorption the revised EMA ERA guideline requires a tier 3 OECD 106 study (i.e. generation of K_F and K_{FOC}) for two sludges and three soils. OECD 121 is no longer acceptable. However, for ERAs that have been assessed according to the old EMA ERA-guideline before September 2024, the previous

accepted OECD 106 study with missing Tier 3 can still be used in the ERA. In rare cases where only an OECD 121 is available for old ERAs, it was used only to check the soil trigger.
Regarding the number of soils, sludges and in rare cases sediments: Already since 2016 two sludges and three soils have been preferred in an OECD 106 study. Therefore, OECD 106 studies in previously and completed ERA contain mostly three soils and two sludges. In rare cases when only single soil/sludge or even sediment values are given, and these single values have been assessed as plausible and valid at the moment of assessment, in principle, no additional studies or adsorption values will be required.
In summary, for new ERAs, an OECD 106 study must be conducted up to Tier 3 but it should be noted that desorption is no longer required. Previous accepted OECD 106 studies with Tier 2 or less soils or sludges are still acceptable in the context of previously accepted ERAs.

3.5. Tailored Testing Strategy

Regarding tailored testing strategies, the following aspects were discussed during the webinar:

a) The possibility to avoid performing a fish full lifecycle test (DRP no. 95, OECD 240) and instead use any available in vitro assays or other approaches in order to determine endocrine activity of an active substance.

b) Clarification which mandatory studies may not be required under a tailored testing strategy for example for endocrine active substances (EAS) and how to determine acceptability of study exclusion.

A summary of the responses to the above points is provided below:

a) Presently, the only option for not conducting a fish full lifecycle test for an EAS is to conduct screening studies with OECD 229 or OECD 230. If these studies generate a negative outcome (no indication of endocrine effects on secondary sexual characteristics/gonad histology), it may be possible to justify the absence of an OECD 240 or DRP no. 95 study (in such cases, the standard OECD 210 approach is to be used instead). An alternative justification approach, based on the fact that the OECD 240 or DRP no. 95 are focused on sex steroid hormone regulation (e.g., oestrogens, androgens, progesterone), is to demonstrate that the drug does not bind to any relevant target protein(s) in fish (e.g., oestrogen and androgen receptors, 5α-reductase). However, such studies would need to be standardised (e.g., OECD, ISO, EPA). Another option is to seek scientific advice. In case of aromatase inhibitors, oestrogen receptor antagonists or androgen receptor agonists, the fish sexual development test (OECD 234) or a fish full lifecycle test is appropriate to capture the relevant endpoints and (no)effect values. Table 17 of the EMA ERA guideline provides a more detailed overview of the currently recommended fish and amphibian effect studies.

b) If an EAS-tailored assessment is triggered, then the 'tailored fish studies' are sufficient besides OECD 211. The daphnia reproduction assay (OECD 211) should be performed unless there is evidence that invertebrates are not relevant to the mechanism of action in question. An OECD 210 test is not necessary. Furthermore, it should be emphasized that the OECD 229 and 230 are clearly short-term screening assays only and suitable only for estrogenic, androgenic activity and aromatase inhibition mode of action. Hence, this test is not suitable for deriving apical long-term endpoints with corresponding NOEC values for risk assessment; and this is the reason why it cannot be used for that purpose. The EAS-tailored approach is based on a molecular mechanism approach (linking a molecular mechanism to relevant type of morphological and/or physiological endpoint), and the presence of certain biomolecular targets in the model organism (e.g., steroid receptor proteins) is therefore a premise. Such gene products are generally not present in micro-organisms and highly unlikely to be present in algae. This could be used as a plausible justification for waiving an OECD 209 and OECD 201 test, respectively.

3.6. Groundwater and Soil Triggers

Regarding Table 4 of the EMA ERA guideline in relation to groundwater assessment via bank filtration, the same requirements are valid as in the first version of the EMA ERA-guideline. A risk assessment for groundwater via bank filtration is required when the $K_{FOC, SLUDGE}$ is ≤ 10,000 L kg-1, unless the substance is readily biodegradable. This is clearly mentioned in section 4.2.2. as well as in section 4.2.7.1. The new path groundwater via porewater is only required when soil assessment is triggered. Table 3 can be used to find out which $K_{FOC, SLUDGE}$ to choose.