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PHARMACEUTICALS IN THE ENVIRONMENT

ABSTRACT

Pharmaceuticals are essential for human and animal health. At the same time pollution of waters and soils from pharmaceutical residues is an emerging environmental problem as well as an emerging public health concern. These are sometimes persistent and harmful for the environment. In order to protect the waters and soils in their functions as habitats and drinking water resources in the long term, the entry of pharmaceuticals into the environment must be limited as far as possible. The aim of this review paper is to explain the legislative framework, the scientific requirements, facts, contexts and uncertainties of the topic of "pharmaceuticals in the environment" as well as the risk mitigation measures and solutions to control and possibly reduce the environmental entry.

INTRODUCTION

The treatment of many deseases in humans and animals relies on access to effective pharmaceuticals. At the same time pollution of waters and soils with pharmaceutical residues is an emerging environmental problem and also an emerging public health concern. (COM/2008/0666 final, Directive 2010/84/EU, 2010). There is well-documented evidence of risk to the environment and, particularly in relation to antimicrobial resistance, to human health.

Pharmaceuticals were first identified to pose environmental risks in the 1990s, and since then the number of available monitoring and effect studies has increased steadily. Pharmaceuticals are present in the environment as a consequence of patient use, drug production and formulation, and improper disposal (Boxall et al., 2012). Today, several hundred active pharmaceutical ingredients (APIs) have been found in sewage water, surface water, groundwater, soil, air, or biota in concentrations from sub-ng/L to more than µg/L (BIO Intelligence Service, 2013; Kümmerer, 2009; Küster and Adler, 2014). Extremely high pharmaceutical concentrations, in the order of mg/l, however, have been detected in some industrial effluents and recipient streams, for example in India, China, USA, Korea and Israel (Larsson, 2014). Thus far, there are several examples of APIs convincingly shown to cause effects on organisms in the environment.

In terms of market presence, around three thousand active pharmaceuticals ingredients (APIs) are currently authorised on the EU market as a whole, even if the APIs authorised at national level vary significantly. The consumption of medicinal products (i.e. consumed volumes) varies considerably from one country to another (Goossens at all., 2005; Ministère de l'Ecologie, 2010; Schuster at all., 2008; Verbrugh and de Neeling, 2003), although these numbers should be interpreted with care as the quality of reporting varies across different sources. For human medicinal products, the European Union (EU) is the second biggest consumer in the world (24% of the world total) after the United States of America. Moreover, in the majority of EU Member States, a large share of unused human medicinal products (50% on average) is not collected and some EU Member States do not implement take-back schemes (BIO Intelligence Service, 2013). The human medicinal products recognised as potential environmental and food hazards are primarily medicinal products used in high volumes and medicinal product groups with special properties such as hormones, anticancer medicinal products, pain killers, and antibacterial medicinal products (Halling-Sørensen at all., 1998; Jørgensen and Halling-Sørensen, 2000).

The emerging public health concern has been recognized and resulted with legislative changes and initiatives to define the causes, assessment of the potential environmental risks and hazards of human medicinal products. Recent pharmacovigilance legislation in the EU acknowledges that the pollution of waters and soils with pharmaceutical residues is an emerging environmental issue.

The EU Water Framework Directive has included pharmaceuticals on a dynamic 'watch-list' based on potential for adverse effects in the aquatic environment. This list includes potential water pollutants that should be carefully monitored by the EU

Member States to determine the risk they pose to the aquatic environment and whether EU Environmental Quality Standards (EQS) should be set for them.

REGULATORY

Based on the knowledge that APIs could constitute an environmental risk, the European Medicines Agency's (EMA) guideline on environmental risk assessment (ERA) of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2) came into force in 2006 (EMA, 2006). The guideline is in accordance with the directive for medicinal products for human use (Article 8(3)) (Directive 2001/83/EC, 2001) and has been reinforced through a Q&A-document that clarifies specific issues (EMA, 2016). The current version of the Guideline on the environmental risk assessment of medicinal products for human use will be replaced by new revision EMEA/CHMP/SWP/4447/00 Rev. 1 (EMA, 2018), published for comments in November 2018. The draft guideline has a new structure of a stand-alone document with all technical details needed for ERA included.

The European Commission was asked to deliver a report on the scale of the issue, the causes, and possible policy options to mitigate impacts. In the framework of the adoption of the Directive regarding priority substances in the field of water policy, the European Commission is obliged to develop a strategic approach to water pollution from pharmaceutical substances according to Article 8c of Directive 2008/105/EC (amended by Directive 2013/39/EU) and to propose measures to be taken at EU and/or national level, to address the possible environmental impact. In this regard, a study was carried out by BIO Intelligence Service on the environmental risks posed by medicinal products. The study had a broad scope since its objectives were to characterise the scale of the risk, and to identify possible solutions.

Legislative factors of influence

At EU level, European Directive 2001/83/EC (as amended) and Regulation 726/2004/EC37 set out the conditions for the authorization of medicinal products. One of the key legislative factors influencing the presence of the medicinal products in the environment is the current framework for Environmental Risk Assessment (ERA), which is a part of the Market Authorisation process. The purpose of conducting regulatory environmental risk assessments is to avoid ecological catastrophes in the future; to protect the most vulnerable wildlife populations, ecosystem services and, by association, the wider human population.
In the European Union (EU) an environmental risk assessment is required to new marketing authorization applications for products that were put on the EU market after the ERA guideline came into force in 2006. However, the ERA results cannot lead to denying an authorisation, even if some Risk Mitigation Measures (RMM) can be required when considered necessary.
Four procedures exist for the MA process: three procedures are Community procedures (centralised, decentralised and mutual recognition procedures), and the fourth is the national procedure which applies when the MA application is limited to the territory of one MS.

Under the centralised procedure, unlike in the Committee in charge of the evaluation of veterinary medicinal products (CVMP) that has a member appointed specifically due to his expertise on environmental risk assessment, the one dedicated to human medicinal products (CHMP) does not necessarily include an environmental expert.

In the decentralised and mutual recognition procedures the level of ERA expertise and therefore the level at which an ERA is analysed depends in practice on the considered MS and is therefore very heterogeneous. This might lead in certain cases to parallel procedures for the same product followed in different (critical versus less critical) countries.

The ERA for human medicinal products is often incomplete or altogether absent from some MA applications. In these cases, the MA is therefore often granted with "post-marketing commitments" which are de facto not mandatory, since these results are not considered for the risk-benefit analysis and thus have no weight to obtain an MA.

When, based on the ERA results, a risk to the environment exists, Risk Mitigation Measures (RMM) are recommended. However, compliance with RMM therefore has only a voluntary character, and their implementation is not systematically verified nor followed up on. Nonetheless, a Member State may suspend the use at a national level of a medicinal product for human use, if urgent action is essential to protect human health or the environment.

Finally, environmental datasets produced in the context of ERA are often not publicly, or at least not easily, available. The level of accessibility might vary depending on the considered MS, but it is generally limited to risk assessors only and confidentiality reasons are invoked to justify the absence of publicly available datasets or their partial publication. When published, the quantity and quality of disclosed information vary depending on the type of procedure followed and on which MS was responsible for the evaluation (Reference Member State).

Other legislation

Apart from the MA framework, several legislative texts could be relevant to address the issue of medicinal products in the environment at EU level. These include Registration, Evaluation, Authorization and restriction of Chemicals (REACH), the Industrial Emissions Directive (IED), and the Water Framework Directive (WFD), among others.

Under the REACH legislation there is an exemption for Active Pharmaceutical Ingredients (APIs) but other compounds used in manufacturing development (starting materials and reagents) are covered. REACH restricted substance list (Annex XVII) does not currently impose restrictions regarding APIs. There are derogations for medicinal products from certain restrictions applicable to the use and placing on the market of carcinogenic, mutagenic and reprotoxic (CMR) substances as substances or in mixtures for supply to the general public; but restrictions could target certain APIs, or the manufacturing process itself. A potential gap therefore lies in the fact that the EU legislation on medicinal products does not cover all lifecycle stages of the products, but at the same time medicinal products are exempted from many Titles under REACH.

Industry manufacturing emissions from manufacture of pharmaceutical substances are covered by the Industrial Emissions Directive which applies to most EU industrial sectors. However, even if APIs could fall within certain groups of water pollutants listed in Annex II, the IED does not yet include any active pharmaceutical ingredients in the list of polluting substances, and therefore does not set emission limit values nor require their monitoring.

EU legislation does not address the issue of soil contamination. Therefore, the issue of a soil contamination by medicinal products is not legally covered at EU level. The majority of the existing MS national soil legislation does not cover this specific issue either. Similarly, there is no obligation to monitor or regulate medicinal product residues present in sewage sludge originating from water treatment plants. This issue is however considered sporadically by the national legislation: the use of sludge in agriculture is for instance restricted in Bavaria and Nordrhein-Westphalia to take into account the environmental risks posed by the presence of pharmaceutical residues. (BIO Intelligence Service, 2013).

Under the Water Framework Directive (WFD), the surface water Watch List (WL) is a list of potential water pollutants that should be carefully monitored by the EU Member States to determine the risk they pose to the aquatic environment and whether EU Environmental Quality Standards (EQS) should be set for them. The first WL was published in 2015. It included ten substances amongst which three APIs (17α-ethinyl estradiol (EE2), 17β-estradiol (E2) and Diclofenac). The Joint Research Centre (JRC), the European Commission's science and knowledge service, reviewed the first WL based on the data gathered during the first year of monitoring (2016), and made recommendations for the 2nd list in a recently published report (Loos at all, 2018). The JRC report concludes that five substances should be removed from the WL, amongst which is diclofenac, as sufficiently high-quality monitoring data were available for them, and proposed three new substances to be included. The report also gives the relevant Predicted No Effect Concentrations (PNECs) and identifies possible methods of analysis for the proposed substances. The three new substances to be included comprise one pesticide and two antibiotics (amoxicillin and

ciprofloxacin). The inclusion of the antibiotics is consistent with the European One Health Action Plan against Antimicrobial Resistance (AMR), which supports the use of the WL to 'improve knowledge of the occurrence and spread of antimicrobials in the environment'. This list is to be updated every 2 years. Member States are obliged to monitor substances on the watch list at least annually at a limited number of representative monitoring stations for up to four years. Listing as a priority substance would not compromise their therapeutic value but would consider the potential adverse effects on fish and other organisms living in water. Member States may also identify and monitor medicinal products as specific pollutants pursuant to existing provisions of the Water Framework Directive.

EU food legislation requires the monitoring of veterinary medicinal products residues in foodstuffs of animal origin but does not refer to medicinal products for human use. Consequently, EU food legislation does not address the issue of indirect transfer to humans of residues of medicinal products for human use, which may be present and have accumulated in the natural environment and may be transferred to food animals including fish.

Marketing authorization (MA) process and Environmental risk content of the MA application

The marketing authorization process for medicinal products is governed by Directive 2001/83/EC for human use, and by Regulation 2004/726 laying down Community procedures for medicinal products, as amended.

A marketing authorization must be obtained before placing a product on the EU market. The MA process may follow different procedures, namely one of the procedures established by the European Union (centralised, decentralised or mutual recognition procedures) or a national procedure, when the application concerns only one MS. In most cases, the MA application must include an ERA. An ERA must be presented in the MA dossier for human medicines, but its weight and impact in the risk/benefit analysis differ depending on the type of medicinal products.

Special rules exist for the authorisation of medicinal products for paediatric use, orphan medicinal products, traditional herbal medicinal products, vaccines and clinical trials.

The provisions on what the MA application for medicinal products for human use must contain are included in Article 8 and Annex I of the Directive 2001/83/EC. Pursuant to EU legislation, environmental risks are included in the risk/benefit analysis for veterinary medicinal products, but not for medicinal products for human use. Consequently, a MA may be refused on environmental grounds only for veterinary medicinal products.

The centralized procedure came into operation in 1995, following the legislation creating the European Agency for the Evaluation of Medicinal Products in 1993 (EMEA, now the European Medicines Agency –EMA– since Regulation 2004/726). This procedure is compulsory for certain medicinal products listed in the Annex to Regulation 726/2004, and optional for any other products containing new active substances not authorized in the Community before 20 May 2004 (when Regulation 726/2004 entered into force) or for products which constitute a significant therapeutic, scientific or technical innovation or for which a Community authorization is in the interest of patients or animal health at Community level.

The MA application is submitted to the EMA and assessed by the Committee for Medicinal Products for Human Use (CHMP). The CHMP are part of EMA (pursuant to Articles 5 and 30 of Regulation (EC) No 726/2004). They are responsible for drawing up the opinion of the EMA. The CHMP appoints one of its members as rapporteur and one as co-rapporteur. The CHMP is composed of members nominated for each of the 27 MS, and for Iceland and Norway, and of up to 5 co-opted members who provide additional expertise in a particular scientific area. Unlike the CVMP that includes an environmental risk assessor among these co-opted members, and other environmental experts in its working party on environmental risk assessment, none of the CHMP co-opted members is an environmental risk assessor. The rapporteur,

nominated by the CHMP, must be supported by a team of national experts in the different areas of the assessment. However, not all MS have experts with enough ERA experience to perform it according to the guideline; this remark also applies to the mutual recognition and decentralised procedures (BIO Intelligence Service (2013). The MA is ultimately granted or refused through a Commission decision. The MA granted to applicants under the centralised procedure is valid throughout the EU.

In the case of the mutual recognition and decentralised procedures, the MA application dossier is submitted at MS level: it must be identical in all MS where it is submitted. In these procedures, one of the MS acts as "reference MS" (RMS) and the other ones are "concerned MS" (CMS).

The main difference between the two procedures lies in that mutual recognition applies when a medicinal product, has already received a marketing authorisation in one MS: the CMS must then recognise the marketing authorisation granted by the RMS. The decentralised procedure, which was introduced in 2004 for both human and veterinary medicinal products, applies to medicinal products, which have not received a marketing authorisation in a MS at the time of application (the MA application dossier is submitted simultaneously in all MS). In both cases, the RMS prepares an assessment report, which is sent to the CMS and to the applicant together with the summary of product characteristics (SmPC), labelling and package leaflet (PL).

A CMS may refuse to grant the marketing authorisation on various grounds, which differ depending upon whether the MA concerns medicinal products for human use or for veterinary use. In the first case, a CMS may only refuse "on the grounds of potential risk to public health", whereas in the second case the refusal may be based "on grounds of a potential serious risk to human or animal health or to the environment". The difference of grounds results in the place granted to the environmental risk assessment in the risk/benefit analysis.

In case of such disagreement, all MS (reference and concerned MS) try to reach an agreement on the action to be taken. If the agreement is not reached, the matter is referred to the EMA. MA may still be granted in those MS that have approved the procedure, without prejudice to the outcome of the referral procedure. The matter will be assessed by CHMP or CVMP (depending on whether the pharmaceutical is for human or veterinary use), and the Commission will take the final decision (on the granting or not of the MA).

The level of requirement may vary from one MS to the other, and parallel procedures for the same product can be followed in different (critical versus less critical) countries. This may allow for a the MA applicant, under the decentralised and mutual recognition procedure, to choose as RMS a country that is less critical and demanding as to the quality of the ERA performed. In addition, the decentralised and mutual recognition procedures may sometimes lead to different assessments in different MS of similar and/or different products containing the same API (BIO Intelligence Service, 2013).

MAs subject to national procedures are available for medicinal products, which are to be marketed only in one MS, i.e. the MA application is limited to the territory of one MS. Depending on the MS, national procedures are not always widely used. In Germany, about 50% of the market approvals are related to nationally authorised products. (BIO Intelligence Service, 2013).

Supplementation of the Directives by EMA guidelines

The provisions of Directive 2001/83/EC for medicinal products for human use are supplemented with specific guidelines adopted by the EMA. These include guidelines on ERA. For the preparation of guidelines within the framework of Community legislation, a delegation of power is given to the European Commission (EC), which may in turn delegate the drafting of these guidelines to the EMA, in particular with regard to scientific guidelines. The ERA scientific guidelines aim

to provide a basis for practical harmonisation of the manner in which MS and EMA interpret and apply the requirements set forth in the relevant EU directives.

The current ERA for medicinal products for human use is subject to the guideline adopted by the CHMP and it took 7 years to be adopted and came into effect on 1 December 2006 (EMA, 2006). The wording, and therefore the content of this obligation, evolved and new guideline is drafted and released for comments on 15th of November 2018 and has not yet reached the adoption phase. The revision of the ERA guideline is based on a concept paper issued in 2014 and the work of a group of experts led by the Safety Working Party of EMA's human medicines committee. It builds on the twelve years of experience gained since the original guideline was published and aims to facilitate the work for both applicants and regulators in the interest of environmental protection.

Environmental risk content of the MA application

Article 8 of Directive 2001/83/EC provides that the MA application must be accompanied by, among other particulars and documents: evaluation of the potential environmental risks posed by the medicinal product, which is to be performed in accordance with guidelines adopted by the EMA, which include specific scientific requirements. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged (art.8(3)(ca));
Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment (art.8(3)(g)).

However, the results of tests assessing the potential environmental risks posed by the medicinal products for human use are not listed among the results of tests to be included in the MA application (art.8(3)(i)).
The availability of ERA data and results also varies depending on the type of MA procedure followed and the MS involved.

Medicinal products for human use for which an ERA is required

In respect of medicinal products for human use, an ERA is required (EMA, 2006) for new MA applications submitted after 30 October 2005, Type II variations ("major variations"), but only if an increase in environmental exposure is expected, Extension applications according to Annex II of Commission Regulation (EC) No. 1085/2003, if there is a potential increase in the environmental exposure and Generics, as defined under the Directive.
It results from the above that medicinal products marketed before 30 October 2005 are not subject to the obligation of carrying out an ERA. Indeed, although an "indication of any potential risks presented by the medicinal product for the environment" is required since January 1995, when Directive 93/39/EEC entered into force, the requirement for an evaluation of potential environmental risks was introduced only by Directive 2004/27/EC (amending Directive 2001/83/EC), which came into force on 30 October 2005.

In practice, there is a lack of ERA results for many human medicinal products currently consumed, as numerous active pharmaceutical ingredients contained in such medicinal products were authorised prior to 30 October 2005, which is when a proper ERA became an obligation for human medicinal products. Hence, the environmental risks of numerous active pharmaceutical ingredients/medicinal products authorized before 2005 and still widely consumed have not been assessed or at least not accurately assessed. In Germany for instance, no ERA is available for certain medicinal products for human use that contain active substances that have been measured at high concentrations in surface water (>0.1 µg/L). Figure 1 and 2, show the active substances measured at high concentrations in surface water in Germany and availability of environmental data, accordingly.

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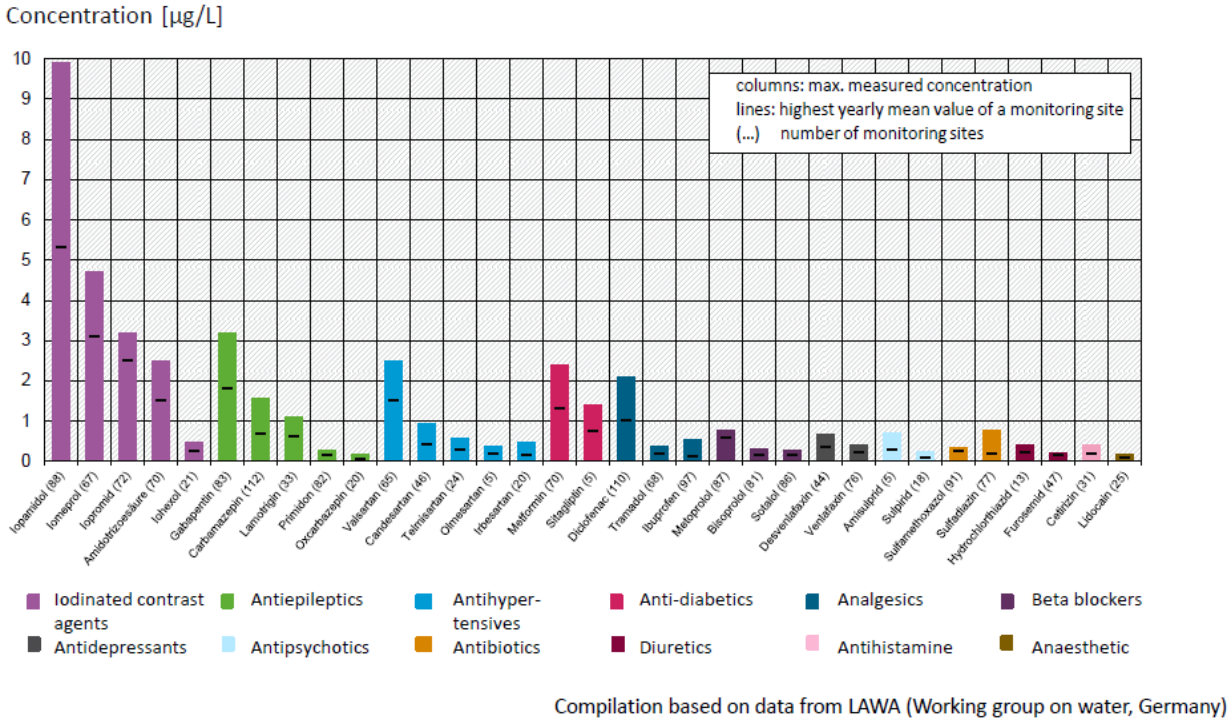

Figure 1: Active substances in surface water (> 0.1 µg/L, Germany 2015)

Source: German Environment Agency, Environmental risk assessment of human medicinal products, A regulatory perspective, Medicines for Europe: 18th Regulatory and Scientific Affairs Conference, Ines Rönnefahrt, London, 31 January 2019

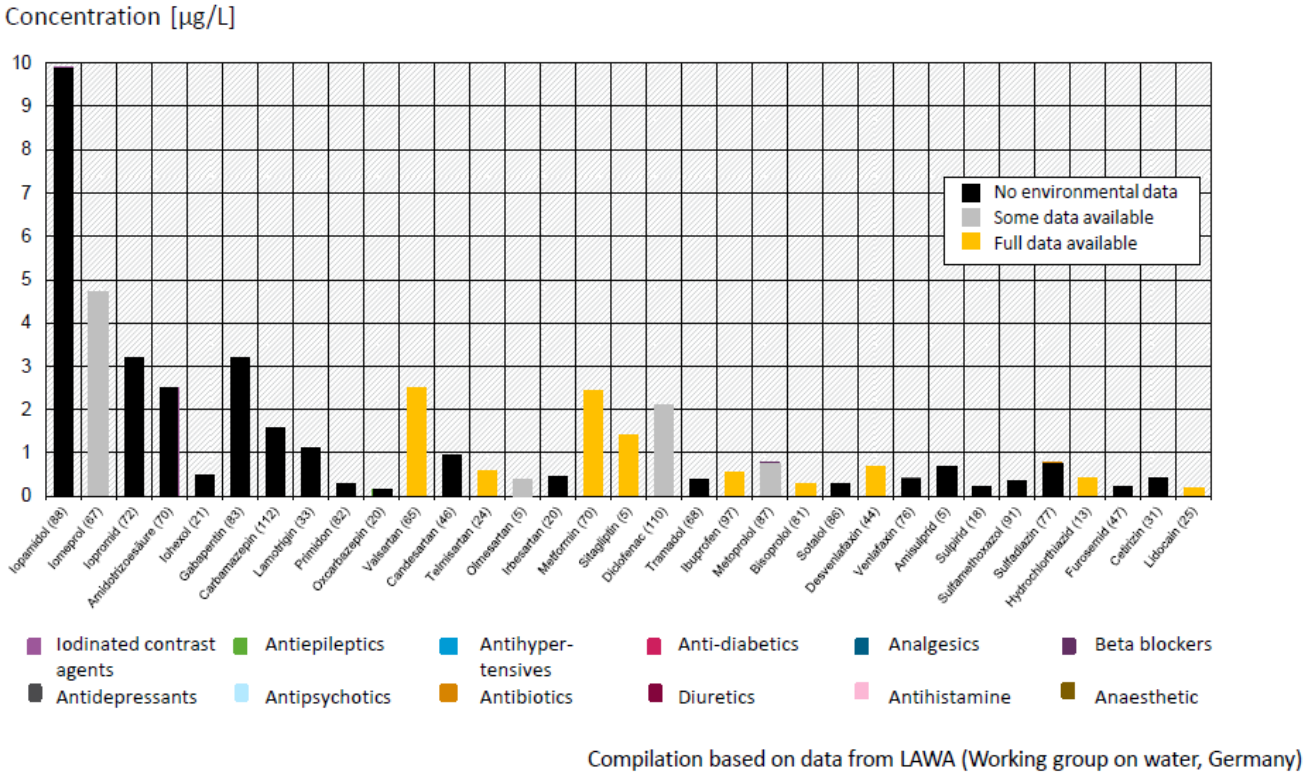

Figure 2: Active substances in surface water (> 0.1 µg/L, Germany 2015)

Source: German Environment Agency, Environmental risk assessment of human medicinal products, A regulatory perspective, Medicines for Europe: 18th Regulatory and Scientific Affairs Conference, Ines Rönnefahrt, London, 31 January 2019

In addition, as previously indicated, the ERA guideline on medicinal products for human use came into effect on 1 December 2006, which means that MA applications submitted between 30 October 2005 and 1 December 2006 do not include an ERA performed in accordance with the adopted CHMP guideline. Consultation of reports regarding authorizations granted by EMA (under the centralized procedure) during this interval tends to show that, for certain medicinal products, MA applicants used the draft guidelines. However, this may not be affirmed for all medicinal products, as the information is not available. Additionally, the market of medicinal products has reached a level of stability and the arrival of new active pharmaceutical ingredients on the market is likely to remain minor when compared to the past.

In addition, in the current ERA process, which is organised in three phases, not all medicinal products undergo a thorough environmental risk assessment, since the assessment of products fulfilling specific criteria stop after the first phase.

The CHMP ERA guideline states that in some cases the absence of an ERA could be justified (in the case e.g. of MA applications for generic medicinal products or type II variations), insofar as a rationale is provided for such absence, taking into consideration a possible significant increase of environmental exposure to the medicinal product substance. The "questions and answers" EMA/CHMP/SWP/44609/2010 Rev 1, released by EMA (CHMP) on said guideline slightly differs, as it indicates that the justification of the absence of significant increase of the environmental exposure could be accepted to justify the absence of a complete ERA (and not the absence of an ERA altogether). Additionally, the "questions and answers" on Guideline on the environmental risk assessment of medicinal products for human use states: "Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the introduction of a new generic medicinal product in a member state where the reference product is not marketed."

A practical example can be seen in the published PARs where no ERA was provided, and the agencies indicate "suitable justification has been provided for non-submission of an [ERA]. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an [ERA] is accepted," or "The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of the particular active substance released into the environment. It does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal." or "The marketing authorization of a new generic product will therefore not lead to a significant increase in the environmental exposure of a particular API and would thus not be expected to have an adverse effect upon the environment." Such practice is used in a large majority of MS.

However, in the proposed draft guideline no explanations or exceptions for generics are present, even though previous documents are confirming that no increased impact for the environment exist for generic products. Generic medicinal products are therefore not exempted from providing an ERA. However, cross reference to the ERA dossier of the originator is permitted with consent from the originator, which, as approach might be questionable, as explained in the next section.
The responsibility for generating environmental data for APIs that have insufficient data to conclude on environmental risk can be recognized as coherent approach, however, for the human medicinal products with a full set of ecotoxicity data, which pose low or insignificant risk to the environment through patient use (Gunnarsson et al., 2019; Kuster and Adler, 2014; Roos at all., 2012); even in many cases with worst case environmental exposure assessments, this approach can lead to unnecessary generation of repetitive testing data and likely conflicting ERAs, especially through national and decentralised procedures. In this regard, debate on the possibility, under the new guideline, for generic applicants to still include justification for not submitting ERA studies based on the claim that increase in the environmental exposure is not expected is ongoing, if for that specific API it's previously demonstrated to present no environmental risk. The special cases where a generic do increase an impact for the environment should be specified (MDD increase, added indication, additional pharmaceutical form).

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In addition, no ERA needs to be performed for authorization renewals, Type IA and IB variations, not for substances such as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines, and herbal products.

Limitations on re-use of ERAs for human medicinal products, Data Accessibility, Study Repetition and Ethical Considerations

An ERA is required for every medicinal product to be put on the market, whether a pharmaceutical is for human or veterinary use, notwithstanding the fact that an ERA may have been previously performed for another medicinal product using the same active pharmaceutical ingredient. This means that an ERA must be performed regardless of the different products containing the same active substance, and that this active substance might have been previously assessed. However, the related information cannot be reused as it is deemed confidential and therefore protected. Indeed, synergies of industrial stakeholders' evaluation efforts are not possible under the current framework, as applicants are very keen on protecting all data submitted during the MA process, arguing that it would otherwise give an unfair advantage to a possible competitor who will not have had to incur the same level of costs (e.g. in the case of generics). The applicants must own the data submitted (do their own tests) or submit data from the public domain to a reliability assessment. Apart from being inefficient and costly, it may also result in inconsistent conclusions between applications as the same active substance could thus be considered as posing environmental risks in one case and none in another. In addition, even if a competent authority knows from other MA applications that an active pharmaceutical ingredient has a lack of environmental risk, the dossier must still be complete and include the ERA, with a repetition of previous studies.

The draft guideline ambition however is to reduce repetition of the testing states through sharing of the data. In order to avoid unnecessary repetition of studies, and in particular animal studies, applicants are encouraged to share their data. If the current applicant has access to an ERA that was performed earlier by another marketing authorisation holder, this ERA (including study reports) may be submitted, including a letter of access. However, to realise this ambition, it would critical to develop a centralised ERA database to facilitate data transparency and accessibility. The transparency of the data, especially for products registered through national or decentralised procedures, is still an issue that needs to be addressed. Data that are available in European Public Assessment Reports (EPARs) are also presented in an inconsistent manner and have to be accessed on a product-by-product basis. Unless improvements to data transparency and data accessibility are addressed, the proposed guideline has the potential to increase the repetition of data generation, particularly for established products that have lost exclusivity where generic applicants may not have visibility to existing datasets and where those data exist.

Furthermore, a generic product itself would probably not lead to an increased consumption of an active compound (API), because the market demand of a specific API does not change significantly and is independent from the number of Marketing Authorization Holders present on the market. Based on the fact that a generic product would not increase the risk for the environment and because of the fact that the ERA is API specific and does not differ between the innovator and generic product having the same indications, MDD and pharmaceutical form, and the generic product demonstrates essential similarity with the innovator product, the request for performing an ERA for each generic product would not result in any benefit for the environment, since this result would be unnecessary study repetitions. These actions could possibly end up in conflict with the basic principles of ERA, where protecting the environment is the main goal, with unnecessary repetition of studies (3R principles, Replacement, Reduction and Refinement). In particular, the ERA phase II studies are API specific and their endpoints are used in ERA reports independent of the product, consequently the ERA does not differ between the innovator and generic products. This is also the case for new fixed combination products intended for substitution indication where a cross reference to proposed documents of the available mono-compound products could be drawn. The wording proposed in the draft guideline, where, although not exempted from the obligation to provide ERA, generic industry could cross-reference to the ERA dossier of the originator with consent from the originator, could be of benefit only if there is guidance in place on how this can be managed. It should be noted that there is no obligation for

originators to provide access to data. Although reference is made to the PAR/EPAR, the full study reports should be submitted as well. A mechanism for Regulatory bodies to waive ERA studies for compounds where studies have already demonstrated a lack of environmental risk (even with potential increased use) would waive the requirement of sharing of proprietary company data, as proposed in the draft guideline.

Duplication of work under the current framework, apart from being inefficient and costly, it may also result in inconsistent conclusions between applications as the same active substance could thus be considered as posing environmental risks in one case and none in another. In addition, if a competent authority knows from other MA applications that an active pharmaceutical ingredient has a lack of environmental risk, the dossier must still be complete and include the ERA, with a repetition of previous studies.

Furthermore, lack of dossier completeness introduces economic issues: for instance, under the decentralized procedure a MS acting as RMS could require the submission of a full dossier from one MA applicant, whereas another MS (also acting as RMS, but in another procedure) could accept a dossier with only endpoints from another applicant. In such a case, the time and costs borne by these applicants will greatly vary.

ERA guidelines: scientific requirements

The ERA is a tiered assessment, which includes two phases: Phase I and Phase II (including Tier A and Tier B). This means that not all products will undergo the same level of scrutiny, the thorough assessment of products (in Phase II) being performed only if they preliminarily fulfil a number of key criteria, namely related to exposure (in Phase I). The principal idea behind the concept of tiered approach is that a hazard assessment is not necessary if the environmental concentration of the tested product is not likely to trigger effects on potentially exposed species.

For pharmaceuticals ERA follows an initial screening (Phase I) where physico-chemical properties of the compound are determined (e.g. logP) and the expected exposure is estimated. The estimation of environmental concentrations should be based only on the medicinal product substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion. Phase I must include: screening for persistence, bioaccumulation and toxicity (PBT) for medicinal product substances with a log Kow >4.5; and calculation of the Predicted Environmental Concentration (PEC) in surface water (mostly based on consumption data and market penetration factor). According to current EMA guidance (EMEA/CHMP/SWP/4447/00), the Environmental Fate and Effects Analysis must be conducted by evaluating the predicted environmental concentration/predicted no effect concentration (PEC/PNEC) ratio of the API (Phase I). This assessment is based on data from relevant environmental testing ("base set of data") as well as on the predicted environmental concentration.

Predicted No Effect Concentration (PNEC) is established by the application of an assessment factor of 10 to the lowest No Observed Effect Concentration (NOEC) for the endpoints of growth, development and/or reproduction from species representing three trophic levels (European Medicines Agency, 2006) and the PNEC is compared to a predicted environmental concentration (PEC). The PEC is usually calculated assuming the maximum dose is taken daily and that 1% of the population takes that drug (unless robust epidemiology data exist showing otherwise). The PEC also assumes 100% patient use, no wastage, no patient metabolism or sewage treatment removal, 200 l of wastewater per person per day and a dilution factor of 10 in the aquatic environment.

If the PEC value is below the action limit value set at 0.01 µg/L, it must be concluded that the medicinal product is unlikely to represent a risk for the environment. The ERA stops there, without the need to proceed to Phase II for the environmental fate and effects analysis.

If the PEC is >0.01 μg L^{-1} then the pharmaceutical must undergo further testing to assess environmental fate and toxicity. However, it should be noted that substances with a logP >4.5, will trigger a persistence, bioaccumulation and toxicity (PBT) assessments regardless of the Phase I PEC.

A risk quotient (PEC/PNEC) above 1, indicating that relevant amounts of the API are expected to be released into the environment, triggers further evaluations and risk refinement, for example on the use, fate and behaviour of the drug i.e. a Phase II assessment has to be conducted. This assessment is again divided into two parts: The first ("Tier A") compiles the base set of toxicological data, estimating the fate of the API based on physical-chemical properties as well as potential toxic effects on fish, daphnia, algae and microorganisms. The outcome of Tier A contains the PEC/PNEC ratio for different categories (water, groundwater, microorganisms), and for each category, an action limit is defined by the agency. If the action limit is exceeded in one or more categories (indicating a potential environmental impact), a Tier B extended effects assessment is demanded focusing on the parameters that are considered potentially critical.

A PBT screening should always be performed for human medicinal products and, if considered, relevant also a further assessment should be performed according to REACH guidance on PBT, regardless of whether the substances' environmental concentrations meet the trigger value under Phase I.

The general risk, the PBT assessment approach and PEC action limit (0.01 μg/L surface water) have not been changed in the proposed new revision of the guideline on ERA.

The main change with the new revision is guidance on tailored assessment for certain groups of active substances due to their specific mode of action. The tailored assessment is necessary to ensure that the most sensitive and appropriate tests with specific groups of organisms are used in the assessment. The tailored assessment concerns compounds for which the action limit does not apply, such as endocrine active substances (EAS), but may also concern compounds for which the action limit applies, such as antibiotics (Whomsley et al.)

The tailored assessment is now predefined in the guideline, while it was left to a case-by-case decision of the MS before. The rest of the changes can be summarised as: slightly reduced base dataset in Phase II Tier A, slightly extended trigger value for soil risk assessment, new ground water exposure modelling tool for Risk Refinement, assessment of risk of secondary poisoning which is relevant for compounds that accumulate through the food chain, mainly lipophilic compounds (calculation only).

In respect of medicinal products for human use, the relevant guideline provides that in Phase I ("estimation of exposure"), according to ERA procedures, for human medicinal products, a bioaccumulative and toxic substance (PBT) screening should always be performed and, if considered relevant, also a further assessment should be performed according to REACH guidance on PBT, regardless of the fact that the substance environmental concentrations meet the trigger value or not (Phase I). The results of the PBT assessment have up to now no consequences on MA for human medicinal products, since they are not considered in the risk/benefit analysis, as the rest of ERA results. Thus, even if the results of ERA highlight the environmental risk and PBT status of a substance, it is unclear which policy can be followed to manage human medicinal products with proven PBT or very Persistent, very Bioaccumulative (vPvB) properties (Moermond at all., 2012).
PEC is estimated based on worst-case scenarios but also considering a number of simplifying assumptions, including that the sewage system is the main route of entry of medicines into the surface water and that there is no retention of the medicines in the wastewater treatment plant (e.g. through adsorption to sludge). Furthermore, metabolization is not considered.

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Discussion of scientific robustness regarding medicinal products for human use

A number of assumptions and criteria related to exposure-based waiving assessment are subject to discussion. The main issues debated concern the relevance of the action limit values set and the indicators used to assess effects.

The action limit values defined in the ERA guidelines determine the number of medicines that will be exempted from a thorough environmental assessment. In this respect, their relevance may have great impacts on the good status of the environment and/or on human health. The European exposure (PEC) trigger (0.01 µg/l) for toxicity testing is based on historical acute environmental toxicology data only (European Medicines Agency, 2006). Although debated that the action limit of 0.01 µg/L set in the guideline for the environmental assessment of medicinal products may be revised in the future to better reflect environmental exposure, the same has not been changed in the proposed draft ERA guideline.

However, several examples are documented in the literature where medicinal products directly cause effects at concentrations near or even below their respective trigger values (e.g. the anti-mycotic agent Clotrimazole which affects algal communities at picomolar concentrations (Porsbring at all., 2009; OSPAR 2013)). The action limit of 0.01 µg/L (i.e. 10 ng/L) is in the majority of cases conservative enough and consistent with the lowest concentration where environmental effects can be observed, even if a few exceptions exist. By contrast, a higher limit of 0.1 µg/L would be too high. However, it is unclear whether the current action limits are sufficiently protective when possible effects of mixtures are considered. In this respect, the action limits of 0.01 µg/L and 100 µg/kg were challenged, and lower values of 0.004 µg/L and 1 µg/kg were recommended, respectively (Montforts, 2005).

Endpoints in the required toxicity testing are growth, mortality and reproduction. Potential effects on molecular, cell, or tissue level responses or on developmental or behavioral effects are typically not considered. There is growing concern and debate regarding the need to include for example behavioral effects, especially for psychoactive drugs, and other non-standard endpoints such tissue level damage (e.g. as assessed via histopathology). Better understanding of how tissue, developmental and behavioral level effects may be extrapolated to possible impact on wild populations and ecosystem services, is however needed to determine their significance. Equally, however, this also applies to all other chemicals tested in regulatory risk assessment frameworks and this debate is beyond the scope of the analyses conducted here for pharmaceuticals.

The adequacy of the current regulatory test triggers and the effects based assessments are also questioned because they rely on tests developed to determine the acute toxicity of industrial chemicals and do not consider the considerable safety and pharmacology information that is available for pharmaceuticals (Ågerstrand et al., 2015; European Medicines Agency, 2016). Most APIs are designed to be nontoxic, but still affect biological systems in specific ways. Therefore, they may cause other types of effects compared to industrial chemicals. This should be reflected in a relevant test strategy, and therefore refinement of the recommended effect studies in Phase II, Tier A has been recommended as improvement of current ERA guideline mainly related to aquatic vertebrates and not to invertebrates and algae, where the testing approach does not fall short in the same way (Ågerstrand et al., 2015).

The relevance of the PNEC/PEC ratio used to characterize the environmental risk is debated within the scientific community. Although PEC/PNEC quotients are considered a pragmatic approach to assess risk and are well detailed by the European Commission, respective uncertainties related to the estimations of PNEC and PEC limit their relevance (UNEP/IPCS). The PEC/PNEC ratio has been scientifically developed and evaluated through extensive studies, and further used in numerous experiments. The results and uncertainties of this method are therefore well known and could be assessed quantitatively and qualitatively. Yet, the full relevance of this indicator has been questioned because, despite the requirement for chronic data in the EMA Guidelines, current PNEC values may be based on acute studies when chronic data is not available. In addition, PNEC values are often based on mortality, whatever the use of acute or chronic data.

Furthermore, PEC values rely on estimations made in specific environmental conditions. They have been criticized for not taking into account the variability of conditions that can significantly influence environmental concentrations of medicinal products (presence/absence and type of manufacturing sites, level of pharmaceutical use, population demographics, cultural practices, environmental and climatic characteristics, dilution potential of receiving environments and infrastructure related to wastewater and drinking water treatment, etc.) Conclusions from the KNAPPE project highlight that the use of simple models, as the EMA model, to calculate PECs for surface water is in general in good agreement with field measurements (KNAPPE, 2008). However, PEC for other compartments than water column would not be well assessed. (BIO intelligence services, 2013)

The ERA framework has been considered as not being optimal with regards to the specificities of medicines compared to other chemicals (e.g. biocides), namely because it especially relies on endpoints such as "death" that do not adequately reflect sub-lethal and ecologically important effects related to chronic exposure. (BIO intelligence services, 2013)

ERA does not consider metabolites or environmental transformation products in the preliminary exposure assessment, which may represent significant hazard in certain cases.

ERA mainly focuses on the aquatic compartments and only considers possible exposure from sludge and sediments in Phase II where considered relevant, although sorption during wastewater treatment has been demonstrated and sludge reuse identified as a key contamination pathway. (BIO intelligence services, 2013)

Heterogeneity in the interpretations of ERA guidelines and implementation

Compliance with ERA guidelines is not uniform in the various MS, as they may interpret the guidelines differently which is however a common issue with evaluation in general and not specific to ERAs. This may therefore result in a lack of consistency concerning ERAs performed within the EU for medicinal products with the same active substance. Performing an ERA may indeed raise some difficulty as MS may have different interpretations of the ERA guidelines and, as such, have different requirements and implement the ERA differently. Even more, sometimes one MS may interpret and have different requirements for the same active substance in different time points of assessment. EMA recognized that the ERA guidelines could be subject to multiple interpretations. It has also to be noted that depending on MS, very few or no experts with environmental background may be in charge of the assessment of ERA dossiers for medicinal products with the same active substance.

Consumption of medicinal products is diverse in different Member States, as well are environmental conditions. In particular the size of river basins as recipients of discharged APIs or metabolites are different, and they may be easily located in different Member States. This means that 'EU-averaged approach' in risk assessment may appear not sufficient.

Impacts of the ERA results in the MA process

In the case of medicinal products for human use, the ERA is not part of the benefit-risk analysis. The environmental risks are not included in the risk/benefit analysis and, therefore, the ERA results have no impact on the decision to provide an authorization. This is also reflected in the ERA guideline, which states that the environmental impact of such medicinal products "*should not constitute a criterion for refusal of a marketing authorization*" (EMA, 2006), notwithstanding the type of procedure followed for the marketing authorization. Under the mutual recognition and decentralized procedures, this further entails that a CMS could not refuse to grant a MA to the applicant on the ground of a potential risk to the environment. The same approach has been followed in the draft guideline, which explicitly states that the environmental impact should not constitute a criterion for refusal of a marketing authorization.

When the possibility of environmental risks cannot be excluded, risk mitigation measures will be established.

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Considerations on lack of or incomplete ERAs, applicable to medicinal products for human use

Unlike in veterinary medicinal products, where a lack of ERA or an incomplete one would normally lead to a refusal of the MA, in the case of medicinal products for human use, a lack of, or incomplete ERA in the MA application does not prevent the granting of the authorization: EMA then requires a "post-authorization commitment" to perform or complete the ERA. Such examples are included in the PARs, incomplete Phase I: additional studies needed as follow-up measures, Phase I provided, but full Phase II assessment required, Phase I and Phase II-Tier A provided, but a Phase II-Tier B is required. However, companies are not obliged to submit this data as the ERA is not included in the risk/benefit balance. This practice has also been reported in MS acting as RMS. Examples include the public assessment reports published by MS stating that the applicant has committed to conduct Phase II assessment as a post approval commitment (PAC).

The approach has been confirmed with the proposed text in the draft guideline published for consultation i.e. the environmental impact should not constitute a criterion for refusal of a marketing authorisation, although including environmental risks in the risk-benefit analysis has been disscussed as measure to improve the ERA (Ågerstrand at all, 2015).

Availability of ERA data and results

EU legislation sets out a general principle of transparency for public access to European Parliament, Council and Commission documents, which include documents drawn up but also received by them. In the field of environment, the principle of transparency and the obligations it entails are set forth in Directive 2003/4/EC153.

Pursuant to Articles 13(3) and 38(3) of Regulation (EC) 726/2004, the EMA publishes a full scientific assessment report called a European Public Assessment Report (EPAR) for every medicine granted a central marketing authorisation by the European Commission. The EPAR must notably include the reasons for EMA's opinion in favour of granting the MA, after deletion of any information of a commercially confidential nature, as well as a summary understandable to the public. In addition, Directive 2001/83/EC provides that the competent authorities must make publicly available the marketing authorisation and the summary of the product characteristics, and mention the obligation for competent authorities to draw up an assessment report, in the same terms as those of Regulation (EC) 726/2004. However, environmental data (including ecotoxicological data) and ERA results are not mentioned as having to be included in the assessment report and/or made publicly available.

In practice, EPARs contain a chapter called Eco-toxicology/Environmental Risk Assessment but, until recently, this was generally only a brief summary mainly focusing on the first step of the ERA, i.e. Phase I (PEC calculation) (Bouvier at all., 2010). For instance, the EPAR only states that "an assessment of the risk was performed and no significant risk to the environment related to the use of entecavir is anticipated". However, even when a Phase II assessment had been carried out, only a short conclusion might be available, but still no environmental data. As an example, the EPAR provides only that "the regulatory and scientific strategy of ERA chosen by the applicant is reasonable and the scope of studies (Phase I and Phase II, Tier 1) acceptable" or "A phase II environmental risk assessment was conducted as the trigger value was exceeded. The active substance is neither persistent, bioaccumulative or toxic (PBT) nor very persistent, very bioaccumulative (vPvB). Risk to the surface water, groundwater, soil, sediment and sewage treatment plant is acceptable". Recent EPARs are however more exhaustive, providing a "summary of main study results", but environmental data is still generally insufficient. There are sometimes examples of EPARs that include environmental data (endpoints). In order to find such information, it would be first necessary to know that the information is actually in the EPAR, and then look through tens of medicinal products before finding a medicinal product concerning which an EPAR was published with environmental data.

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At MS level, the availability of environmental information included in the ERA varies from one State to another. For instance, in Sweden, environmental data for medicinal products in Sweden is publically available, but this data is not calculated along the ERA guidelines adopted by EMA. However, environmental information is not always contained in the assessment made public by national medicine regulators (Keessen at all., 2007). This has been attributed to commercial sensitivity of data contained in the ERA (Keessen, at all. 2012), which is questionable as, as seen above with recent EPARs for human medicinal products, endpoints are sometimes published.

A number of competent authorities publish a public assessment report, within which information on the ERA can be found. The UK Medicines and Healthcare products Regulatory Agency (MHRA) publishes, in its Product information database, EPAR or PAA for some substances which may include information on ERA results and risk mitigation measures. The Spanish Agency of Medicines and Medical Devices (AEMPS) provides links between its online information center on medicines and corresponding EPARs on EMA website; it does not however seem to provide links to public assessment reports. Germany does not make publicly available environmental data about medicinal products for human use but provides information for veterinary medicinal products. Other countries do not provide any information to the public on ERA results like Belgium, Bulgaria, the Czech Republic or Romania, although in this latter country, publication of such information is planned for the future. In France, very limited environmental information is provided by ANSM for medicinal products for human use authorized by ANSM. In the French public assessment reports consulted, this information can be a mere sentence concluding to the absence of environmental risk. Consequently, this environmental information amounts to no information. Even when published, the ERA endpoints may be hard to find (BIO intelligence services, 2013).

Certain pharmaceutical companies may choose to make some ERA data available on their website on a voluntary basis, but it is not common practice.

Risk Mitigation Measures (RMM) and pharmacovigilance

When, following completion of the ERA (at the end of Phase II Tier B), the environmental risks cannot be excluded, risk mitigation measures (RMM) may be imposed on the applicant, i.e. the future holder of the authorization. Directive 2001/83/EC for medicinal products for human use and their related guidelines provide for precautionary and safety measures to be taken.

Article 8(3)(g) of Directive 2001/83/EC states that the MA application must provide the reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment. The relevant EMA (CHMP) guideline on ERA further specifies that such measures may consist of:

- An indication of potential risks presented by the medicinal product for the environment, in the documents communicated to the public (such as the package leaflet); and
- Product labelling, Summary of Product Characteristics (SPC), Package Leaflet (PL) for patient use, product storage and disposal. Labelling should generally aim at minimizing the quantity discharged into the environment by appropriate mitigation measures.

The MA imposes on the authorization holder to indicate precautions for safety and health protection including measures to mitigate the risk for the environment on the medicinal product's packaging or on the leaflet. However, this requirement is legally binding only for the authorization holder; it has only an informative value for prescribers and consumers.

The draft guideline offers additional measures. Namely, the applicants are encouraged to share details on analytical verification of their active substances in the form of a report on analytical verification on their websites or in a general database, especially for those active substances with a risk to the environment. The same applies for information on fate and

ecotoxicological effects as well as for any other environmental information on the active pharmaceutical substance resp. the medicinal product obtained at any time.

An example of good practice in this regard is the case of Sweden, where a risk classification system was put in place, which allows prescribers to have a clear idea of whether a medicinal product is harmful to the environment (whether it was authorized prior to or after 30 October 2005). This classification allows for a ranking of medicinal products, based on their potential risk to the environment (i.e. the PEC/PNEC results): they are ranked as products with insignificant (PEC/PNEC ≤ 0.1), low (0.1 < PEC/PNEC ≤ 1.0), moderate (1.0 < PEC/PNEC ≤ 10) or high environmental risk (PEC/PNEC > 10). A classification was also adopted regarding biodegradation and bioaccumulation of medicinal products in the environment (FASS, 2007, LIF, 2010).

The growing regulatory and scientific concerns regarding pharmaceuticals in the environment have reached the point where some stakeholders are advocating the inclusion of environmental hazard and risk within the patient-benefit evaluation that underpins the marketing authorisation of a drug (Ågerstrand et al., 2014, BIO Intelligence Service, 2013). Currently the environmental risk assessment is conducted in parallel to Phase III clinical trials, i.e. after significant investment in drug discovery and development. The dataset collated, however, indicates that most drugs pose low risk based on the regulatory test endpoints measured and the usage levels in Europe. Irrespective of the outcome of the ongoing regulatory debate developing predictive in silico, *in vitro* and *in vivo* tools and models remains priority as well as their integration earlier within drug development to identify environmental concerns much sooner than operates within the current industry model. These tools will be useful in helping to identify drugs of potential environmental concern and ensure that the right species are chosen for a tailored environmental assessment. The availability of these tools and models will also assist with the prioritization of the>800 legacy drugs that lack any environmental data for definitive regulatory assessments (L. Gunnarsson, et al.2019).

CONCLUSION

The current guideline has been in place for a period of 13 years during which time the ERA outcomes indicate that most human medicinal products pose low or insignificant risk to the environment through patient use, even in many cases with worst case environmental exposure assessments. However, regulatory data gaps still exist for ‘legacy’ substances, authorized before 2006. These APIs should be prioritized.

Whilst data transparency is increasing data accessibility still poses some significant challenges. In the revised guideline, shared use of environmental data for ERA is expected to prevent repetition of experiments and to allow harmonized ERAs on similar products and harmonized SPCs. The vision of the Authorities is to use ERA Masterfile concept that should save resources of applicants and authorities. This would enable the Regulatory bodies to waive ERA studies for compounds where studies have already demonstrated a lack of environmental risk (even with potential increased use) and no ERA updates would be required based on existing data generated under the current ERA guideline for APIs with a low risk/ high margin of safety. However, there is uncertainty how data sharing of ERA will work. This might increase cost and time for preparation of ERA and result with potential delay of market entry. The draft guideline provides technical guidance to increase consistency in assessment and describes a tailored assessment for certain groups of active substances due to their specific mode of action, such as endocrine active substances (EAS) and antibiotics.

Scientific evaluation does not always allow a risk to be determined with sufficient certainty, in this regard precautionary principle should be applied. Skills and expertise are required to explore risks of older products where data exist. Link between EU pharmaceutical legislation and EU environmental legislation (e.g. Water framework directive) is needed.
It can be concluded that Environmental Risk and its assessment as a very dynamic field requires vigilance, risk mitigation, as well as both, legislative and non-legislative actions.

REFERENCES

1. Ågerstrand, M., Edvardsson, L., Rudén, C., (2014) Bad reporting or bad science? Systematic data evaluation as a means to improve the use of peer-reviewed studies in risk assessments of chemicals. Human and Ecological Risk Assessment: An International Journal 20, 1427–1445.
2. Ågerstrand, M., Berg, C., Bjorlenius, B., Breitholtz, M., Brunstrom, B., Fick, J., Gunnarsson, L., Larsson, D.G.J., Sumpter, J.P., Tysklind, M., Ruden, C., (2015) Improving environmental risk assessment of human pharmaceuticals. Environ. Sci. Technol. 49, 5336–5345.
3. BIO Intelligence Service, (2013), Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers.
4. Bouvier M., Durand F., Guillet R. (2010) Médicament et environnement, La régulation du médicament vis à vis du risque environnemental, Annex 12. Response of French authorities to a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study
5. Boxall, A., Rudd, M.A., Brooks, B.W., Caldwell, D.J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J.P., Verslycke, T., (2012) Pharmaceuticals and personal care products in the environment: what are the big questions? Environmental Health Perspectives, 120: 1222.
6. Buser, H., T. Poiger, et al. (1999). "Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater." Environ. Sci. Technol. **33**: 2529-2535.
7. Communication on "Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector" COM (2008) 666 Final Directive 2001/83/EC of the European Parliament and the council of 6 November 2001 on the
7. Community Code Relating to Medicinal Products for Human Use; European Parliament, 2001.
8. EMA (2006). "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use." EMEA/CHMP/SWP/4447/00 corr 2
9. EMA (2016). "Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'." EMA/CHMP/SWP/44609/2010 Rev. 1
10. EMA (2018). "Guideline on the environmental risk assessment of medicinal products for human use - Draft." EMEA/CHMP/SWP/4447/00 Rev. 1
11. FASS (2007) Environmental classification of pharmaceuticals in www.fass.se – guidance for pharmaceutical companies, 17pp. Available at: www.fass.se/res/RootMedia/Pdf/2007%20Environmental%20classification%20guidance%20document.pdf
12. GACE. (2007) Pharmaceuticals in the environment. German Advisory Council on the Environment Statement April 2007. No. 12. Available at: http://www.umweltrat.de/english/edownloa/statemen/Stellung_Pharmaceuticals_in_the_Environment_2007_eng.pdf
13. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet, 365: 579-587.
14. Gunnarsson L., Snape R.J., Verbruggen B, Owen F.S, Kristiansson E, Margiotta-Casaluci L, Österlund T, Hutchinson K, Marks D.L.B, Tyler R.C (2019) Pharmacology beyond the patient – The environmental risks of human drugs, Environment International 12:9 320–332
15. Halling-Sørensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, Holten Lu¨tzhøft HC, Jørgensen SE. (1998). Occurrence, fate and effects of pharmaceutical substances in the environment—a review. Chemosphere, 36:357–393.
16. Jørgensen SE, Halling-Sørensen B. (2000) Drugs in the environment. Chemosphere, 40:691-9.
17. Keessen A, Freriks A, van Rijswick M. (2012) The Legal Instruments for the control of emissions of medicines for human and veterinary use, Universiteit Utrecht.
18. Keessen A, Freriks A, van Rijswick M, Montforts MHMM, Keessen AM. (2007) The public nature of environmental information acquired at the registration of (veterinary) medicines. RIVM report 601500006/2007.

19. KNAPPE project (2008). Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. Final report, available at: environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf
20. Kümmerer K. (2008) Pharmaceuticals in the Environment: Sources, Fate, Effects And Risks . Berlin, Heidelberg: Springer Berlin Heidelberg
21. Küster, A.; Adler, N. (2014) Pharmaceuticals in the environment: Scientific evidence of risks and its regulation. Phil. Trans. R. Soc., B 369, 20130587. 1-2
22. Larsson DGJ. (2014) Pollution from drug manufacturing: review and perspectives. Phil. Trans. R. Soc. B 369: 20130571. Royal Society 1-6
23. LIF (2010) Swedish environmental classification of pharmaceuticals. 12pp. Available at: http://www.lif.se/default.aspx?id=29916
24. Loos R, Marinov D, Sanseverino I, Napierska D and Lettieri T, Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List, EUR 29173 EN, Publications Office of the European Union, Luxembourg, 2018, ISBN 978-92-79- 81839-4, doi:10.2760/614367, JRC111198
25. Ministère de l'Ecologie (2010) Médicament et Environnement: La régulation du médicament vis-à-vis du risque environnemental. 199p. Available at: http://www.cgedd.developpement-durable.gouv.fr/IMG/pdf/007058-01_rapport_cle2ef48b.pdf
26. Moermond CTA, Janssen MPM, de Knecht JA, Montforts MHMM, Peijnenburg WJGM, Zweers PGPC, and Sijmy DTHM. (2012) Integrated Environmental Assessment and Management — Volume 8, Number 2—pp. 359–371
27. Montforts MHMM. (2005) The trigger values in the environmental risk assessment for (veterinary) medicines in the European Union: a critical appraisal. RIVM Report 601500002/2005.
28. OSPAR (2013). Background Document on Clotrimazole (2013 update). Available at: www.ospar.org/documents/dbase/publications/p00595/p00595_bd%20on%20clotrimazole%20update%202013.pdf
29. Porsbring T, Blanck H, Tjellström H, Backhaus T. (2009) Toxicity of the pharmaceutical clotrimazole to marine microalgal communities. Aquatic toxicology, 91:203–11.
30. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of pharmaceuticals for human and veterinary use and establishing a European Medicines Agency.
31. Regulation (EU) No 1235/2010 OJ L 348 31.12.2010, p. 1-6, Directive 2010/84/EU OJ L 348 31.12.2010, p. 74 (part of so called "pharmacovigilance legislation")
32. Roos, V., Gunnarsson, L., Fick, J., Larsson, D.G.J., Ruden, C., (2012) Prioritising pharmaceuticals for environmental risk assessment: towards adequate and feasible firsttier selection. Sci. Total Environ. 421, 102–110.
33. Schuster A, Hädrich C, Kümmerer K. (2008), Flows of active pharmaceutical ingredients originating from health care practices on a local, regional, and nationwide level in Germany – is hospital effluent treatment an effective approach for risk reduction? Water Air Soil Poll, 8:457–471.
34. Verbrugh HA, de Neeling AJ. (Eds.) (2003), Consumption of Antimicrobial Agents and Antimicrobial Resistance Among Medically Important Bacteria in the Netherlands. SWAB NETHMAP
35. Whomsley, R, Brendler-Schwaab S, Griffin E, Jensen J, Moermond C, Scholz B, Sortvik Nilssen L, Stemplewski H, Roennefahrt I, (2019) Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. Environ Sci Eur (2019) 31:17

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