Ongoing EU regulatory guideline changes for CTD module 1.6

R. Arno Wess
IES Ltd, Benkenstrasse 260, 4108 Witterswil, Switzerland

EPHAR 2021,
Virtual Congress, December 6th to 8th

Introduction and major issues

On 15 November 2018 the European Medicines Agency has released a draft revision of the guideline on the environmental risk assessment (ERA) of medicinal products for human use (EMA 2018) for public consultation. The current guideline (EMEA 2006) describes a tiered testing strategy recommended for the evaluation process. In addition, there is a Questions and Answer (Q&A) document (EMA 2016). Commenting was possible until the 30 June 2019 (deadline for comments). This poster intends to summarize some of the most important changes in order to facilitate the preparation for expectable changes. An explaining commentary from authors working at various European authorities is available (Whomsley et al. 2019). It highlights mayor changes, whereat some are effectively already implemented based on the Q&A document (EMA 2016) or may differ more structurally such as the assessment for Persistence, Bioaccumulation and Toxicity (PBT), which is in the flow diagram placed as a process to be followed in parallel.
Generally the structure of the assessment approach has been changed in that sediment toxicity testing will be a part of the standard aquatic base set testing, whereto the water/sediment simulation study (OECD TG 308) does not belong any more, but this test will probably often be triggered in the course of the new Phase II, Tier A groundwater assessment. Also soil organism effect testing is considered a Phase II, Tier A task, but its performance still depends on triggering, now (newly) based on a combination of adsorption and the initial Predicted Environmental Concentration (PEC) in surface waters. Also a secondary poisoning assessment for bioaccumulating substances is implemented for substances characterized by an BCF in fish of 100 L/kg or higher.

Identified additional issues

Restriction of HPLC-based estimation methods

• Whereas the Q&A document (EMA 2016) simply stated that in lipophilicity measurement the shake-flask method or the slow-stirring method is preferred over the HPLC method (OECD TG 117), the recent draft (EMA 2018) prescribes, that the method may only be used for indicative purposes, e.g. for compounds, which are highly soluble and have a predicted Log Kow <1 at all environmentally relevant pH values (i.e. pH 5-9).

• It used to be acknowledged that the HPLC method (OECD TG 121) for adsorption estimation could be accepted (EMEA 2006), but the Q&A document (EMA 2016) restricts the acceptability to determined Koc of <5000 L/kg and cases when neither the SimpleTreat model is used nor >10% of substance shifted to sediment at or after 14 days in the water/sediment simulation study (OECD TG 308). In the recent draft (EMA 2018) the HPLC-method is not any more mentioned as an experimental option.

All non-OECD methods to be justified

• Similarly any reference to OPPTS 835.1110 (Activated Sludge Sorption Isotherm) lacks in the update draft, however it is mentioned in the Q&A document (EMA 2016). On the other hand EMA (2018) states "*it is recognised that there are other test guidelines, approaches and methods, which are capable of providing an equivalent environmental risk assessment. If methods other than those described in this section are used, a justification should be included in the Environmental Risk Assessment Report.*" This may particularly apply to additional data according to the EQS guidance (EC 2011, 2018), which may be based on ISO, OPPTS, Environment Canada, USEPA OCSPP (formerly OPPTS) and ASTM standards.

Implementation of scientific or regulatory progress

• The NOEC is no longer the stated endpoint as (unfortunately) in the 2006 EMA guideline (EMEA 2006) and the Q&A document (EMA 2016). The obsolete NOEC-concept will be phased out except for limit studies. Thus dose-response study reports should always provide an EC_{10} value. Older study reports may miss the EC_{10} and sufficient data for re-calculation. In such case, study raw data may help out, but in some EU member states the GLP-conform storage period is shorter than the standard of ≥10 years, which applies in Germany (and also in Switzerland). As the NOEC is often lower than the EC_{10}, retesting may be advisable in some cases, e.g. to avoid PBT classification, but is critical in the fish due to the 3R principle.

• The acute earthworm toxicity study (OECD TG 207) as required in the first guideline version (EMEA 2006) was the sole acute toxicity endpoint, which was a little bit astonishing. With the foreseen update an Earthworm (or Enchytraeid) reproduction study (OECD TG 222 or 220) is consequently on the list of studies used in the risk assessment of soil organisms.

• All studies should be assigned a reliability category as according to the assessment method used, and be accompanied by a short study summary. This makes sense as it represents some harmonisation to REACH. No standard for the study summaries is given however application of the OECD templates is nearby. It may thus be useful to enter and store the available information into the IUCLID database format.

• In the context of an envisaged harmonisation of regulations, reference is made to the Water Framework Directive (WFD) EQS-derivation Guidance (EC 2011, 2018). This applies in particular to generic substances where now a comprehensive literature search and evaluation is demanded, and for which an extended scope of endpoints (as in EC 2011, 2018) should be regarded.

• A full dataset for pH-dependency of lipophilicity (D_{ow}), i.e. the determination of the dissociation constant (OECD TG 112) and K_{ow} (of the neutral molecule) is clearly stated in the guidance update draft. Additionally lipophilicity measurement at 3 pH covering the environmentally relevant range (5-9) is the new standard.

• The requirement to undisclose the relation of the assessor (i.e. the author) to the applicant is first stated in the guideline update draft.

• The specific study demands for potential endocrine disruptors are given in more details compared to the Q&A document (EMA 2016). With the update tailored testing is also foreseen for antibiotics, in that the fish endpoint (OECD TG 210) drops, but two given cyanobacteria and one green alga species have to be tested according to OECD TG 201.

• Any DT_{50} values from Environmental simulation studies (i.e. OECD TGs 307, 308 and 309) have to be measured at (highly recommendable) or recalculated to the EU annual average temperature of 12 °C. This calculation may be over-conservative as the activation energy (required key value in the Arrhenius equation to be used for the correction of DT_{50}s to 12 °C) is normally unknown and thus a default value (which is designed to constitute a large safety margin) must be used. Some dubiety remain due to the absence of any hint on an acceptable approach for the determination of a specific activation energy for use in the Arrhenius equation. Nonetheless, the normalization demand is now in line with ECHAs R.7b Endpoint specific guidance, which applies in the PBT assessment.

• Sediment organism effect testing is switched to the standard aquatic testing in Phase II, Tier A. *Hyalella* is not mentioned as a standard test organism in the guidance anymore, but may -due to the reference to the Water Framework Directive (WFD, EC 2011, 2018)- be regarded anyhow if data are available in the literature (generics).

• As the same Assessment Factor (AF) of 100 applies for standard Chironomid tests (OECD TG 218 and 219) and also for Chironomid life cycle EC_{10} (OECD TG 233) the latter one is not useful for mitigation of the Predicted No Effect Concentration (PNEC) in sediment any more, which seems scientifically not consequent as no Tier B option is mentioned. Only additional *Lumbriculus* data reduce the AF to 50.

• The option to correct the initial PEC surface water using marketing data after a base set of experimental information has been determined (EMEA 2006) is phased out. Thus it is much more important to have data allowing the derivation of the fraction of substance excreted ($F_{excreta}$), which has impact on (potentially already ongoing) pharmacokinetic studies.

• The new guideline draft states, that the human metabolites have to be considered as parent substance as long as the "*whole residue approach*" is not abandoned, but on the other hand environmental transformation used in SimpleTreat calculation would allow PEC mitigation. This inconsistency is subject of a comment of the author and may be rectified in one or the other way. Independently the use of indication prevalence data remains an option for PEC correction.

References:

- **EC** European Communities (**2011**). Technical guidance for deriving environmental quality standards. Guidance Document No. 27. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Self-published Brussels, Belgium.
  Technical Report - 2011 – 055 DOI 10.2779/43816 ISBN 978-92-79-16228-2. 204 p. URL https://circabc.europa.eu/sd/a/0cc3581b-5f65-4b6f-91c6-433a1e947838/TGD-EQS%20CIS-WFD%2027%20EC%202011.pdf
- **EC** European Communities (**2018**). Technical guidance for deriving environmental quality standards. Guidance Document No. 27 (Draft). Self-published Brussels, Belgium, updated version endorsed by EU Water Directors at their meeting in Sofia on 11-12 June, last modification 10 December. 210 p. URL https://rvs.rivm.nl/sites/default/files/2019-04/Guidance%20No%2027%20-%20Deriving%20Environmental%20Quality%20Standards%20-%20version%202018.pdf
- **ECHA R.7b:** European Chemicals Agency (2017). Guidance on information requirements and chemical safety assessment Chapter R.7b: Endpoint specific guidance. Version 4.0. Document Reference ECHA-17-G-10-EN, ISBN 978-92-9495-837-2. DOI 10.2823/84188 Self-published, Helsinki, Finland, in June. 279 p. URL https://echa.europa.eu/documents/10162/13632/information_requirements_r7b_en.pdf/1a551efc-bd6a-4d1f-b719-16e0d3a01919
- **EMA** European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (**2016**). Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. Self-Published, London, U.K., 26 May. Document Reference EMA/CHMP/SWP/44609/2010 Rev. 1. 17 p. URL https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf
- **EMA** European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (**2018**). Guideline on the Environmental Risk Assessment of Medicinal Products for Human use. Draft. Self-Published, London, U.K., 15 November. Document Reference EMEA/CHMP/SWP/4447/00 Rev. 1, 48 p. URL https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf
- **EMEA** European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (**2006**). Guideline on the Environmental Risk Assessment of Medicinal Products for Human use. Self-Published, London, U.K., 01 June. Document Reference EMEA/CHMP/SWP/4447/00 corr 2. 12 p. URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf
- **Whomsley** R, Brendler-Schwaab S, Griffin E, Jensen J, Moermond C, Scholz B, Sortvik Nilssen L, Stemplewski H, Roennefahrt I (**2019**). Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. DOI 10.1186/s12302-019-0198-9 Environ Sci Eur 31:17. 4 p. URL https://enveurope.springeropen.com/track/pdf/10.1186/s12302-019-0198-9 .

a.wess@ies-Ltd.ch I www.ies-ltd.ch

Contribution ID: 242