Changes foreseen according to EMAs new draft guideline on the environmental risk assessment (ERA) of medicinal products for human use

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Introduction

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 environmental assessment (EMEA 2006) describes a tiered test strategy recommend. For the evaluation process. In addition, there is a Questions and Answer (Q&A) document (EMA 2016). As the commenting is 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 timely submission of comments. An explanation commentary from authors working at various European authorities is available (Whomsley et al. 2019). It highlights major changes, whereas 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, whereas 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 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 a 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 would be used to acknowledge that the HPLC method (OECD TG 121) for adsorption estimation could be accepted (EMEA 2006), but the Q&A document (EMA 2016) restricts the acceptance of the HPLC adsorption 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 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 methods, 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 2008, 2011), 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 results should always provide an EC10 value. Older study results may miss the EC10 and sufficient data for recalculating the NOEC raw data may help, but this is not any more a standard of 2010 years, which applies in Germany (and also in Switzerland). As the NOEC is often lower than the EC10, retesting may be advisable in some cases, e.g. to avoid PBT classification, but is critical in the fish due to the 3K rule.

• 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 ICILID 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 for 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 formal and complete submission item characterisation will be required. The submission item (the subject of assessment in the ERA) may be at variance to used test items as e.g. readily biodegradable organic anions or cations will deteriorate OECD TG 301 studies for ready biodegradability. Also Hydrochloride formulations should be endpoint-corrected in that the H+ will directly dissociate and thus the weight of the dissolved actual active molecules, which should be the subject of the ERA.

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References


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