Environmental risk assessment of human and veterinary medicinal products - Challenges and ways of improvement

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Abstract

Assessment of the environmental impact, the risk posed by application of medicinal products for human and veterinary use is a legal obligation, and must be performed to evaluate and limit potential adverse effects of medicines on the environment.
An environmental risk assessment (ERA) is performed in a stepwise approach in European Union, which starts with an initial screening phase (Phase I), aimed at identifying the environmental exposure of pharmaceuticals based on their potential for bioaccumulation and persistence in the environment. If, following this preliminary assessment, significant environmental exposure is anticipated, or if specific risks are identified due to compound-specific characteristics, a number of studies should be performed (Phase II) based on the guidance documents issued by European Medicines Agency (EMA).
The Phase II tests identify the fate of medicinal products in the environment and their potential effects on representative organisms (e.g. fish or daphnids, for the aquatic environment). For this purpose, the results of various internationally accepted test methodologies (laid down mainly by the Organisation for Economic Co-operation and Development, OECD) form the basis of the risk-assessment process, which may be further extended on a case-by-case basis, depending on the outcome of the assessment.
However, several studies have been published revealing considerable residue levels in surface waters, in rivers and lakes throughout Europe that rise the question whether the current legislation and environmental risk assessment system of human and veterinary medicinal products are sufficiently protective.

Introduction

The pollution of water and soil with pharmaceutical residues is an emerging environmental concern worldwide. In Europe in August 2013, in the framework of the adoption of Directive 2013/39/EU as regards priority substances in the field of water policy, the European Commission has been asked to develop a strategic approach to pollution of water by pharmaceutical substances by the end of 2015. BIO Intelligence Service carried out a study on the risks of environmental effects of medicinal products that together with other relevant studies and reports, provides the basis to develop the strategic approach (BIO Intelligence Service, 2013).

There is increasing evidence that human and veterinary medicines are damaging wildlife. The report "Pharmaceuticals in the Environment: A growing threat to our tap water and wildlife" published by CHEMTrust in 2014 also highlights that medicines continuously pollute rivers and have harmed wild birds and fish (Warhurst, 2014). Other species have also been affected, and people are also worryingly exposed.

This report also states that assessments of the environmental risks from human medicines in use before 30th October 2005 were not required and are often absent.

Elizabeth Chadwick of the Cardiff University (UK), who was part of a three-year study looking at pharmaceuticals in otter tissue, expressed based on her research that as the human population grows and gets older, the level of pharmaceuticals being pumped into the environment is ever-increasing. It is one of the most serious threats to our environmental health. Post-launch coverage includes The Pharmaceutical Journal of 21st February 2015, and a detailed feature on pharmaceutical pollution in the April 2015 issue of ENDS Report (Owens, 2015).

Over a dozen pharmaceuticals have been reported in the environment at many locations worldwide, including anti-inflammatory and analgesic agents (diclofenac, ibuprofen, naproxen, paracetamol, acetylsalicylic acid), antibiotics (sulphamethoxazole, trimethoprim, ciprofloxacin, ofloxacin, norfloxacin), the anti-epileptic carbamazepine, the lipid lowering clofibric acid as well as the residues of estrogenic substances, used in the contraceptive pill and to treat the menopause. (Warhurst, 2014). In the peer-reviewed literature recent studies have also demonstrated that despite the relatively low concentrations of pharmaceuticals in the environment (typically in sub-parts-per-billion levels) pharmaceuticals are of ecological concern due to their potential long-term adverse effects on humans and wildlife (Boxall et al, 2004, Ankley et al., 2007, Zhou et al., 2008).

Existing regulatory requirements of environmental risk assessment of medicinal products for human use

The European Medicines Agency's (EMA) guideline on the environmental risk assessment (ERA) of medicinal products for human use came into force in 2006 (EMA, 2006). In the scope of the guideline, it is stated that in accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered. In any event, this impact should not constitute a criterion for refusal of a marketing authorisation.

The EMA guidelines shall be applied to all new marketing authorization applications. However, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted, since they are considered unlikely to result in significant risk to the environment. In addition, there are veterinary use of active pharmaceutical ingredients (APIs), and

pharmaceutical substances consisting of genetically modified organisms (GMOs), that should also be considered in the environmental risk assessment.
In Phase I of the risk assessment procedure described in the EMA guidance, the predicted environmental concentration (PEC) for surface water shall be calculated and the octanol−water partition coefficient (Kow) shall be measured (Table 1).

Table 1: The phased approach in the environmental risk assessment

Stage in regulatory evaluation	Stage in risk assessment	Objective	Method	TEST / DATA REQUIREMENT
Phase I	Pre-screening	Estimation of exposure	Action limit	Consumption data, logKow.
Phase II Tier A	Screening	Initial prediction of risk	Risk Assessment	Base set aquatic toxicology and fate
Phase II Tier B	Extended	Substance and compartment-specific refinement and risk assessment	Risk Assessment	Extended data set on emission, fate and effects

If the PEC-value is equal to or above 0.01 µg/L, a Phase II assessment shall be performed. Active pharmaceutical ingredients (APIs) with a logKow > 4.5 are screened for PBT properties (Persistence, Bioaccumulation, Toxicity). APIs that are known a priori to affect reproduction of vertebrates or invertebrates at concentrations below 0.01 µg/L should also enter Phase II, following a tailored risk assessment strategy that addresses its specific mechanism of action. In Tier A of Phase II, physicochemical, fate, and effect studies (standard studies are recommended) are reviewed and the predicted no effect concentration (PNEC) for water, groundwater and microorganisms is calculated (Table 2).

Table 2: Physicochemical, fate and effect studies recommended in Phase II Tier A

Study Type	Recommended Protocol
Adsorption - Desorption Using a Batch Equilibrium Method	OECD 106/ OECD 121/OPPTS 835.1110* * One study is generally sufficient
Ready Biodegradability Test	OECD 301
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308
Algae, Growth Inhibition Test	OECD 201
Daphnia sp. Reproduction Test	OECD 211
Fish, Early Life Stage Toxicity Test	OECD 210
Activated Sludge, Respiration Inhibition Test	OECD 209

If the ratio PECsurfacewater:PNECwater is above 1, an extended environmental fate and effect assessment, according to Tier B in Phase II, is required (Table 3).

Table 3: Terrestrial fate and effects studies recommended in Phase II Tier B

Study Type	Recommended Protocol
Aerobic and anaerobic transformation in soil	OECD 307
Soil Micro organisms: Nitrogen Transformation Test	OECD 216
Terrestrial Plants, Growth Test	OECD 208
Earthworm, Acute Toxicity Tests	OECD 207
Collembola, Reproduction Test	ISO 11267

Regulatory requirements of environmental risk assessment of veterinary medicinal products

In 1998 the EMEA issued a note for guidance on Environmental Risk Assessment for Veterinary Medicinal Products (VMP) other than GMO (genetically modified organism)-containing and immunological products (EMEA, 1998). The guidance rests upon a logical, tiered approach with a cut-off trigger between a basic characterisation of the veterinary medicinal product and an in-depth assessment of its fate and ecotoxic effects.
Phase I of the environmental risk assessment for a VMP starts with questions on the physical and chemical properties of the VMP, its use, dose route, frequency of dosing, animal husbandry and routes of excretion into the environment. It is assumed that VMPs with limited use and limited environmental exposure will have limited environ- mental effects and thus stop in Phase I. Phase I also identi fi es VMPs that require a more extensive environmental risk assessment under Phase II. Once a VMP has reached Phase II its predicted environmental concentration (PEC) is compared with its lowest effective concentration from standard ecotoxicity tests in soil and / or water to assess a probable environmental risk. After the toxic potential of the substance or its metabolites is assessed, the value is multiplied by an appropriate safety factor to create a predicted no effects concentration (PNEC). If the ratio of the predicted concentration to the predicted no effects concentration is greater than 1, further and more detailed studies on fate and effects of the VMPs have to be performed in order to refine the PEC as well as the PNEC. A decline of the expected environmental concentration is a function of hydrolysis, photolysis (chemical transformation) and biodegradation (mineralisation and biotransformation) of a VMP in the environment. The results from a short-term laboratory base set of ecotoxicity tests may be refined by long-term, semi-field or field data. At the end of the Phase II assessment, a VMP may not be expected to cause a significant harm to the environment or, if the PEC / PNEC ratio remains greater than 1, a risk to the environment is assumed. In the latter case, risk mitigation measures have to be linked with the authorisation for use of the product (Koschorreck et al., 2002).

Table 4: Recently modified Environmental Risk Assessment Guidelines produced by EMA Committee for Medicinal Products for Veterinary Use (CVMP):

Assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products
Assessing the toxicological risk to human health and groundwater communities from veterinary pharmaceuticals in groundwater
Determining the fate of veterinary medicinal products in manure
Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38
Higher-tier testing of veterinary medicinal products to dung fauna
Plant testing strategy in the risk assessment for veterinary medicinal products
VICH GL6 Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I
VICH GL38 Environmental impact assessments for veterinary medicinal products - Phase II

Challenges and ways of improvement

Pharmaceuticals have been reported in the environment at many locations worldwide. Although not limited to ethinyl estradiol, concerns about the effects of ethinyl estradiol (contraceptive pill and to treat the menopause) on wildlife included, as at many locations

downstream of sewage treatment works, male fish have been feminised and have reduced sperm production. Many of these male fish abnormally make the female egg yolk protein and have eggs in their testes. Research has shown that ethinyl estradiol has contributed to causing these effects, often in combination with other hormones or hormone mimicking substance (Owens, 2015).
Fish and other wildlife species may also be under threat from diclofenac (a non-steroid inflammatory drug, NSAID), because its concentration exceed the PNEC in many rivers worldwide. In the UK, a recent research paper, using modelled data and comparing with actual available data, suggested that this level might be exceeded in 4.5% of river reaches. Also, for example, a laboratory study has noted that environmentally realistic concentrations of diclofenac can impair osmo-regulation in the shore crab (Carcinus maenas) (Warhust, 2014).
Medicines used against parasites, for example the ivermectin, can be excreted in the faeces of treated animals and adversely affects invertebrate organisms that live in or feed on dung (Liebig et al., 2010). It can therefore also reduce the amount of food available to birds and bats.
An EU funded research project (PHARMAS) has also highlighted that model predictions show that ciprofoxacin and levofloxacin (used for the treatment of urinary tract infections) may approach concentrations in some European rivers that could trigger ecological damage (Lamoree, 2011).
Sándor et al. (2011) reported that only tetracyclines were detected in the studied Hungarian natural and waste waters in relatively low concentrations (<0.05-0.21 ng/ml) between 2007 and 2010. Negligible amounts of two other antibiotics (sulfamethazin and nitrofuran) were detected in all water samples. Well detectable amount of NSAID were measured in the sampled influent waste water (ibuprofen, naproxen, ketoprofen and diclofenac: 2.55, 0.45, 11.67 and 2.30 ng/ml, respectively). Their results have shown that considerable amount of NSAIDs might be decomposed through the waste water treatment (41.7-94.9%). The highest concentrations of NSAIDs were detected in all samples from fresh sludge (ibuprofen, naproxen, ketoprofen and diclofenac; 7.71, 27.61, 145.2 and 18.56 ng/ml, respectively). Negligible NSAID concentrations were found in the control samples of river Körös and oxbow lake of it. Results have shown that NSAIDs might be decomposed at least with 50% during the storage of sludge. As a conclusion, studied Hungarian waste waters are tainted with relatively low amounts of antibiotics and NSAIDs. However, these results might confirm that the adsorption and accumulation of antibiotics in sludge and sediments might be high and these processes can also damage the bacterial flora of biological wastewater treatment systems, which reduces the removal efficiency of other substances.
As it is demonstrated, several studies have been published revealing considerable residue levels in surface waters, in rivers and lakes throughout Europe that rise the question whether the current legislation and environmental risk assessment system of human and veterinary medicinal products are sufficiently protective?
On 26 March 2015, the EMA published a draft Questions and Answers Document ("Q&A Document") for consultation concerning the EMA's Guideline on the environmental risk assessment of medicinal products for human use ("EMA Guideline"). The purpose of the Q&A Document is to clarify and harmonise the use of the EMA Guideline. The draft Q&A Document, if adopted, will revise the current Q&A document that was adopted on 17 March 2011. The Q&A Document was open for consultation until 30 June 2016.

During the XV. Italian-Hungarian Symposium on Spectrochemistry: Pharmacological Research and Analytical Approaches (Pisa, 2016), several recommendations have been made

to improve the ERA of medicinal products and allow to decrease the risk posed by pharmaceutical residues in the environment.
These recommendations included the requirement of environmental risk assessment also for products put on the market before 2006, additional requirements to be included to the legislations to assess the risk for development of antibiotic resistance, refinement of the tiered approach, improvement the collection system of the used and remaining packages of medicinal products, up to perform combined toxicity assessments on active pharmaceutical ingredients with similar modes of action.
It was recommended that environmental risks should be included in the risk-benefit analysis when a product is considered for market authorization. This would increase the importance of the environmental risk assessment and motivate pharmaceutical companies to perform the assessment on time. It was also recommended to update the environmental risk assessment of APIs, when significant new environmental information is available.

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