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Comparison of Environmental Risk Assessment Scheme on Pharmaceuticals between EU and Japan

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1 Environmental Risk Assessment for Pharmaceuticals in EU and Japan

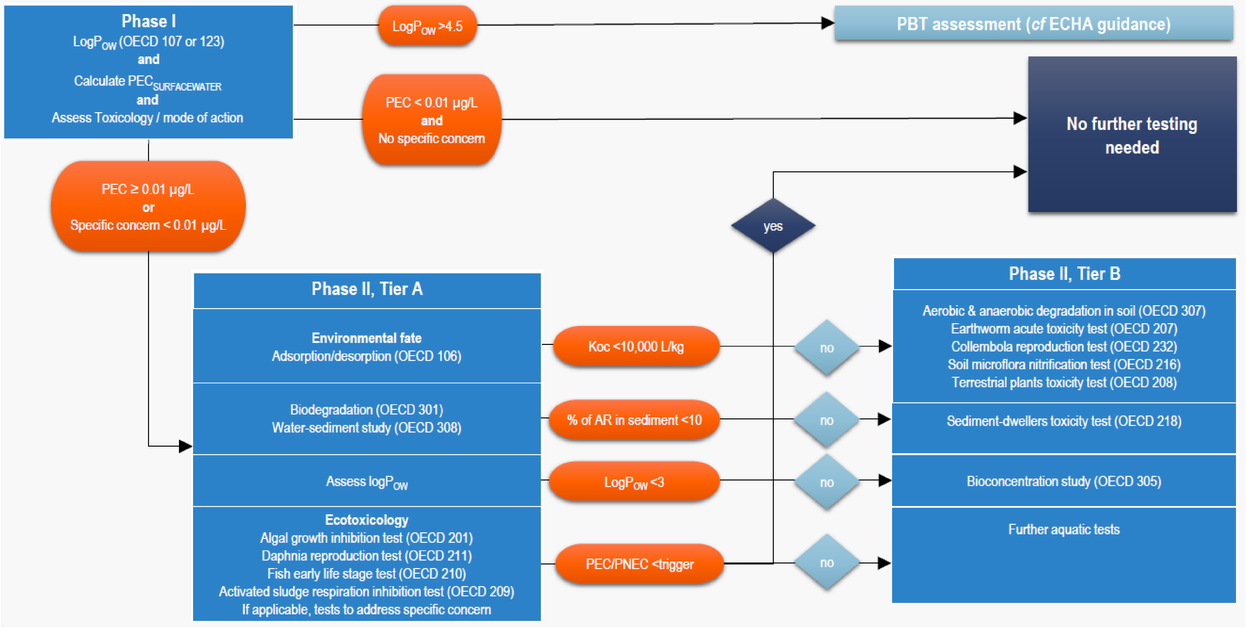
In March 2016, the Ministry of Health, Labour and Welfare (MHLW) in Japan released the Guidance of Environmental Risk Assessment (ERA) on New Pharmaceuticals[1] , which explains the requirement of Predicted Environmental Concentration (PEC) calculation and testing of environmental toxicity and fate. The MHLW Guidance is the only official document that is now referred to for assessment of adverse effects against the environment in Japan caused by exposure of marketed pharmaceuticals through uptake in the patients followed by excretion and disposal via wastewater. However, contrary to the guidances adopted in EU and US, details on PEC calculation and environmental testing are not included in the MHLW guidance. Therefore, it is difficult for pharmaceutical companies to estimate the cost associated with ERA for their authorization applications in Japan in the forthcoming future. From a global perspective, ERA assessments follow step-wise approaches that characterize the potential risk of the pharmaceuticals. Particularly in the EU, the tiered approach is well described for the ERA, starting with a screening Phase I and leading into testing Phase II (Tiers A and B). This poster presentation compares the ERA scheme currently suggested in Japan to that used in the EU, and discusses the potential consistency of PEC calculation and testing for environmental toxicity and fate that should be taken into consideration by pharmaceutical companies in Japan.

2 EU Step-wise Approaches

In the EU, Phase I starts with 3 items of screening endpoints simultaneously:

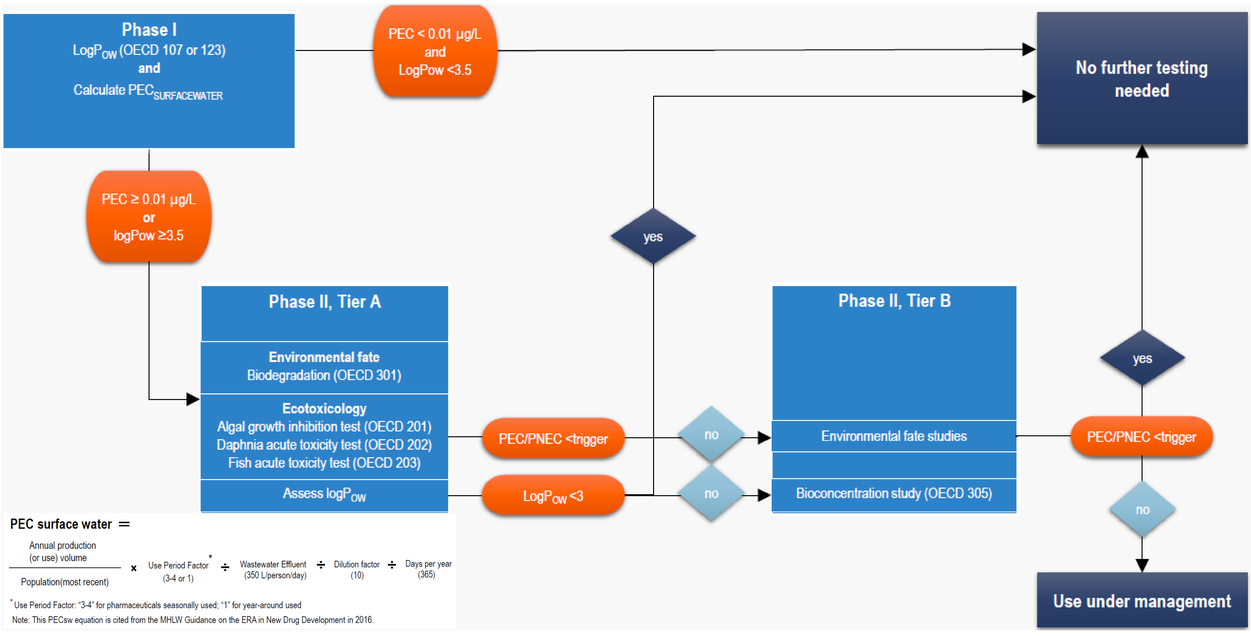
1. PEC SURFACEWATER: Calculated from maximum daily dose and Fpen (trigger value: 0.01 µg/L)
2. Assessment of applicability of action limit (i.e. specific concern): Phase II is always needed if effects on reproduction cannot be excluded below trigger value 0.01 µg/L.
3. LogPow: Determined by OECD 107 or 123 (trigger value: 4.5)

In Phase II Tier A, the "initial e-fate" testing is conducted to determine if soil and sediment assessment is needed, and the "initial effects" testing for PNEC derivation. With the purpose of clarifying necessity of Phase II Tier B testing, risk assessment by PEC/PNEC ratios, and hazard assessment based on triggers for Log Pow (**trigger value: 3**), Koc, and fraction of added amount of substance shifting to sediment are conducted. The outcome of Phase II Tier B testing is referred to for risk assessment for compartments indicated in Tier A.



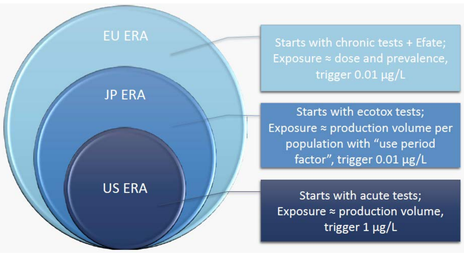
3 Japan Step-wise Approaches (proposal scheme deduced from the MHLW Guidance)

In order to avoid possibly additional e-fate assessment during post-marketing surveillance, Phase I should determine logKow (**trigger value: 3.5**) and PEC (trigger value: 0.01 µg/L) simultaneously. In the MHLW Guidance, the screening logKow trigger value 3.5 is cited form that used by the US FDA. In the US, logKow determines if testing starts with acute or chronic toxicity studies but neither e-fate nor effect testings are detailed in the MHLW Guidance besides readily biodegradation and the acute daphnia, algae, and fish studies; Furthermore, necessity of bioaccumulation assessment by aquatic species (OECD305 equivalent) should be discussed given that Japan Substance Control Law for industrial chemicals, comparable to EU REACH, requires that evaluation at the lower market volume (below 10t).



4 Discussion: Points-to-be-Considered for Development of Japanese ERA scheme

In the EU, PBT assessment triggers differ between Phase I and Phase II, which is linked to the level of exposure and concern. Substances remaining in Phase I have a low PEC and expected low toxicity, but they can still represent a risk when they are very persistent or bioaccumulative. In Phase II, if PEC and/or expected toxicity are higher, even substances showing lower levels of persistence and bioaccumulation may lead to risk when compared to substances remaining in Phase I. This is the reason why the logPow trigger is higher in Phase I than in Phase II. PBT assessment is triggered by logPow value >4.5 in Phase I which is not linked to Phase II assessment. In Phase II, a bioconcentration study is triggered when logPow is >3 but Phase II testing is not dependent on the logPow value. Furthermore, in the EU, the PEC (predicted environmental concentration) is calculated from the dose of the drug and the prevalence of the indication (i.e. how many persons take how much active pharmaceutical ingredient (API) on how many days per year); In the US, the EIC (estimated introduction concentration) is calculated from the production volume. In Japan, with regards to PEC calculation, the Japan Pharmaceutical Manufacturers Association has suggested the utilization of API based distribution information released in the public database of the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)[2]. Given the step-wise scheme and logPow (Kow) values stated in the MHLW Guidance, the current Japanese ERA scheme is considered a combined EU and US approach. The criteria of action limit and time-and-cost effective approach should be carefully discussed for development of an ERA scheme that suits the environmental conditions and drug prevalence in Japan.



Reference:
1) Ministry of Health, Labour & Welfare (MHLW), 2016. Guidance on the Environmental Risk Assessment in New Drug Development. Available from: https://www.pmda.go.jp/files/000214195.pdf.
2) Sato K, Watanabe H, Ikeda T, *et al.* Estimation of total prescription weights of active pharmaceutical ingredients in human medicines based on a public database for environmental risk assessment in Japan. Regulatory Toxicology and Pharmacology 99 (2018) 98-104

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