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Human pharmaceuticals: Why and how to reduce their presence in the environment

Audrey Courtier, Axelle Cadiere and Benoit Roig

The presence of human pharmaceutical products in the environment is a source of concern for both the environment and public health. Numerous options exist to reduce the release of pharmaceuticals, with several approaches being previously described. This article aims to describe the new trends.

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Introduction

In recent decades, the presence of human pharmaceutical products (also known as pharmaceutical residues; PPs) in the environment has become a growing environmental concern worldwide. These substances are of particular interest given that some are produced and used in large quantities and may end up in the aquatic environment, where they are persistent or pseudo-persistent [1,2]. In addition, they can have a biological effect on non-target organisms (Table 1) [3–5].

PPs also have the potential for bioaccumulation in aquatic and terrestrial organisms in the environment [6,7], thus becoming a major threat to fauna, flora, and, potentially, human health security (in particular from indirect exposure through the food chain [8] or the antibiotic resistance [9]).

Sources of PPs in the environment have been well identified: they are not only direct via patient excretion, industrial activities, and livestock activities, but also indirect via improper discharge or untreated wastewater.

Many studies have indicated the relative and often-limited effectiveness of wastewater treatment in wastewater treatment plants [10–15] due to especially the molecules considered and processes implemented. Main consequence is the release of PPs and/or their residues into the environment at concentrations in the order of ng to µg/L. These substances are found either in unchanged forms or in metabolized or transformed forms [16–18]. Environmental organisms are thus exposed, and many questions have been raised concerning the risks to the environment and, to a lesser extent, to human health [19,20].

The regulations are quite limited concerning pharmaceuticals and the environment. The Environmental Risk Assessment (ERA) of PPs in drug development is now well established (since 2006) and allows "substances of concern" to be identified before marketing authorization in line with EU guidelines. However, PPs are not identified in the existing environmental legislation (e.g., Groundwater, Drinking Water, and Water Framework Directives), although the European Commission has recognized in a communication dated 2008 (objective 12 [21]) that the pollution of water and soil by pharmaceutical residues is an emerging environmental and public health problem against which measures should be taken.

In its statement proposing an action plan to counter the growing threats of antibiotic resistance (2011), the European Commission noted that environmental pollution by antibiotics contributes to accelerating the emergence and spread of resistant microorganisms [22]. In 2015, the Commission established the first EU-wide vigilance list for substances subject to monitoring under Article 8 ter of Directive 2008/105/EC. The substances on this list were selected based on their likelihood to present a significant risk to or via the environment in light of available information. These include the following pharmaceutical substances: 17-alpha ethynyl estradiol, 17-beta estradiol, estrone, diclofenac, as well as three macrolide antibiotics, namely erythromycin, clarithromycin, and azithromycin. A recent revision presented an update of the list with a proposal of 2 other pharmaceutical products, namely amoxicillin and ciprofloxacin [23]. The European Commission also committed to developing a strategic approach for the consideration of the problematic of pharmaceuticals in the environment, including legislative and non-legislative solutions such

Table 1

Example of effect on non-targets organisms recently described.

Molecule	Species	Effects	Exposure dose	Ref.
CBZ	Venerupis decussate, Venerupis philippinarum (clams)	induction of glutathione reductase, superoxide dismutase and cytochrome P450 3A4 activities	0.03–9 µg/L	[3]
Diclofenac	*Mytilus galloprovincialis* (marine bivalve)	Down or up regulation of gene transcription in early developmental stages	1 µg/L	[4]
Antidepressant (fluoxetine, citalopram, venlafaxine, ...)	Various invertebrates, fishs, amphibians	Various effects such as altered swimming, predation or sexual behavior, decrease of reproduction, ...	ng to µg/L	[5]

as the development of improved source control approaches and end-of-pipe solutions, and better data sharing to ensure a coherent basis for ERA [24]. More recently on 10 April 2018, the European Federation of Pharmaceuticals Industries and Association (EFPIA) signed a joint declaration "recognizing and understanding the concerns regarding the presence of pharmaceuticals in the environment" [25].

Thus, in this context of limited regulation and uncertainties about the environmental and human health risks associated with the presence of PPs in the environment, numerous initiatives are now being taken to reduce their release and therefore this environmental pressure.

These initiatives concern two complementary approaches. The first seeks to find solutions before PPs are released into the environment by addressing the issues of the production, prescription, distribution, and use of medicines. The second approach is implemented once PPs are in the environment and preferably concerns treatment, remediation, and monitoring. While various publications have already described the reduction actions [26,27], the remainder of this article will summarize the initiatives already implemented and explain new trends in both the "***upstream***" (before release) and "***downstream***" (after release) approaches.

The life cycle of the produced pharmaceuticals can be simplified into three main phases: (1) development and production, (2) usage, and (3) environmental behavior. In each of these phases, actions and actors are identified as summarized in Figure 1.

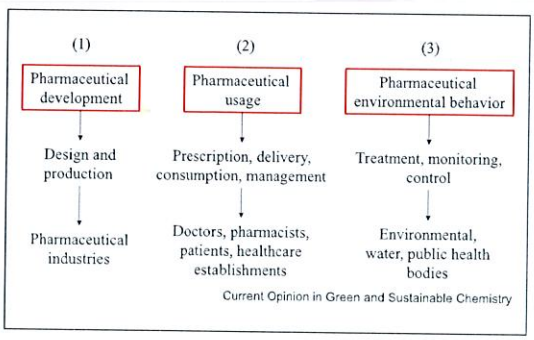
Trends in upstream initiatives

It is possible to act during the three phases of the pharmaceutical life cycle to reduce the impact of PPs in the environment as already detailed in the literature.

Kümmerer et al. [28] described the concept of benign by design in green pharmacy. As the complement to green chemistry, which involves developing more environmentally compatible industrial processes, green pharmacy applies to the manufacture of a new generation of PPs with safer environmental behaviors while maintaining the pharmacological properties and therapeutic efficacy of molecules. For example, substances with very specific actions that are more biodegradable and metabolized into inactive by-products will have a limited environmental impact: they will have no effect on non-target organisms, will be excreted in non-active residues, and have a lower persistence. However, initiatives in this direction are extremely limited because of the low interest of industries to modify existing molecules (expensive and without compensation) as well as the trend of new-generation molecules such as monoclonal antibodies [29].

In terms of usage, training and information for health professionals should promote a better consideration of environmental issues related to health activities. This is a delicate task, because it is not a question of encouraging environmental risk to the detriment of medical good. This ethical issue is beginning to emerge as described by Balch et al. [30] regarding the use of antibiotics. He particularly suggested that Van Rensselaer Potter's original conceptualization of bioethics can be used to balance clinicians' obligations to protect individual, public, and environmental health.

Figure 1



Pharmaceutical life cycle and actors.

However, actions at the consumer level must be at the forefront. Indeed, it is well recognized that the main source of PP release into the environment is individual households in particular for human medicines in industrialized countries (*vs* emerging markets).

Patient education can begin at the level of health professionals. As early as 2005, Sweden was the first country to propose an environmental classification to doctors, allowing them to prescribe the drug with the lowest possible environmental impact with equivalent therapeutic activity [31,32]. More recently, in France, an association of health professionals [33] has worked within the framework of eco-prescription. In a very simple way, the doctor puts an "ECOP" (i.e., eco-prescription) easel on his desk, highlights the poster "stop drugs in stock," indicates "return unused medicine" on the prescription, and favors the molecule with the lower persistence, bioaccumulation, and toxicity (PBT) index (based on the Swedish environmental classification). Subsequently, the pharmacist promotes the eco-responsible attitude of the population during the delivery of treatment.

Patient education can also be done through public health advertising campaigns. Indeed, unlike commercial campaigns that are the source of overconsumption (especially for over-the-counter medicines), national campaigns have shown their effectiveness. The example of antibiotics is very significant in this respect. The first campaigns in France in 2001 using the slogan "antibiotics are not automatic" made it possible to reduce consumption by more than 25% over 5 years [34]. Since then, national campaigns in many other countries have also been launched in Europe and around the world along with the European and World Antibiotic Awareness Day, respectively [35,36].

Consumption can also be modified by financial incentives. Several countries are experimenting with different approaches such as in France (agreement with health insurance to prescribe less or better), the UK (prescription budget negotiated with the NHS), and the USA (pre-authorization via insurers). Financial incentives can also affect patients with delisting procedures for certain drugs. Examples have shown falls in sales via this process, even if they are generally accompanied by an increase in the sales of alternatives [37].

Medical practices must also play a role in reducing consumption. Beyond the doctor–patient relationship, which has evolved considerably in recent years, particularly in terms of patients' use of the Internet, new practices are also being tested. In France, for example, consideration is given to pharmacists' method of payment. Currently, pharmacists are paid based on sales, and the more they sell, the higher their turnover. Several countries are experimenting with therapeutic meetings between patients and pharmacists in order to have a global vision of the pharmacist regarding the totality of the patient's drug intake and thus be able to envisage a more coherent and overall lower intake [38,39]. Medicine is also evolving with more personalized healthcare and better diagnostics as discussed recently by Straub [40].

Changes in sales methods are also being tested. In many countries, medicines are distributed in boxes (such as Belgium, Austria, Sweden, Italy, and France). However, the trend to sell the exact number of pills, as already implemented in some countries (the Netherlands, UK, and Czech Republic), is now expanding. France is testing this approach in several regions for the sale of certain antibiotics. The first year showed a 10% decrease in the number of pills supplied and an improvement in the compliance to antibiotic treatment [41].

As for patients, it is essential that their behavior toward drugs changes. Overconsumption is generally caused by three main phenomena: non-adherence to the treatment, most often resulting in relapse and therefore a new treatment; self-medication; and the management of leftover drugs. Moreover, precautionary principle should also be applied: no pain, no drugs. These aspects have been well described by Daughton et al. [42].

Trends in downstream initiatives

Concerning the environmental behavior of PPs after their release into the environment, many articles describe the need for sanitation and drinking-water treatment on the one hand and monitoring and control tools on the other [43,44]. Numerous developments have been made in terms of new processes and high-performance analytical methods. However, in both cases, advanced solutions are not entirely relevant to the issue. Indeed, given the diversity of pharmaceutical molecules on the market, no treatment is completely effective for all molecules (for example, adsorption by activated, membrane bioreactor [45]. Therefore, a coupling of processes would be necessary to ensure the total elimination of drugs, although this is too expensive to be implemented on a large scale [46,47]. Alternative solutions of elimination are currently being proposed based on processes with a lower carbon footprint and, above all, lower costs. They are mainly used as tertiary treatment such as for examples wetlands [48], plant-based remediation capitalizing on the uptake potential of certain plants [49], or bioremediation using bacteria [50], fungi [51,52], and enzyme-type [53,54] biomolecules seem to provide interesting results.

Concerning control and monitoring, the limitations relate to the number of substances potentially analyzed as well as the relevance of measuring increasingly low

concentrations for which the impacts are unknown (unexpected). Thus, after spending decades developing advanced analytical techniques, developments are moving toward more global and predictive systems based on generic tests or the use of proxies or indicators. For example, like polycyclic aromatic hydrocarbons of which benzo[a]pyrene is often a representative, increasing numbers of studies are exploiting the presence of carbamazepine as a marker of drug contamination and, more generally, urban contamination [55]. To help healthcare managers to analyze and manage their effluent without facing exorbitant analytical costs, recent work has described the use of an environmental establishment indicator based on a calculation that takes into account the predicted environmental concentration, predicted no effect concentration, and PBT index [56].

Conclusion

PPs are necessary for the survival of humankind, but today they represent an important threat (for the environment and potentially human health) that should be taken into account. Many studies have been undertaken over the past 30 years to understand the sources and fate of PPs in the environment and their impact on aquatic and terrestrial populations (including humans). Solutions have been and are regularly implemented to reduce their presence in the environment.

However, there remains a gap in the assessment of the risks associated with the presence of PPs. Even if studies have been conducted on this issue and demonstrated that environmental risks are expected for certain substances, there are still many uncertainties due to the lack of knowledge about new parameters: for example, the transfer from water to soil and edible plants, the translocation of PPs in plants, risks linked to irrigation and water reuse, long-term molecular effects on biological organisms, and the impact on the F2 and F3 generations. This is the challenge for the years to come. It should be noted that a similar challenge is required for veterinary pharmaceutical product [57].

Conflict of interest statement

Nothing declared.

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