29 June 2015

Submission of comments on Questions and answers on ‘Guideline on the environmental risk assessment of medicinal products for human use’ – EMA/CHMP/SWP/44609/2010 Rev. 1

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA – Sini Eskola (sini.eskola@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
| **EFPIA** | EFPIA are currently assessing on how ERA could be refined to include post approval refinement of environmental risks e,g, where multiple products with the same active substance have entered the market and environmental exposure may be higher than that captured within a product specific risk assessment. We wish to continue this dialogue with EMA in the near future.This remainder of the response to this consultation concentrates on the revised Q&A sections and areas where the current ERA guidance could be improved. |  |
| **EFPIA** | This Q&A update is helpful in many respects in terms of clarifying what is required under the existing guideline. |  |
| **EFPIA** | However EFPIA recommend that EMA consider more fundamental revisions to the ERA guideline. One aspect of the ERA guidance that requires particular attention is the environmental fate and exposure guidance described within Phase II. Our specific concerns are focused on the requirement of an OECD 308 study at Phase II Tier A and the lack of robust data describing removal in a sewage treatment plant. The OECD 308 test is a complex study that adds little value to the overall environmental exposure and persistence assessment. An assessment of the OECD 308 has recently been published by Ericson et al (2014) titled “Experiences with the OECD 308 Transformation Test: A Human Pharmaceutical Perspective” (Integrated Environmental Assessment and Management; 10 (1) 114–124). With regard to improving the scientific and environmental relevance of the exposure assessment of human medicinal products we would propose that:* An activated sludge dieaway test (e.g. OECD 314B or OECD 303) is conducted at Phase II Tier A. This reflects the down the drain nature of environmental exposure via the sewage treatment plant, and
* The most appropriate persistence study, focused on the most relevant environmental compartment, should be considered at Phase II Tier B, for compounds that have a high Kow.

For pharmaceuticals which have a low Kow (or Dow), and hence clearly will not fulfil the PBT or vPvB criteria, the OECD 308 study is only of academic value since the data are not used to refine the risk assessment. EMA should also consider removing the trigger for a sediment effects assessment (OECD 218/219) from the OECD 308 study and include the sediments effect study at Phase II Tier A.These approaches would also be much more consistent with structured testing approaches found elsewhere (e.g. in the REACH technical guidance).  |  |
| **EFPIA** | It would be helpful to include revisions to ERA guideline (2006 EMA ERA Guideline corr 2) and changes in EMA Pre-meeting requirements (addition of the review of draft ERA) in the ERA ‘Q&A’ update. Both are pivotal for the applicant in developing the appropriate ERA strategy for marketing authorisations and in the preparation for EMA meetings. Efpia recommend that all new corrected versions to the ERA guidance are shown with a front page that clearly describes and dates the specific corrections that have been made. |  |
| **EFPIA** | The PBT assessment for products below the Phase I action limit, that have a high log Kow (>4.5), and the PBT assessment for products that trigger a Phase II assessment under the ERA guidance are fundamentally different. Low PEC products (< 10 ng/l) with a high Log Kow conduct a PBT assessment according to REACH guidance. This is far more intelligent and flexible that the guidance currently provided within the EMA Phase II guidance. For reasons of consistency for (i) human medicinal product assessment and (ii) harmonisation across chemical guidelines we recommend that all PBT assessments of human medicinal products assessed by the EMA are conducted according to the REACH Guidance. |  |

1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Line 65 |  | Comment: Should Q&A No 41 actually be Q&A No 53 “When do I have to submit an Environmental Risk Assessment (ERA)? *Rev. Oct 14*”?Proposed change: replace 41 with 53. |  |
| Lines 71-75 |  | Comment:It would be helpful if the Q&A document could clarify whether it is permissible to use market forecast data to justify an insignificant increase in the extent of use in comparison to recent overall consumption data. |  |
| Lines 169-172 |  | Comment: Most previous studies have typically been undertaken across the pH range 5-9. This pH range is consistent with the guidance on regulatory Kow determination for ionisable substances in the 2014 ECHA Guidance “Chapter R.7a: Endpoint specific guidance”. It is impossible to test many chemicals in biotic tests at pH 4 or pH 10; a degree of pragmatism is required within the guidance.Proposed change: replace (pH 4-10) with (pH 5-9). |  |
| 166-172 |  | It is currently unclear which log Kow value will trigger a persistent, bioaccumulative and toxic (PBT) assessment and/or bioaccumulation study e.g. will the log Kow of the neutral molecule trigger a PBT assessment or a bioaccumulation study when it exceeds the value of 4.5 or 3, respectively, even if the neutral species occurs outside the environmentally relevant pH range. Efpia believe that a PBT assessment or a bioconcentration study should only be triggered if a logD (or logKow) determined in the environmentally relevant pH range exceeds the trigger value of 4.5 or 3, respectively. |  |
| 210 |  | Comment: Could you please clarify in how far non-extractable residues are still bioavailable and why they should be included in the trigger for the sediment risk assessment? The trigger for sediment risk assessment should only include the extractable compounds (at or after 14 days, >10% of applied either parent or metabolite)Proposed change (if any): “Results from the OECD 308 test should be (1) the amount of compound ***~~(including Non –Extractable 209 Residues = NER)~~*** 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 total system; (3) kinetic model, chi2 error level of fitting……” |  |
| 215 |  | Comment: The sentence ‘Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life’ requires further elaboration and more pragmatism. Whilst ideally this may be ‘preferred’ the presence of bound (non-extractable) residues often makes determination of degradation half-lives impossible in practice. Consequently the concept of a ‘total system’ half-life has proved useful and is used routinely for agrochemicals and veterinary medicines. This should be acknowledged in this guidance. Other regulatory guidance compares the total system half-life values obtained from the study to the sediment persistence criterion of 120 days. Proposed change : Replace ‘Please note that calculation of a degradation half-life is preferred over a dissipation (disappearance) half-life’ with ‘Ideally, a degradation half-life is preferred over a dissipation (disappearance) half-life, however it is recognised that this may not be possible if there are significant bound or non-extractable residues, in which case the Total System half-life should be reported.’  |  |
| 409 |  | A non-extractable residue is as such non-bioavailable (otherwise it would be extractable) and should therefore not be relevant for the PEC calculation. The PEC is meant to be the predicted environmental concentration which is likely to cause adverse effects, which means that the compound needs to be bioavailable and not irreversibly bound to soil/sediment.EFPIA recommend that the current EMA guidance refers to the recent ECETOC guidance for the interpretation and characterization of non-extractable residues.ECETOC (2013). Understanding the relationship between extraction technique and bioavailability. Technical report 117. Brussels.ECETOC (2013). Development of interim guidance for the inclusion of non-extractable residues (NER) in the risk assessment of chemicals. Technical Report 118. Brussels. |  |
| 242 |  | Comment: The revised document requires adsorption data “for at least 2 sludges”. We request that clarification is provided on if and how these sludges might be required to differ. |  |

Please add more rows if needed.