Pharmaceutical Pollution: The Brazilian Context

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Definition

The occurrence of pharmaceuticals in the environment is an everyday recognized concern worldwide, and drugs as environmental contaminants have been detected in water and soil systems, posing risks to humans and wildlife. Drugs in wastewater, groundwater, and even drinking water occur in several countries, including Brazil, where the pharmaceutical market is expanding over the years. The adverse, harmful effects of pharmaceuticals in the environment range from the spreading of antimicrobial resistance and species survival to the interference with reproduction and increased cancer incidence in humans. The awareness of emerging contaminants in the environment, besides the joint effort of authorities, consumers, and the general public nationwide, will be required to avoid pharmaceutical/drug pollution and achieve an eco-friendly environment and a sustainable society.

1. The Pharmaceutical and Healthcare Market and Industry in Brazil

By a recent report of the Association of the Pharmaceutical Research Industry (INTERFARMA, Brazil), a non-profit association that represents almost 50% of all Brazilian pharmaceutical retail, which comprises drugstores and pharmacies, the revenues in the Brazilian pharmaceutical market increased from US$21.89 to 80.6 billion, from 2005 to 2018, This market volume reached a cumulative revenue of US$586.6 billion, as estimated by the Brazilian Medication Market Regulating Chamber. The Brazilian pharmaceutical trade is expected to reach a value of over US$40 billion by 2023, exclusively regarding prescription, over-the-counter, generic, and similar medicines. In Latin America, Brazil is one of the main markets, besides Mexico, Colombia, and Argentina, with more than two hundred regularized pharmaceutical laboratories. Such data and estimates point that Brazil can reach a position among the top five major global pharmaceutical markets currently led by the U.S., China, Japan, and Germany [1]. Globally, the Brazilian pharmaceutical trade and industry is only a fraction of an anticipated US$1.5 trillion global market by 2028 [2], but still, a significant growing market with a large horizon to expand. In this context, higher sales and consumption imply higher quantities of chemicals entering the environment. Only in São Paulo city, the region most economically active and with the highest gross domestic product in Brazil, several metric tons of non-steroidal anti-inflammatory drugs, anti-diabetic and antihypertensive drugs, and steroid hormones have been consumed in the last years [3]. In Brazil, among the most commercialized medicines, muscle relaxants, and medications to treat deep venous thrombosis leads to internal sales (Table 1), in a commercial volume that exceeds the third-place medicine ranked among the best-seller drugs in the world.

Table 1. Medicines and pharmaceutical products with the highest sales in Brazil, according to their active ingredient(s) and therapeutic indication(s).

Ranking	Pharmaceuticals Products	Therapeutic Indication
1	Dorflex® (dipyrone monohydrate, orphenadrine citrate, and caffeine)	To relieve pain associated with muscle contractures, including tension headache

Ranking	Pharmaceuticals Products	Therapeutic Indication
2	Xarelto® (rivaroxaban)	To prevent venous thromboembolism in adult patients undergoing elective knee or hip arthroplasty surgery
3	Saxenda® (liraglutide)	Chronic weight control in adults with a Body Mass Index of 27 kg/m^2 or more
4	Neosaldina® (dipyrone, isomethetene mucate, and anhydrous caffeine)	To treat various types of headache, including migraines, or for the treatment of colic
5	Addera D3® (cholecalciferol)	Auxiliary treatment of bone demineralization (removal of minerals) before and after menopause, rickets, osteomalacia, osteoporosis and in the prevention of falls and fractures in older adults with vitamin D deficiency
6	Glifage XR® (metformin hydrochloride)	To treat type 2 diabetes in adults, alone or in combination with other oral anti-diabetics. Also used to treat type 1 diabetes in addition to insulin therapy and indicated to treat Polycystic Ovary Syndrome
7	Torsilax® (caffeine, carisoprodol, diclofenac sodium and paracetamol)	To treat rheumatism in its acute and chronic inflammatory-degenerative forms: acute gout crisis, acute inflammatory, post-traumatic and post-surgical states, acute exacerbations of rheumatoid arthritis or other rheumatic arthropathies, osteoarthritis, and acute states of rheumatism in extra-articular tissues, low back pain or low back pain. Also, an adjunct to severe inflammatory processes resulting from infectious conditions
8	Victoza® (liraglutide)	Chronic weight control in adults with a Body Mass Index (BMI) of 27 $kg\ m^{-2}$ or more
9	Anthelios® (avobenzone, homosalate, octisalate, octocrylene and oxybenzone)	Sun protection

Ranking	Pharmaceuticals Products	Therapeutic Indication
10	Puran T-4® (sodium levothyroxine)	In patients with hypothyroidism of any etiology (except for transient hypothyroidism, during the recovery phase of subacute thyroiditis), a replacement therapy or hormonal supplementation. Suppression of pituitary TSH in the treatment or prevention of various euthyroid goiter types, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), thyroid-dependent follicular and papillary carcinomas. Upon diagnosis in suppression tests, aiding in the diagnosis of suspected mild hyperthyroidism or an autonomous thyroid gland.
11	Selozok® (metoprolol succinate)	Arterial hypertension: reduction in blood pressure, morbidity, and risk of mortality from the cardiovascular and coronary origin (including sudden death); Angina pectoris; Adjuvant in the therapy of symptomatic chronic heart failure, mild to severe; Changes in heart rhythm, including especially supraventricular tachycardia; Maintenance treatment after myocardial infarction; Functional cardiac changes with palpitations; Migraine prophylaxis
12	Aradois® (losartan potassium)	To treat hypertension and the treatment of heart failure when therapy with ACE inhibitors is no longer adequate.
13	Sal de Eno® (sodium bicarbonate, sodium carbonate and citric acid)	Relief from heartburn, poor digestion, and other stomach disorders, such as excess stomach acid and acid indigestion
14	Novalgina® (dipyrone monohydrate)	Analgesic and antithermic
15	Jardiance® (empagliflozin)	Diabetes mellitus type 2
16	Alenia® (budesonide and formoterol)	To improve and control shortness of breath in patients with bronchoconstriction or bronchospasm in patients with bronchial asthma.
17	Prolopa® (levodopa and benserazide)	Parkinson's disease
18	Galvus Met® (vildagliptin and metformin)	Diabetes mellitus type 2

Ranking	Pharmaceuticals Products	Therapeutic Indication
19	Ninho Fases 1+® (milk infant formula)	Food supplement
20	Venvanse® (tablisdexanfetamine)	Attention deficit hyperactivity disorder.

Source: Interfarma, 2019; Sanofi, 2014; Bayer, 2018; Novo Nordisk, 2016; Takeda Pharma Ltd., 2013; Mantecorp Farmasa, 2019; Merck S/A, 2014; Neo Química, 2019; Novo Nordisk, 2014; Sanofi, 2020; AstraZeneca, 2018; Biolab, 2019; GlaxoSmithKline Brasil, 2019; Sanofi, 2017; Boehringer Ingelheim, 2018; Biosintetica, 2014; Produtos Roche Químicos e Farmacêuticos S.A., 2019; Novartis, 2018; Shire, 2019.

2. Pharmaceutical (Drug) Pollution

In such an expanding pharmaceutical and healthcare market and industry, in Brazil, drug pollution emerges as an unprecedented local and worldwide public health concern, even if it is not perceptible as an environmental and health threat by the general public [4]. Besides the steadily bulky discharges of untreated or inappropriately treated industrial wastewater, pharmaceutical pollution includes the active ingredients and the final medicinal products (micropollutants) discarded by residences and healthcare systems [5][6]. Even illicit drugs and their metabolites related to drug abuse, like cocaine, methamphetamine, opioids, ketamine, benzoylecgonine, among others, have been detected in wastewaters of several urban localities, contributing to increasing the problem with water quality [7][8].

One of the most significant environmental and public health concerns is related to the active pharmaceutical ingredients (APIs) and medicines discharged in the water bodies. This preoccupation is because their hazardous concentrations do not necessarily follow a typical dose-response curve of toxicity, by which their cumulative quantities of contaminant could cause a deleterious effect [9]. Notably, this is the case of the endocrine-disrupting chemicals (EDCs) that are harmful to wildlife and humans at low, minute concentrations. Other factors that make environmentalists' and scientists' concerns alarming are the potential persistence of APIs in the environment and their metabolism, which occurs through biotransformation and can increase and perpetuate these bioactive substances' harmful effects on the environment [10]. Thus far, the emission of APIs/PPCPs as pollutants in the environment is a critical issue that needs to be evaluated and widely discussed because of its inherent local and global relevance. Significantly, this issue relies on the fact that attention is usually focused on environmental pollution caused by large quantities and volumes of hazardous residues from chemical and processing industries and final products, like plastics, rather than the APIs. The healthcare industry's expansion correlates with a concomitant increase in the volume of pharmaceutical waste due to the increase in the number of consumers and patients, consumption of over-the-counter and prescription medicines, and excessive production of medications [11]. Moreover, the increase in the production, diversification, and consumption of PPCPs, which includes facial creams and cleansers, sun blockers, repellents, fragrances, among others, contribute to the overall concern and overload of APIs/PPCPs in the environment that could result in drug contamination and pollution [12].

3. Disposal of Expired, Unused, or Unwanted Medicines

Invariably, medicines purchased and maintained by consumers are unintentionally accumulated in their homes and become useless for different reasons, like expired date, the excessive amount due to changes in the treatment or dosage regime, prescription in excess or excessive dosage, preservation for presumable usage in the future, over-the-counter medicine retailers and leftover from finished treatment,

to mention a few [13]. Indeed, in most places of the world, these leftovers are commonly and inappropriately discarded by citizens in the ordinary garbage and sewers, as lack of own personal attention, lack of understanding, knowledge, and education, or even by absence of proper governmental and healthcare authorities' directions and regulations [11]. Controlling the discharge of pharmaceutical pollutants in the environments, particularly aquatic systems, requires different strategies and technologies, like, for example, the commitment of manufacturers to avoid the emission of harmful APIs, application of green-chemistry principles for production process and remediation, and medicine-disposal and educational campaigns, like reverse logistic, and regulation for consumers and traders [11][14][15]. In an attempt to draw guidelines for the proper disposal of drugs that become useless, many developed countries have already established some strategies, programs, and regulations to minimize the pharmaceutical pollution risk posed to the environments caused by the improper disposal of expired, unused, or unwanted medicines [11][15]. Despite international attention on pharmaceutical pollution as a growing environmental threat, locally, the subject's legislation is still unfinished in Brazil. Only draft directives are under consideration and waiting for a final definition by vote since the last decade in the lower deputy house [16]. However, few isolated actions by private institutions and governmental authorities in some Brazilian states and cities joined efforts to collect and handle this category of micropollutants.

4. Pharmaceutical Pollutants in Water Bodies

Pharmaceuticals are biologically active substances of which the occurrence in distinct environmental compartments, particularly water systems, and the potential health risks they pose to living organisms, including humans, cannot be underestimated. Usually, effluent treatment in conventional WWTPs is not sufficiently efficient to remove all physicochemically diverse APIs discharged in wastewaters. The efficiency of pharmaceutical and chemical removal varies according to the technologies of wastewater treatment, and these technologies do not work well to remove the entirety of bioactive chemicals from sewage effluents [7][10]. For instance, Komolafe et al. [17] investigated the occurrence and effectiveness elimination of several chemicals from different classes (e.g., triclosan, polycyclic aromatic hydrocarbons, estrogens, and polybrominated diphenyl ethers), ranging from 0.1 to 49 μg L^{-1}, in three technologically diverse full-scale WWTPs. These technologies comprised conventional activated sludge (CAS), waste stabilization ponds (WSPs), and up-flow anaerobic sludge blanket reactors (UASBs) and represent the leading technologies used for wastewater treatment in Brazil. Accordingly, the wastewater treatment system that best performed for such bioactive chemicals was the WSP with an 89–99% removal efficiency, comparable to CAS. However, despite the considerable high capacity of removal achieved by all three waste treatment systems, the residual effluent concentrations of bioactive compounds (triclosan and estrogens) were above their environmental quality standards, posing the aquatic biota at potential risk [17]. These facts are of crucial importance concerning pharmaceutical pollution nationwide. Brazil, which reached a population of over 213 million in 2020 and has one of the most expressive extensions of coastal seawater (~8000 km) and resources of surface freshwater globally (~12% of the total), counts with less than 3000 WWTPs. In terms of the number of WWTPs in operation, the configuration most commonly adopted is an anaerobic pond followed by a facultative pond. Another design of WWTPs operating in Brazil comprises the UASBs followed by CAS [18]. These WWTPs account for only 40% of sewage treatment, based on the volume of sewage treated to the volume of water consumed, or approximately 70% if it is considered the volume of sewage treated regarding the volume of sewage collected [18][19].

In Table 2, some APIs and PCPPs found in several kinds of water bodies and sediments in Brazil are summarized.

Table 2. Some reported APIs and PCPPs found in water bodies and sediment in Brazilian territory.

Environment Compartment	Sampling Locality (Brazilian State)	API/PCPP Pollutants (Mean or Range of Concentration)	Refs.
Water Reservoir	Water source (SP)	acetominophen (0.03 μg L^{-1}), benzophenone-3 (170.87 μg L^{-1}), diclofenac (0.02 μg L^{-1}), ibuprofen (0.01 μg L^{-1}), methylparaben (1.14 μg L^{-1}), naproxen (0.01 μg L^{-1}),	[20]
River (Surface Water)	Urban water (SP)	norfloxacin (8–18 ng L^{-1})	[21]
River (Surface Water)	Lagoon Complex (RJ)	acetaminophen (0.09–0.14 μg L^{-1}), bisphenol a (0.22 μg L^{-1}), diclofenac (1.37–39.86 μg L^{-1}), salycilic acid (1.65–4.81 μg L^{-1})	[22]
River (Surface water)	Urban stream (SP)	atenolol (1182 ng L^{-1}), caffeine (14955 ng L^{-1}), carbamazepine (71.9 ng L^{-1}), diclofenac (92.6 ng L^{-1}), 17-α-ethinylestradiol (<0.16 ng L^{-1}), 17-β-estradiol (1.85 ng L^{-1}), estrone (6.90 ng L^{-1}), ibuprofen (185.3 ng L^{-1}), naproxen (103.7 ng L^{-1}), paracetamol (3702 ng L^{-1}), propranolol (15.2 ng L^{-1}), triclosan (35.2 ng L^{-1})	[23]
River (Surface Water)	Suburban water (MG)	bisphenol A (8.6–168.3 ng L^{-1}), diethyl phthalate (5.0–410.9 ng L^{-1}), 17-α-ethynylestradiol (5.6–63.8 ng L^{-1}), 17-β-estradiol (5.6–63.8 ng L^{-1}), nonylphenol (25.9–1435.3 ng L^{-1})	[24]
Tap water	Source/drinking water (SP)	Cocaine (6–62 ng L^{-1}), benzoylecgonine (10–1019 ng L^{-1})	[25]
Coastal water	Urban surface runoff (SP)	acetaminophen (18.3–391.0 ng L^{-1}), atenolol (0.1–140.0 ng L^{-1}), benzoylecgonine (0.9–278.0 ng L^{-1}), carbamazepine (0.1–8.0 ng L^{-1}), chlortalidone (0.1–0.4 ng L^{-1}), citalopram (0.2–0.4 ng L^{-1}), clopidogrel (0.1–0.2 ng L^{-1}), cocaine (0.2–30.3 ng L^{-1}), diclofenac(0.9–79.8 ng L^{-1}), enalapril (2.2–3.8 ng L^{-1}), losartan (3.6–548.0 ng L^{-1}), orphenadrine (0.2–1.5 ng L^{-1}), rosuvastatin (2.5–38.5 ng L^{-1}), valsartan (19.8–798.0 ng L^{-1})	[26]

Environment Compartment	Sampling Locality (Brazilian State)	API/PCPP Pollutants (Mean or Range of Concentration)	Refs.
Amazon wetland	Surface water and sediment (MA)	Surface water: acetaminophen (455–1716 ng L^{-1}), albendazole (<4–22 ng L^{-1}), caffeine (29–7940 ng L^{-1}), carbamazepine (7–3 ng L^{-1}), diclofenac (<100–463 ng L^{-1}), ethylparaben (<52 ng L^{-1}), furosemide (<52–112 ng L^{-1}), ibuprofen (<100–320 ng L^{-1}), lidocaine (<20–41 ng L^{-1}), mebendazole (4–18 ng L^{-1}), methylparaben (<20–660 ng L^{-1}), sulfamethoxazole (<20–120 ng L^{-1})Sediment: albendazole (1–13 ng g^{-1}), avobenzone (51 ng g^{-1}), benzophenone-3 (<3–17 ng g^{-1}), caffeine (6–20 ng g^{-1}), enalapril maleate (1 ng g^{-1}), ketoconazole (<5–277 ng g^{-1}), mebendazole (<1–4 ng g^{-1}), methylparaben (<5–14 ng g^{-1}), nifedipine (75–105 ng g^{-1}), propranolol (2–2 ng g^{-1}), triclocarban (<1–1318 ng g^{-1}), triclosan (50–137 ng g^{-1})	[27]
Marine sediment	Submarine sewage outfalls (SP)	nonylphenol (13.3 to 72.5 ng g^{-1}), octylphenol (49.2 ng g^{-1}), triclosan (3.3 ng g^{-1})	[28]
Marine sediment	Watershed, Bay (BA)	atenolol (0.48–9.84 ng g^{-1}), carbamazepine (<0.10–4.81 ng g^{-1}), diazepam (<0.10–0.71 ng g^{-1}), diclofenac (<0.10 to 1.06 ng g^{-1}), erythromycin (<0.10–2.29 ng g−1), ibuprofen (0.77–18.8 ng g^{-1}),	[29]
Wastewater Effluent	Urban catchments (RS)	ibuprofen (0.5 µg L^{-1}–1.26 µg L^{-1}), paracetamol (0.4 µg L^{-1}–3.0 µg L^{-1})	[30]
Hospital Effluent	University Hospital (RS)	bromazepam (137–195 ng L^{-1}), carbamazepine (461 ng L^{-1}–590 ng L^{-1}), clonazepam (57 ng L^{-1}–134 ng L^{-1}), diazepam (571 ng L^{-1}–641 ng L^{-1}), lorazepam (42 ng L^{-1}–96 ng L^{-1}),	[31]
WWTPs (Influent)	Metropolitan area (MG)	estriol (17.1 µg L^{-1}–148.8 µg L^{-1}), estrone (3.3 µg L^{-1}–5.4 µg L^{-1}), triclosan (0.72 µg L^{-1}–7,42 µg L^{-1}),	[17]
WWTPs (influent)	Raw sewage (MG)	bezafibrate (94.4 ng L^{-1}), diclofenac (99.9 ng L^{-1}), sulfamethoxazole (13.0 ng L^{-1}), trimethoprim (61.5 ng L^{-1})	[32]

Pharmacological category/application of APIs and PCPPs: analgesics (acetaminophen/paracetamol, ibuprofen), antibiotics (erythromycin, trimethoprim, sulfamethoxazole, salicylic acid), antihypertensive (atenolol, enalapril, losartan, nifedipine, valsartan), anticholesterolemic/lipidemic (losartan, rosuvastatin, bezafibrate), antidepressant (citalopram), antifungal (ketoconazole), anthelmintic (albendazole,

mebendazole), anti-inflammatory (diclofenac, naproxen, orphenadrine), antiplatelet (clopidogrel), antiseptic (triclocarban, triclosan), non-ionic surfactants alkylphenol ethoxylates and metabolites (nonylphenol, octylphenol), diuretic (chlortalidone), plasticizer (bisphenol A, diethyl phthalate), natural estrogens (estrone, 17-β-estradiol, estriol), estrogenic contraceptive (17α-ethynylestradiol), illicit drug and metabolite (cocaine, benzoylecgonine), preservatives (benzophenone-3, ethylparaben, methylparaben), psychoactive drugs (bromazepam, carbamazepine, clonazepam, diazepam, lorazepam), stimulant (caffeine), sunscreen (avobenzone).

5. Conclusion

Pharmaceutical pollution is an emerging public health concern worldwide associated with the increased production and consumption of pharmaceutical and healthcare products. The inappropriate disposal of active pharmaceutical ingredients from medicinal and personal care products can be detrimental to the environments even at low concentrations, demanding joint public efforts to deal appropriately with medicine residues, through regulations, technical directions, and educational campaigns nationwide.

Based on the current knowledge and the Brazilian context, in Table 3, we summarize some concerns about APIs and PCPPs entering the environment, annotate the flaws in the local legislation to overcome, and indicate several scientific and technological measures that could control pharmaceutical/drug pollution.

Table 3. Some concerns and recommendations about pharmaceutical/drug pollution in the Brazilian context.

Main concerns
- Flaws in the legislation and regulations that preclude strict compliance of consumers and manufacturers
- Lack of educational and official programs to collect expired, unused, and unwanted medicines, such as take-back program and reverse logistic;
- Lack of a local, official flush list and directions for solid-residues disposal for useless medicines
- Public unawareness of the increasing pharmaceutical/drug pollution and its ecotoxicological effects
- Lack of legislation that regulates the MCL of APIs and PCPPs in drinking water and the environment.
- The low number of installed WWTPs and variable efficiency of WWTPs in eliminating APIs and PCPPs from domestic, industrial, and hospital sewages
- Use o biosolids to fertilize crops in extensive agriculture that disperse APIs and PCPPs in the soil
- Absence of systematic analytical programs to assess the level of pharmaceutical pollution nationwide

Recommendations

- Fill the gap of imperfect legislation and regulation about the proper disposal of medicines

- Uniformize the directives nationwide on the disposal of medicines for human and veterinary uses

- Adopt national take-back programs and reverse logistic strategies to collect useless medicines and avoid pharmaceuticals ending in the environment

- Update the directives by taking into account the PBT index of pharmaceuticals and chemicals

- Conduct consistent and periodical ecological risk assessment to nurture policies of drug pollution;

- Aware the general public of the harmful effects on human health and wildlife regarding the presence of APIs and PCPPs in the environment

- Orientate consumers about the proper way to discard or return useless medicines

- Educate students of all academic levels about the short- and long-term detrimental effects of APIs and PCPPs on the Earth biome

- Establish a regular monitoring program using high sensitive analytical procedures to detect APIs, PCPPs, and metabolites in critical water systems

- Adopt biological/ecological filtration to treat wastewater before discharge into the water stream

- Adopt advanced oxidative processes (e.g., UV/H_2O_2) and membrane separation (e.g., reverse osmosis) for APIs and PCPPs removal in WWTPs

Note: MCL, maximum contaminant level; UV, ultraviolet;

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Keywords

pharmaceutical pollution;drug pollution;active pharmaceutical ingredients;environmental pollution;hazardous waste;drug disposal;xenobiotics