Impact of the new ERA guidance on the conduction of Pharmacokinetic and Toxicity studies

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Introduction

The environmental risk assessment (ERA) is a requirement for the registration of a Human Medicinal Product (HMP) as module 1.6 in the (electronic) Common Technical Document ((e) CTD) format. Although a dossier can be rejected if the ERA lacks, the outcome of it cannot be a reason for denial of the Market Authorisation Application (MAA).

A **leaflet warning** however, may be a consequence of an unfavourable ERA. Therefore the conduct of specific environmental fate and effect studies is often considered rather late, but it must be commenced more than one year before submission in order to present a complete dossier. Authorities often do not consider some unfinished studies as an incomplete dossier and normally grant an extension, provided a letter of commitment had been signed. Accordingly, the ERA and its requirements are more or less out of mind during the toxicity and pharmacokinetic (PK) studies necessary for registration of a HMP. These studies always played a certain role in the ERA in that they had to be considered in the CMR (Carcinogenicity, Mutagenicity and toxicity to Reproduction) assessment and thus the applicability of the environmental action limit. As this is only a question arising for Active Pharmaceutical Ingredients (API) with a maximum daily dose below 2 mg, the impact of the toxicity studies can in all other cases be neglected.

On 15 November 2018 the European Medicines Agency has released a draft revision of the guideline on the 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). 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.

Impact of the ERA guideline update on mammalian studies / Avoidance of unnecessary leaflet warnings

Avoidance of unnecessary, unfavourable leaflet warnings (with negative marketing impact) should be envisaged during the conduct of the studies required for registration. An impact of the ERA guideline update will be to affect also the study design of preclinical mammalian studies.

A **secondary poisoning assessment** for bioaccumulating substances will be implemented for active pharmaceutical ingredients (API) characterized by an BCF in fish of 100 L/kg or higher. Mammalian repeated oral toxicity data from studies of a minimum duration of 28 days form the point of departure (POD) for the derivation of the new demanded Predicted No-Effect Concentration in biota ($PNEC_{BIOTA}$), which is equivalent to the Quality Standard for secondary poisoning expressed in biota ($QS_{biota, secpois}$), which is the term used in the applicable guidance for derivation (EC 2011, 2018). If no dose-response curve can be established to conclude on an actual mammalian threshold level, the choice of the dose levels / spacing factor may unfavorably shift die POD and thus an overestimated ($PNEC_{BIOTA}$) could result. The $PNEC_{BIOTA}$ is then converted into a PNEC for surface water secondary poisoning ($PNEC_{SW, SECPOIS}$) by dividing it by the BCF and (if available) the biomagnification factor (BMF). Using this approach, when the $PNEC_{SW, SECPOIS}$ is higher than the Predicted Environmental Concentration in surfacewater (PEC_{SW}), a risk due to secondary poisoning is identified, which in consequence would require a leaflet warning.

In case a risk is identified in the ERA only a **mitigation of the PEC_{SW}** can avoid further, more chronical studies on the environmental effects. Most frequently used and important for the avoidance of environmental leaflet warnings was the option to reduce the initial PEC_{SW} using sales forecast / marketing data after the aquatic base set of experimental information was determined (EMEA 2006), but this refinement option will be phased out according to the new draft guidance update. An alternative possibility for PEC refinement is to employ data from additional environmental fate study types, which are in the ERA guideline update encouraged for use in the simple treat (model).
Unlike environmental transformation products human metabolites have to be considered as parent substance as long as the "*whole residue approach*" is not abandoned, but this inconsistency (compared to transformation products) in the guidance update is subject of a comment of the author and may be rectified in one or the other way*. Abandonment of the "*whole residue approach*", means costly determination of full ERA datasets data for all degradation products >10% of applied radioactivity, which may double, triple, quadruple (or more) the total ERA cost.
In consequence the calculation of a Factor of excretion ($F_{excreta}$) from PK study data may the preferable option for PEC_{SW} mitigation, but it depends on the performance of API and metabolite quantification in both, the faeces and urine, which is thus of significantly increased importance. Accordingly it becomes much more important to have data allowing the derivation of the fraction of substance excreted ($F_{excreta}$) than it used to be. This may impact the consideration for the study design of (potentially already ongoing) PK studies.

Conclusions

Prevention of environmental leaflet warnings by refinement of the PEC_{SW} to reduce the Risk Quotient (RQ) below 1 in ERA phase II

- Sales forecast / marketing data based PEC_{SW} correction used to be the mayor option, but is foreseen to be discontinued.
- Environmental transformation will still be supported for PEC_{SW} mitigation in the guideline draft, but the additional data generating studies are costly.
    - In the update additional environmental fate study types are encouraged for use in the simple treat (model).
    - (Human) metabolisation from PK studies usage (intended to drop as an option), is under review but this option may be continued (there is an inconsistency in the guideline draft, see above*)
        - Last option unless abandonment of the "*whole residue approach*", which means costly determination of effect data for all degradation products >10% of applied radioactivity, is thus the use of PK data.

PK studies

- Excretion data for both, faeces and urine, and identification of parent and metabolites carrying 10% or more of applied radioactivity are required for calculation of an $F_{excreta}$. Therefore analytical quantification may be considered in the PK study design to enable the use of PK information in the course of the ERA.

Preclinical Toxicity studies

- Due to the foreseen future requirement to assess on secondary poisoning, significant impact on the dosing scheme results. The final $NO(A)L_{oral}$ / $NO(A)EC_{oral}$ are the starting point for $PNEC_{BIOTA}$ and $PNEC_{SW, SECPOIS}$ derivation and they should thus be close to the threshold level in order to prevent PNEC overestimation.

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