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**BEFORE THE HON'BLE NATIONAL GREEN TRIBUNAL**  
**SOUTHERN ZONE BENCH AT CHENNAI**  
**ORIGINAL APPLICATION NO. 126 OF 2021**

**IN THE MATTER OF:**

M/s. Sri Mahalakshmi Hatcheries  
Represented by its Proprietor  
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..... APPLICANT

-Vs-

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1



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**7. M/S DIVIS LABORATORIES LIMITED**

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..... RESPONDENTS

I, Dr.V.Kripa Daughter of Shri Madhav Vasant Rao aged 59 years and working as Member Secretary, Coastal Aquaculture Authority do hereby solemnly affirm and sincerely state as follows:

1. I submit that I am the 6<sup>th</sup> respondent herein. I am well acquainted with the facts of the case on the basis of records available in my office. I read the affidavit filed in support of the Writ Petition. I deny all the averments made therein except those that are specifically admitted hereunder
2. India has an estimated potential brackish water area of 1.24 million ha along 8,129 kilometres of coastline available. India with huge aquatic resources has registered a phenomenal growth in fisheries production with 1.392 million tons (mt) in 2018-19 from mere 0.75 mt in 1950-51. India is the world's second largest fish producer (at 13.4 million tons) excluding seaweed cultivation and stands only next to China.

2



Fisheries contribute about US\$ 30 billion to the India's economy (1.0 percent of GVA in 2018-19 and in value terms nearly equals to rice production at US\$ 33 billion and much above wheat at US\$ 19 billion). Being one of the top fish producers and 2<sup>nd</sup> in aquaculture production in the world, India also has a thriving seafood export market (about 5 percent of the global sea food trade), earned about US\$ 6.73 billion / Rs. 46589.37 crore (2018-19) through exports. India has exported 6,52,253 MT of frozen shrimp in 2019-20 and earned US\$ 4,889.12 million/Rs.34,152 crore foreign exchange from export of cultured shrimp. Fish is the largest agriculture export commodity of India. India has shown continuous and sustained increments in shrimp production from the level of 75,000 MT during 2008-09 to the level of 7.5 lakh MT during the year 2019-20. It is obvious that, no other food production sector in the country has achieved such high growth rates as aquaculture in the past 10 years. Aquaculture and Fisheries has become an inevitable source of nutritional security for the human population with high quality of protein at cheaper cost. **The sea food export from India, though comprises of both captured and cultured aquatic food, the cultured shrimp with its 68.26% stake stands as the single largest commodity exported.**

3. It is submitted that the rural population, numbering about 16 million, comprising many poor and historically excluded people, are directly employed in fishing, and another about 30 million in associated activities especially coastal aquaculture which utilizes saline areas along the coastline, which are not suitable for other activities. Larger investment of public and private funds has also been made in the farming activity. If these farms are closed down, it may lead to unemployment of these large number of people. Hence, it was considered necessary to save the employment of the workers and also the investment already made in this economic activity and to provide for future growth of aquaculture farming in a manner, which is consistent with the requirement of safeguarding the environment. Therefore coastal aquaculture contributes significantly to the livelihood and development in the rural areas.
4. It is submitted that the Coastal Aquaculture Authority was established under the Coastal Aquaculture Authority Act, 2005 for regulating activities connected with coastal aquaculture in coastal areas (as provided under Clause (c) and Clause (d) of sub-section 1 of Section 2 of CAA Act, 2005 and Sub Para 7.1 of Para 7.0 in the Annexure-I to the CAA Rules, 2005) and for matters connected therewith or



incidental thereto to ensure that coastal aquaculture does not cause any detriment to the coastal environment and that the concept of responsible aquaculture is followed. The main objective of the Authority is to promote sustainable development without causing damage to the coastal environment following responsible coastal aquaculture practices and to protect the livelihood of various stakeholders living in the coastal area.

5. The Authority is empowered to make regulations for the construction and operation of aquaculture farms in coastal areas, inspection of farms and hatcheries for *L. vannamei* to ascertain their environmental impact, registration of aquaculture farms and hatcheries, removal or demolition of coastal aquaculture farms which cause pollution, fixing standards for all coastal aquaculture inputs, viz., seed, feed, growth supplements, chemicals, etc., used in coastal aquaculture and for the overall monitoring and regulation of coastal aquaculture activities in the country. Appropriate Rules, Regulations and Guidelines have been formulated and notified under the provisions of CAA Act, 2005 by the Govt. of India for this purpose. The CAA is entrusted with the responsibility to regulate the coastal aquaculture through Rules, Regulations and guidelines issued from time to time for the regulation aquaculture activities in coastal areas.
6. It is submitted that Clause (d) of sub-section 1 of Section 2 of CAA Act , 2005 defines 'coastal area' as an "Area of land within a distance of two kilometres from the High Tide Line (HTL) of seas, rivers, creeks and backwaters" as coastal aquaculture is essentially to be carried out in high quality sea water for sustainability of the sector.
7. The CRZ regulations from the day it came into existence in 1991 to this day, has consistently treated the Hatchery activity as a permitted activity in CRZ and excluded or exempted it from the prohibitions imposed by the CRZ Notification (Annexure 1), considering the indispensability for the requirement of oceanic quality Seawater and seafront access for a Hatchery. A Hatchery requires pristine seawater of oceanic quality for the broodstock holding, maturation, larval and Juvenile rearing of all marine organisms. Hence, a Hatchery is essentially a Seafront activity requiring access to oceanic quality Seawater as provided in Para 7.4 of Guidelines for Regulating Coastal Aquaculture issued as Annexure -I under Rule 3, Chapter 2 of CAA Rules 2005.



8. It is submitted that a Hatchery is an indoor facility where Marine organisms viz. Fish, Crustaceans, Molluscs, Seaweed and other marine life forms are bred for Natural stock enhancement of the seas or for Aquaculture. Hatchery is completely an indoor unit comprising of source water treatment systems for purifying the source water to the highest level, water storage reservoirs, and production tanks made of concrete in which the matured adult shrimps are made to produce eggs under the controlled condition. These eggs are made to hatch out and reared in the larval and post larval tanks using sea water of oceanic quality to enable them to metamorphose through different stages of its life cycle.
9. It is submitted that the microscopic shrimp eggs metamorphose through different life stages to reach the post larval stage and all these life stages are highly primitive and fragile in nature and they feed mainly natural food such as plankton. They are very sensitive to changes in the water quality as well as to strong chemicals. Hence, pesticides or chemicals which are harmful to the natural systems cannot be used in the hatcheries. It is submitted that the hatcheries do not discharge any chemical effluent and they are discharging only the water filtered and treated with high precision technologies used for the rearing of larval forms of Shrimp. Hence the water discharge from the Hatcheries contain planktons which are the natural food for all aquatic organisms and there is no source of contamination with any contaminants or pollutants in this water as they are detrimental to the (shrimps) organisms reared in these facilities. However, these discharges are mandatorily treated through the Effluent Treatment Systems as notified by this Authority and discharged into the sea. The entire facility being indoor and on concrete structure, the possibility of sea water seeping into the land is highly remote. Further all these hatcheries are established along the coast close to shore for the access of sea water and hence the majority of the areas in which they are established are saline in nature.
10. It is submitted that the quality of water available in the site has strong influence on the success of the coastal aquaculture farm. Wide fluctuation in pH and salinity will be detrimental to the cultured species. The water source should be free from any industrial pollution. The optimal levels of various water quality parameters for survival and growth of shrimps is provided under para 6.1 of Annexure –I of rule 3 of CAA Rules, 2005.



11. The use of antibiotics in coastal aquaculture is strictly prohibited as their use may result in development of pathogens resistant to such drugs and this resistance might get transferred to higher trophic levels in the food chain. 20 antibiotics/pharmacologically active substances are presently banned for use in aquaculture as provided under para 11.7 of Annexure –I of rule 3 of CAA Rules, 2005. Further, CAA is issuing certificates of compliance for the antibiotic free aquaculture inputs. All the coastal aquaculture farmers and hatchery operators are advised to use CAA certified aquaculture inputs to ensure that there is no possibility of accumulation of such antibiotic residue in the food chain and the environment.
12. It is submitted that the proper operation and viability of coastal aquaculture hatcheries depend on the availability of a continuous source of clean water, and proper treatment of their effluents before discharging to the surrounding environment, particularly in areas where several hatcheries may coexist. The treatment of the effluent from the hatcheries is inevitable for the survival of the hatcheries themselves and hence are to be followed scrupulously.

**The following extracts / excerpts from published scientific reports on the discharges from pharmaceutical manufacturing are submitted for the kind perusal**

13. It is submitted that there is scientific evidence that even low concentrations of pharmaceuticals in the environment have harmful effects on animal and plant life, with effects include including: renal failure in vultures, impairment of reproduction in fish, or inhibition of growth of certain aquatic species. Evidence shows that uncontrolled discharges from pharmaceutical manufacturing have devastating impacts on water systems as well as on people and animals coming into contact with the resulting resistant bacteria. This is especially true in India and China - where most Active Pharmaceutical Ingredients (APIs) for pharmaceutical products (including pharmaceuticals sold on the EU market) are manufactured. The production of APIs and finished dose antibiotics occurs in specific locations where point-source pollution results in incredibly high concentrations of APIs, encouraging the development of drug resistance. Recent studies from Hyderabad (India) reveal excessively high concentrations of pharmaceuticals exceeding maximum regulatory limits or safe exposure levels. Pharmaceutical manufacturing is a source of pharmaceutical pollution that is further exacerbated by poorly enforced



environmental legislation in countries such as India and China. Pharmaceutical pollution from drug manufacturing represents a global challenge that cannot be tackled without engaging the numerous stakeholders across supply chains. (Annexure 2)

14. Removal rates for pharmaceuticals in wastewater treatment plants (WWTPs) range from less than 10 to almost 100% in some cases for wastewater from pharmaceutical manufacturing. Pharmaceutical metabolites and transformation products can be more persistent and more toxic than the parent compound.(Annexure 3)
15. Several reports have confirmed the presence of pharmaceuticals in effluents of pharma industries and in municipal wastewaters and these have been recognized as a major source of drugs and pharmaceuticals in drinking water. The long term exposure of lower concentration of complex pharmaceutical mixtures on stream biota may result in acute and chronic damages, behavioral changes, and accumulation in tissues, reproductive damage and inhibition of cell proliferation. Several studies have demonstrated that fish exposed to wastewater effluents can exhibit reproductive abnormalities. Moreover, fish exposed to trace levels of birth control pharmaceuticals in the range of concentrations found in the environment show dramatic decreases in reproductive success, suggesting population level impacts are possible. Globally, the detection of waste pharmaceuticals in the environment creates the risks, which are associated with their introduction into human, aquatic life and wildlife and is becoming a serious problem equally for both regulators and the pharma industry. Significant success on this issue is simply not achievable with the currently limited state of knowledge on environmental transport, fate, and effects of pharmaceuticals. There is need to take into consideration the possible growing effects of different drugs affecting the same receptors<sup>12</sup>, Risk assessment of the pharma chemicals involves the detection of the inherent hazards at each stage and an estimation of the risks due to these hazards. (Annexure 4)
16. It is submitted that currently, pharmaceutical compounds are being discharged into the environment in extremely large quantities regularly and present system of regulations of their release is not able to control the untreated or partially treated



pharma effluents. These drugs are entering into and occurring in ecosystems, is causing impact on the biota and humans.

17. The negative impact of the production of pharmaceutical products on the natural environment is well known. However, this remains largely unregulated, meaning the extremely toxic impact it has on both animals and humans continues with no clear end in sight. Lord Jim O'Neill noted this trend in his 2016 UK government-funded independent Review on Antimicrobial Resistance. Although it is a global issue, like other environmental issues, pharma pollution more directly and seriously affects those living near production plants whose water and food sources are contaminated with waste pharma products. "The production of both active pharmaceutical ingredients (APIs) and finished dose antibiotics is concentrated in specific locations so the resulting point, source pollution, is in incredibly high concentrations and encourages the development of drug resistance," says HCWH Europe pharmaceuticals policy officer Dr Adela Maghear. "This practice has a detrimental impact on vulnerable populations living near manufacturing facilities and wastewater treatment plants in these countries." This grievous level of pharma pollution exists despite NGO, governmental and judicial pressure on companies operating in the area to clean up their act. In 2009, the Patancheru-Bollaram zone was classified in India's national pollution index as '**critically polluted**' and in 2016, **the country's Hon'ble Supreme Court ordered pharma companies to implement a zero liquid waste policy.** (Annexure 5)
  
18. Pharmaceutical plants are often incapable of filtering out all the chemical compounds used in their manufacturing process and as such, the chemicals will seep into the surrounding freshwater systems and eventually into the oceans, lakes, streams, and rivers. Wastewater from pharmaceutical manufacturers is also sometimes discharged into open fields and nearby water bodies, thereby increasing the pharmaceutical waste or their by-product load in the environment, landfills, or dumping areas. **All this is basically known as pharmaceutical pollution (Annexure 6)**
  
19. Pharmaceutical compounds are being used for several beneficial purposes in modern society but simultaneously pharma industries are releasing very toxic contaminants in the environment directly or after chemical modifications. Intermediates and raw



materials could be present in wastewater discharged from pharmaceutical industry. Traditional wastewater treatment methods, such as activated sludge, are not sufficient for the complete removal of active pharmaceutical ingredients and other wastewater constituents from these waters. Consequently, pharmaceuticals find their way into the aquatic environment, where they directly affect aquatic organisms and can be incorporated into food chains. In a recent study, the extraordinarily high levels (mg/L) of several drugs were found in the effluents from local wastewater treatment plant near Visakhapatnam in India. Moreover, higher concentrations of antibiotics can lead to change in microbial community structure and ultimately affect food chains. Many pharmaceutical industries are responsible to generate toxic effluent as a consequence of their operation. (Annexure 4). Further it is submitted that the US Food and Drug Administration (US FDA) has issued import alert on the Unit 2 facility of M/s. Divis Laboratories Limited at Visakhapatnam of Andhra Pradesh (Who is the 7th respondent in this case). It may be noted that a company cannot export products into the US from a site under import alert until the drug regulator reverses its action (Annexure 7)

20. It is humbly submitted that a joint committee has been constituted by the District Collector, SPSR Nellore district, based on the representation made to the Hon'ble Chief Minister of Andhra Pradesh. The committee inspected the site on 07.03.2020 and reported that industrial discharge will settle residues of antibiotics and other harmful substances thus have strong influence on the agriculture, aquaculture and the hatchery activities in the area.
21. It is submitted that the said industry is proposed to be set up amidst the highly productive and sustainable coastal aquaculture farms falling under a declared Aquaculture Zone and food grain producing agricultural fields makes it a concern at large, though the above stated facts about the effluent treatment and the pharmaceuticals discharged into the open environment are universal for any pharma industry.
22. It is submitted that this authority believes from the above mentioned facts that the mechanism and the machinery used in the effluent treatment plants at such pharmaceutical industry do not efficiently remove the harmful substances from the



effluents they release into the environment. Therefore the Hon'ble NGT may constitute a larger committee which will thoroughly study the ETS and provide a report elaborating the aspects of effluent treatment process, components of the final discharge and their impact in the environment, the biology of the aquatic animals being cultured in the region and the agriculture sector.

23. Accordingly the following are submitted for the kind consideration of the Hon'ble NGT;

- I. The impact cause by pharmaceuticals, their metabolites and transformation products in the environment magnified many fold in this particular case since the location of the pharmaceutical manufacturing facility is in an area which has high dense production of aquatic organisms though coastal aquaculture and food grains through agriculture. It has a potential hazard to contaminate the food production from this area thus ultimately impacting a large number of human consumers from within the area and outside.
- II. Considering the presence of residual pharmaceuticals in the effluence and discharges of pharmaceutical industry, the Hon'ble Supreme Court of India issued orders to pharma companies to implement a zero liquid waste policy.
- III. Considering the sensitiveness of the location which mainly consists of Agricultural fields and Aquaculture farms involved in food production in which the pharmaceutical manufacturing facility is proposed to be established, implementation a zero liquid waste policy may be made mandatory for the pharmaceutical manufacturing facility to thwart the potential hazard from the residual pharmaceuticals
- IV. Considering the threat perception and perceived possibility of contamination of coastal aquaculture produces and agricultural produces by the pharmaceuticals which is expected to contaminate the surrounding environment around the proposed pharma manufacturing facility, it is submitted to consider constitution of a larger committee of domain experts from all sectors to assess the threats and propose appropriate mitigation measures before the commissioning of the project

  
RESPONDENT

10



**डॉ. वी. कृपा / Dr. V. KRIPA**  
सदस्य सचिव / Member Secretary  
भारत सरकार / GOVERNMENT OF INDIA  
मत्स्य पालन, पशुपालन व डेयरी उद्योग मंत्रालय  
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## Annexure: I

### Exclusion or Exemption of Hatchery from CRZ Notifications

#### I. CRZ Notification 1991

Sub para (i) & (iii) of Para 2 of the CRZ Notification 1991 excludes/exempts the hatchery activity from the prohibited activities in the CRZ. It provides for as under

“2. Prohibited Activities :

The following activities are declared as prohibited within the Coastal Regulation Zone, namely :

- (i) setting up of new industries and expansion of existing industries, except those directly related to water front or directly needing foreshore facilities;
- (ii) Xxxx
- (iii) Setting up and expansion of fish processing units including warehouse (excluding hatchery and natural fish drying in permitted areas) ;”

#### II. CRZ Notification 2011

Sub para (i)a & (iii) of para 3 of the CRZ Notification 2011 excluded the hatcheries from the prohibited activities in CRZ. It provides as under:

“3. Prohibited activities within CRZ,- The following are declared as prohibited activities within the CRZ,-

- (i) Setting up of new industries and expansion of existing industries except,-
  - (a) those directly related to waterfront or directly needing foreshore facilities;

*Explanation:* The expression “foreshore facilities” means those activities permissible under this notification and they require waterfront for their



operations such as ports and harbours, jetties, quays, wharves, erosion control measures, breakwaters, pipelines, lighthouses, navigational safety facilities, coastal police stations and the like.;

(ii) Xxx

(iii) Setting up and expansion of fish processing units including warehousing  
**except hatchery and natural fish drying in permitted areas:”**

### III. CRZ Notification 2019

Sub para 1.2(vii) of Para 5 of CRZ Notification 2019, under the regulation of permissible activities in CRZ, permits hatchery and natural fish drying in CRZ-I B – the inter tidal areas. It provides as under:

“5. **Regulation of permissible activities in CRZ:**

5.1 **CRZ-I**

5.1.1 **CRZ-IA:**

xxxx

5.1.2 **CRZ-IB- The inter tidal areas**

Activities shall be regulated or permissible in the CRZ-I B areas as under:-

(i) xxx

(ii) xxx

(iii) xxx

(iv) xxx

(v) xxx

(vi) xxx

(vii) Hatchery and Natural fish drying.”





# THE ENVIRONMENTAL IMPACT OF PHARMACEUTICAL MANUFACTURING:

How does industry address its own waste?



## INTRODUCTION

Pharmaceutical pollution is increasingly recognised as a threat to ecosystems and human health globally. Pharmaceuticals can enter the environment at all stages of their life cycle (production, use, and disposal), meaning they can ultimately end up in our drinking water as well as accumulate in vegetables and fish. Pharmaceutical residues have been detected in surface water, sewage effluents, groundwater, drinking water, manure, soil, and other environmental matrices globally.<sup>1,2</sup>

There is scientific evidence that even low concentrations of pharmaceuticals in the environment have harmful effects on animal and plant life, with effects include including: renal failure in vultures, impairment of reproduction in fish, or inhibition of growth of certain aquatic species.<sup>3,4,5</sup>

Critically, the discharge of pharmaceuticals into the environment has also been linked to the development of antimicrobial resistance (AMR), which is recognised by UN Environment as one of the biggest global public health concerns that we face.<sup>6</sup> Evidence shows that uncontrolled discharges from pharmaceutical manufacturing have devastating impacts on water systems as well as on people and animals coming into contact with the resulting resistant bacteria. This is especially true in India and China - where most Active Pharmaceutical Ingredients (APIs) for pharmaceutical products (including pharmaceuticals sold on the EU market) are manufactured.<sup>7,8,9,10,11,12,13</sup>

The production of APIs and finished dose antibiotics occurs in specific locations where point-source pollution results in incredibly high concentrations of APIs, encouraging the development of drug resistance. Recent studies from Hyderabad (India) reveal excessively high concentrations of pharmaceuticals exceeding maximum regulatory limits or safe exposure levels.<sup>9</sup> Exposure to environmental sources of antimicrobial drugs is placing vulnerable populations, such as pregnant women from low-income backgrounds at a higher risk for community acquired AMR.<sup>14</sup> Contamination of water sources with antimicrobial drugs (combined with the mass misuse of antibiotics and poor sanitation) has grave consequences in India, where an estimated 58,000 new-borns die annually from multidrug-resistant infections.<sup>15</sup>

Pharmaceutical manufacturing is a source of pharmaceutical pollution that is further exacerbated by poorly enforced environmental legislation in countries such as India and China.<sup>16</sup> Several studies show that polluting factories breeding resistant bacteria are exporting to EU markets and directly selling drugs to EU-based healthcare providers and buyers (e.g. German insurance companies).<sup>17</sup>

Furthermore, European patients are often not fully informed about pharmaceutical supply chains - packaging labels almost always refer to the final stage in the supply chain (where medications are packaged) as the manufacturing location, instead of providing information about where the APIs or the finished doses were actually manufactured. To increase transparency, patients and health professionals should have access to accurate information regarding the origin of drugs they use so that they can make an informed decision - knowing more about suppliers allows users to find out more about the environmental and social conditions under which the drugs were manufactured.<sup>10</sup>

Recognising the problems highlighted above, Health Care Without Harm (HCWH) Europe conducted a survey to identify best practice and gather information about how pharmaceutical companies manage manufacturing waste throughout their supply chains.

The survey was sent to the top 50 pharmaceutical companies worldwide (according to Pharmaceutical Executive's annual ranking)<sup>18</sup> and covered aspects such as waste and pollution management, environmental sustainability, governance, and transparency (page opposite). Participating companies were evaluated according to their responses, as well as any publicly available information. A traffic light system was used as an assessment tool with the following performance indicators:

-  **Red** - Low implementation/ no measures
-  **Yellow** - Average implementation of measures
-  **Green** - High implementation/ measures present

## ASSESSMENT AREAS

### A. ENVIRONMENTAL SUSTAINABILITY FRAMEWORK

- What are the company's environmental policies?
- How are these policies implemented?

### B. SUPPLIER ASSESSMENT

- Does the company require external suppliers to have environmental policies in place?
- How does the company verify that its suppliers' policies are being implemented?

### C. ENVIRONMENTAL GOVERNANCE

- Is there a department in the company in charge of reducing its environmental footprint?
- What are the company's commitments in terms of reducing its environmental footprint?

### D. TRANSPARENCY

- Does the company publicly report environmental monitoring data?
- Is the list of the company's external suppliers publicly available?



## RESULTS

Five companies participated in the survey.

Three directly responded to the survey as drafted by HCWH Europe:

- AstraZeneca (AZ)
- GlaxoSmithKline (GSK)
- F. Hoffmann-La Roche (Roche)

Others compiled answers in their own format covering the areas of interest in the survey:

- Mylan
- Teva

All the companies surveyed manufacture medicinal products for human use only, three develop original drugs, and three produce antibiotics.

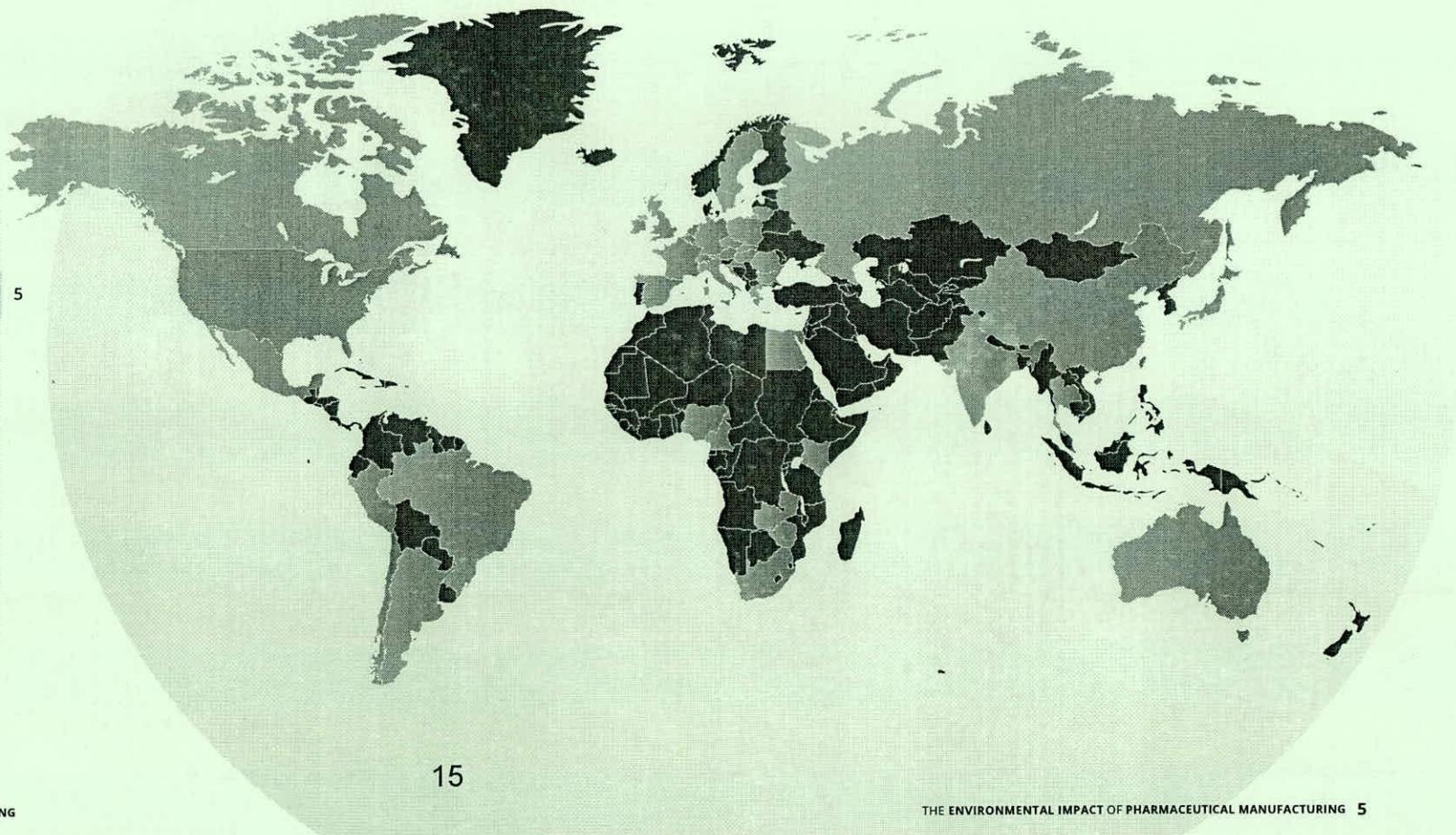
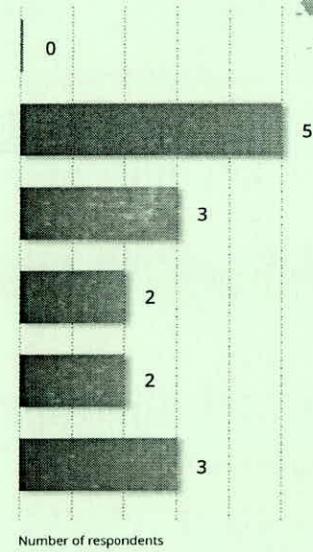
All participating companies operate manufacturing sites in developed as well as emerging and developing countries (as defined by the IMF).<sup>19</sup> The UK, USA, Germany, Ireland, Canada, Australia, and Japan were the most frequently mentioned developed countries with manufacturing sites, whilst China, Brazil, India, Thailand, and Argentina were the most popular sites in emerging and developing countries.

### LOCATION OF PARTICIPANTS' MANUFACTURING SITES

Argentina	China	Italy	Puerto Rico	Thailand
Australia	Czech Republic	Japan	Romania	UK
Austria	Egypt	Kenya	Russia	USA
Belgium	France	Lithuania	Singapore	Zambia
Brazil	Germany	Mexico	Slovakia	Zimbabwe
Bulgaria	Greece	The Netherlands	South Africa	
Cameroon	Hungary	Nigeria	Spain	
Canada	India	Peru	Sweden	
Chile	Ireland	Poland	Switzerland	



Products for veterinary use  
 Products for human use  
 Original drug developer  
 Generics manufacturer  
 Do not produce antibiotics  
 Produce antibiotics



## A. Environmental sustainability framework

All five companies indicated that they have implemented environmental policies or guidelines for managing and processing pharmaceutical manufacturing pollution. The comprehensiveness of these policies or guidelines, however, differs between the companies, as does their implementation.

Implementing widely recognised standards for manufacturing practice and environmental management is a common way for pharmaceutical companies to limit the negative environmental impacts of their manufacturing activities. One such example is the International Organization for Standardization's ISO 14001 certification, which requires an environmental management system to be in place and helps organisations improve their environmental performance.<sup>20</sup>

Among the study participants, two companies have all their sites ISO 14001 certified; the remaining three companies did not provide specific data for all of their manufacturing sites.

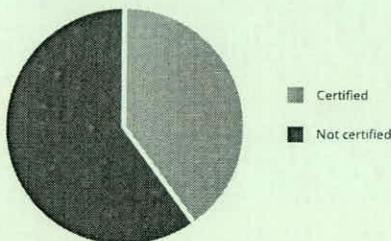
The ISO 14001 standard does not contain specific environmental performance criteria, but provides a framework for the holistic improvement of a company's environmental performance. Other measures are therefore usually taken (in place of or in addition to the ISO certification) to address the environmental impacts of manufacturing processes.

Examples of such measures listed by participating companies include:

- Written standards and procedures
- Environmental risk assessments
- Internal and quality audits
- Air emissions, water, and soil contamination controls

### ENVIRONMENTAL SUSTAINABILITY

ISO 14001 certification of all manufacturing sites (5 respondent companies)



- Safe discharge programmes
- Waste management programmes
- Training of staff and suppliers

### Waste and pollution management

Responsible environmental management requires controlling the amount of APIs entering the environment. In terms of waste and pollution management practices, all participants indicated having implemented hazardous substance management programmes, aimed at reducing hazardous waste.

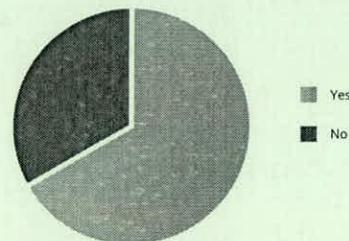
To determine the potential environmental impact of APIs, all the participating companies monitor their facilities and evaluate the discharge of wastewater to surface waters.

Three companies make use of Common Effluent Treatment Plants, which also collect and treat domestic sewage, and are not designed to specifically treat effluent from pharmaceutical manufacturing sites.<sup>21</sup> Notably, three companies indicated that they implement zero liquid discharge wastewater treatment systems at either their own sites or at their suppliers' sites. These systems have the potential to limit the discharge of liquid waste into the environment.<sup>22</sup>

Emissions to the air from manufacturing operations are also assessed at all five companies, but only two companies provided information about detailed measures taken to reduce air pollution at their facilities. These measures include containment and local exhaust ventilation, as well as the use of other air cleaning equipment (e.g. HEPA filtration, electrostatic precipitation, and/or carbon beds).

Finally, two of the three companies producing antibiotics confirmed that they take measures to limit their discharge, including discharge limits and specific wastewater treatment methods.

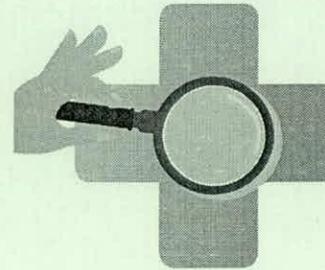
Companies producing antibiotics that take measures to limit their discharge (3 respondent companies)



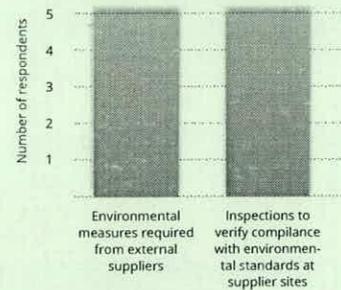
## B. Supplier assessment

The majority of responding pharmaceutical companies outsource their API production. Two companies provided responses showing that 10% and 40% of their APIs are produced in emerging and developing countries. Two further companies indicated that they use APIs produced in emerging countries, but no specific percentages were provided.

All five companies require external suppliers to have environmental policies for hazardous waste management, wastewater discharge, or air emissions as part of their Supplier Code of Conduct. In order to ensure environmentally responsible operations at supplier sites, all surveyed companies undertake inspections verifying compliance with environmental standards and examine appropriate authorisations on a regular basis. Three respondents specified how many audits/inspections take place at their or their suppliers' sites per year, and the other two companies indicated the number of audits that took place in 2017.



### ENVIRONMENTAL GOVERNANCE OF SUPPLIERS



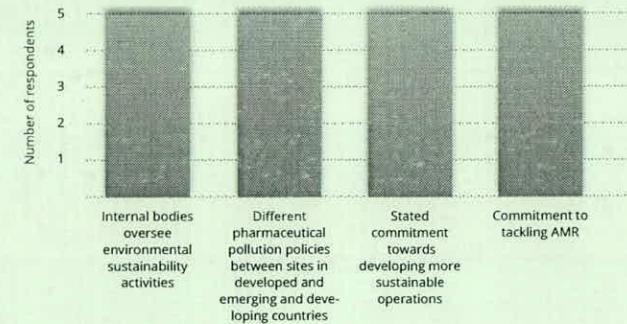
## C. Environmental governance

All companies reported having internal governance structures overseeing activities related to environmental sustainability at their manufacturing sites. These most commonly comprised safety, health, and environment departments, as well as sustainability and social responsibility divisions.

Examining governance practices in different parts of the world, participating companies indicated that their pharmaceutical pollution policies do not differ between manufacturing sites located in developed countries versus those in emerging and developing countries. Furthermore, aware of the environmental impacts of manufacturing activities, all surveyed companies have established specific goals and targets towards more sustainable operations. Some examples relevant to this study include: goals related to the quality of effluent discharges, safe discharge limits, the minimisation of waste, and unintended releases. Only two companies explicitly mentioned that they require external suppliers to follow their sustainability commitments.

Finally, all five companies recognise the threat posed by AMR; they fund relevant research (e.g. to develop new antibiotics and detection methods) and support measures to reduce pharmaceutical pollution. All surveyed companies are also signatories of the 2016 Davos Declaration, mobilising the pharmaceutical industry to accelerate efforts to reduce the development of antimicrobial resistance,<sup>23</sup> and are also part of the AMR Industry Alliance - a coalition initiated to provide sustainable solutions to curb AMR.<sup>24</sup>

### ENVIRONMENTAL GOVERNANCE FOR OWN-OPERATED SITES



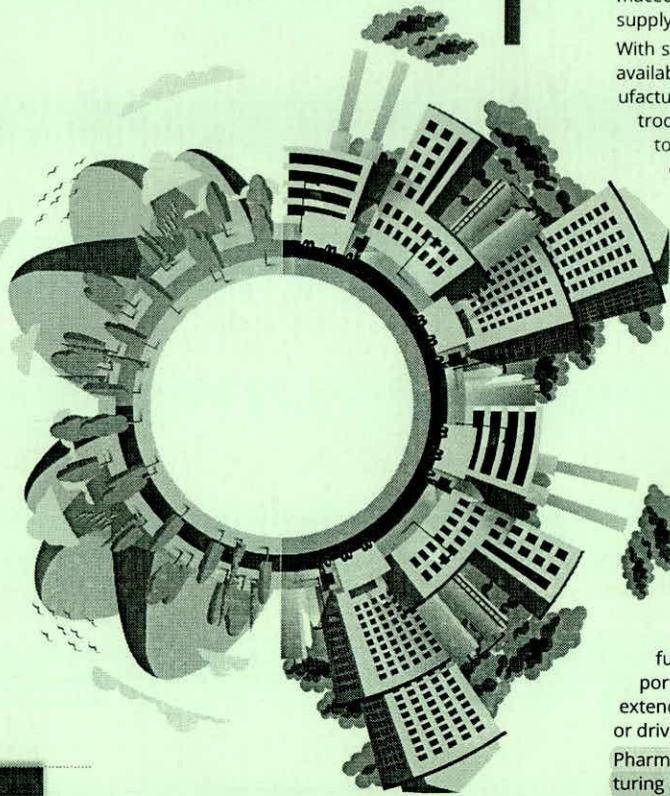
## D. Transparency

All surveyed companies make general information about their environmental policies and guidelines publicly available through their websites and relevant corporate documents (e.g. annual and sustainability reports).

All five companies also publish general statistics on their resource conservation (greenhouse gas emissions, and energy and water consumption), waste management (both hazardous and non-hazardous), as well as appropriate reduction or increase trends.

No company, however, provides site-specific information and none of the participating companies make their list of suppliers publicly available.

Only one company indicated that they publicly disclose information related to environmental incidents occurring at its manufacturing sites and the appropriate remediation.



## CONCLUSIONS

Through its operations, the pharmaceutical industry has a substantial impact on the environment. Not only do pharmaceutical manufacturers have a critical role to play in addressing these issues, they also have a responsibility to foster environmental sustainability and reduce pharmaceutical pollution at source, throughout their supply chains.

With such a small sample size, and little publicly available information from pharmaceutical manufacturers, this study provides only a general introduction to the subject and is not intended to offer a representative sample or showcase best practices.

The limited response, however, demonstrates an industry-wide lack of transparency and reluctance to acknowledge the industry's responsibilities in terms of manufacturing to protect the environment from pharmaceutical pollution.

The results of this study show that although these companies frequently disclose general data related to environmental sustainability and governance, detailed information relating to specific measures taken to prevent pharmaceutical pollution at own-operated and supplier facilities remain unavailable to the public. There is a need for greater transparency from the industry in this regard. Increased transparency could encourage further responsible practices such as reporting environmental incidents, promoting extended environmental risk assessment, and/or driving technology investments.

Pharmaceutical pollution from drug manufacturing represents a global challenge that cannot be tackled without engaging the numerous stakeholders across supply chains. The EU has an important role to play in proposing ambitious legislation to deal with pharmaceutical pollution, including the global threat of AMR.

For example, the long-awaited Strategic Approach to Pharmaceuticals in the Environment<sup>25</sup> from the European Commission (which should have been published in September 2015 but has yet to be finalised) should call for the Environmental Risk Assessment (ERA) to be considered in the market authorisation process.<sup>26</sup>

Further measures, such as broadening the Good Manufacturing Practices (GMP) framework to cover environmental impacts of pharmaceutical

manufacturing, or imposing stronger rules on Environmental Risk Assessments as part of market authorisations for pharmaceutical products, are imperative to curb the negative impacts of pharmaceutical manufacturing.

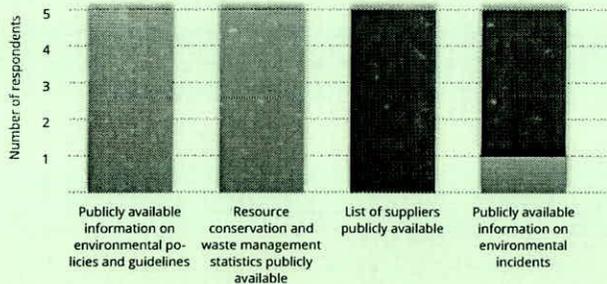
The problems associated with pharmaceutical pollution, however, seem to be neglected by key actors, including the industry and European legislators. For example, the Strategic Approach to Pharmaceuticals in the Environment is already three years overdue - it was originally scheduled for release in 2015. It is hoped that its publication will trigger more action from Member States and pharmaceutical manufacturers.

In the absence of action from regulators and manufacturers, it is imperative that civil society and the public continue to highlight this important issue and the need for appropriate action. To this end, HCWH Europe is committed to repeating this study in the future, in order to increase transparency and highlight gaps in both knowledge and legislation.



This study is part of HCWH Europe's Safer Pharma campaign, initiated to protect the environment from pharmaceutical pollution at all stages of their lifecycle. The campaign seeks to challenge the pharmaceutical industry to clean up its production and raise awareness within the healthcare sector about the impact of pharmaceuticals in the environment, encouraging rational prescription practices. It also aims to raise awareness amongst citizens about the impact of pharmaceuticals in the environment and the steps they can take to tackle the problem. For more information, please visit [www.saferpharma.org](http://www.saferpharma.org).

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Published: December 2018

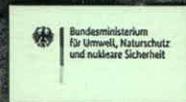
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HCWH Europe gratefully acknowledges the financial support of the European Commission (EC's LIFE+ programme, the Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety (BMU) Germany, and the German Environment Agency (UBA). HCWH Europe is solely responsible for the content of this project and related materials. The views expressed do not reflect the official views of the EC, BMU, or UBA.



## Sources, impacts and trends of pharmaceuticals in the marine and coastal environment

Sally Gaw, Kevin V. Thomas and Thomas H. Hutchinson

*Phil. Trans. R. Soc. B* 2014 **369**, 20130572, published 13 October 2014

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"Data Supplement"

<http://rstb.royalsocietypublishing.org/content/suppl/2014/10/07/rstb.2013.0572.DC1.html>

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## Review

**Cite this article:** Gaw S, Thomas KV, Hutchinson TH. 2014 Sources, impacts and trends of pharmaceuticals in the marine and coastal environment. *Phil. Trans. R. Soc. B* **369**: 20130572.

<http://dx.doi.org/10.1098/rstb.2013.0572>

One contribution of 18 to a Theme Issue 'Assessing risks and impacts of pharmaceuticals in the environment on wildlife and ecosystems'.

### Subject Areas:

environmental science

### Keywords:

pharmaceuticals, ecotoxicology, risk assessment, water quality, marine, coastal

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Electronic supplementary material is available at <http://dx.doi.org/10.1098/rstb.2013.0572> or via <http://rstb.royalsocietypublishing.org>.



# Sources, impacts and trends of pharmaceuticals in the marine and coastal environment

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There has been a significant investment in research to define exposures and potential hazards of pharmaceuticals in freshwater and terrestrial ecosystems. A substantial number of integrated environmental risk assessments have been developed in Europe, North America and many other regions for these situations. In contrast, comparatively few empirical studies have been conducted for human and veterinary pharmaceuticals that are likely to enter coastal and marine ecosystems. This is a critical knowledge gap given the significant increase in coastal human populations around the globe and the growth of coastal megacities, together with the increasing importance of coastal aquaculture around the world. There is increasing evidence that pharmaceuticals are present and are impacting on marine and coastal environments. This paper reviews the sources, impacts and concentrations of pharmaceuticals in marine and coastal environments to identify knowledge gaps and suggests focused case studies as a priority for future research.

## 1. Introduction

Over the last 15 years increasing attention has been paid to understanding the presence and impacts of pharmaceuticals entering or detected in freshwater ecosystems [1]. By contrast, significantly less attention has been paid to understanding releases of pharmaceuticals from sewage and other routes into coastal environments and their potential marine impacts. There is now widespread recognition of the need for a cradle-to-grave stewardship of medicines for minimizing environmental exposure while promoting human and animal health [2]. Large centres of human population are often found in coastal areas and pharmaceutical releases via municipal effluent discharges are probable. For example, Martínez *et al.* [3] reported that based on 2003 data, over 2.3 billion people live within coastal limits (representing 41% of world global population) and more than 50% of coastal countries have 80–100% of their total population within 100 km of the coastline. Twenty-one of the world's 33 megacities (cities with more than 8 million inhabitants) are on the coast and face a range of environmental management issues [4]. Global demographic trends towards coastal conurbations suggest increasing numbers of people living along coastlines, while waste management from coastal megacities is increasingly recognized as a major challenge [3,5,6]. These trends suggest the potential for increasing inputs of human pharmaceuticals into coastal environments and therefore the need to address potential exposure scenarios and implications for marine risk assessments of drug residues and their transformation products [7–9]. Marine risk assessments for pharmaceuticals are also relevant to veterinary medicines used in aquaculture [10–12].

More broadly, if releases of pharmaceuticals into coastal ecosystems are high enough to induce biological impacts, they may act as additional stressors on marine ecosystems already impacted by climate change, eutrophication and over-fishing [13]. It is estimated that 49% of marine ecosystems worldwide are strongly impacted by anthropogenic stressors with significant economic implications [3,14]. If unmanaged, multiple anthropogenic impacts on marine

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ecosystems may also affect coastal fisheries and aquaculture. For example, human health concerns linked to aquaculture include exposure to pharmaceuticals through consumption of seafood and the induction and spread of antibiotic resistance [15,16]. This paper reviews the sources, concentrations and potential impacts of human and veterinary pharmaceuticals in coastal environments to support risk assessments and to identify key knowledge gaps as priorities for future research. The scope of the review has been limited to human pharmaceuticals and antibiotics used as veterinary medicines.

## 2. Sources of pharmaceuticals in marine environments

### (a) Sewage

Sewage effluent is recognized as a major source of multiple pharmaceuticals, including their metabolites, entering aquatic environments. Removal rates for pharmaceuticals in wastewater treatment plants (WWTPs) range from less than 10 to almost 100% and depend on the physico-chemical characteristics of the pharmaceutical and type of treatment technology [17]. Sources of human pharmaceuticals in sewage include patient use in the community, discharges from hospitals and, in some cases, wastewater from pharmaceutical manufacturing [18]. Sewage can be discharged into marine environments through coastal and ocean outfalls for WWTPs combined sewer overflows and via rivers receiving WWTP effluents [19,20]. For example, the Yangtze River in China transports sewage from 400 million people out to sea and releases an estimated 152 tonnes of pharmaceuticals annually [21]. Sewage may also be discharged into the marine environment from boats. Ships, including cruise liners, may discharge (under Annex IV of MARPOL 73/78 ships) treated sewage into the sea 4 nautical miles from the nearest land and 12 nautical miles for untreated sewage [22]. The volumes of sewage discharged can be significant as cruise liners can have passenger numbers equivalent to populations found in small towns. Sewage effluents from small boats, on the other hand, may not receive any treatment prior to being discharged. Typhoon shelters for small boats were a point source of antibiotics in Victoria Harbour, Hong Kong [23]. As discussed by Kookana *et al.* [24] in this issue, many large cities in Asia still rely on septic tanks with poorly managed septage which can contaminate surface and groundwaters with pharmaceuticals and ultimately be discharged into coastal areas.

Sewage impacted groundwater can also be a source of pharmaceuticals entering coastal waters. Pharmaceuticals have been detected in a coastal aquifer on the Yucatan Peninsula, Mexico injected with municipal sewage discharges [25]. Reuse of treated domestic wastewater for irrigation contributed to pharmaceutical contamination in groundwater on Mallorca [26]. Throughout the world rural and peri-urban areas including popular coastal holiday areas are reliant on septic tanks or small decentralized systems for sewage treatment disposal [27]. Depending on their treatment efficiency and the capacity of the local soils, these systems are a potential source of pharmaceuticals in coastal waters via leakage to ground and surface waters [28,29].

### (b) Aquaculture

Globally the production of seafood through aquaculture is rapidly increasing with over 90% of aquaculture based in

Asia [30]. A range of veterinary medicines including antibiotics, also registered for human use, is used prophylactically and to control disease outbreaks in marine aquaculture. Up to 75% of the administered dietary dose of a veterinary medicine can be lost to the surrounding environment. The loss mechanisms include dispersal of non-ingested pellets, gill and renal excretion of the unprocessed drug, and renal and faecal excretion of drug metabolites [31]. Other marine organisms in the vicinity including wild fish feed on leftover food and faecal material from marine aquaculture potentially further spreading pharmaceuticals and their transformation products. Pond-based farms located in coastal areas are also a source of antibiotics entering coastal waters through leaks and discharge of wastewaters which can contain elevated concentrations of pharmaceuticals. Extremely high antibiotic concentrations of up to  $2.5 \text{ mg l}^{-1}$  were measured in water samples from shrimp ponds in Vietnamese mangroves [32]. The ancient practice of wastewater- (human and animal) fed aquaculture, although declining, still occurs in some parts of Asia [30]. Aquaculture practices including the use of antibiotics vary greatly between countries [33].

### (c) Animal husbandry and horticulture

Animal husbandry and horticulture along rivers and in coastal areas may also contribute to loadings of pharmaceuticals entering coastal waterways [17,34]. Antibiotics are added to animal feeds and in some cases drinking water to treat disease particularly in feedlots housing large numbers of animals [35]. The use of low doses of antibiotics in feed as growth promoters still occurs in some regions of the world despite being banned in Europe [36]. Some countries permit the use of antibiotics including oxytetracycline and streptomycin on horticultural crops [17]. Application of municipal biosolids to farmland as fertilizer is a further source of pharmaceuticals entering agricultural systems [37].

### (d) Waste disposal

Waste disposal in coastal areas is a further source of pharmaceuticals entering the marine environment. Leachate from coastal landfills and seafills may be a pathway for pharmaceuticals disposed of in household and clinical wastes to enter coastal waters. Landfill leachate on the island of Mallorca contained up to  $27\,000 \text{ ng l}^{-1}$  total concentration of pharmaceuticals [26]. Historically, in some regions drug manufacturing waste, sewage sludge and animal manure were dumped at sea [38,39].

### (e) Environmental fate of pharmaceuticals in marine environments

Once discharged into aquatic environments, pharmaceuticals and their metabolites can undergo biotic and abiotic transformation (degradation) and sorb to suspended particulate matter (SPM) and sediments, and in some cases accumulate in the tissues of aquatic organisms [40]. Existing data for the environmental fate of pharmaceuticals generated for freshwater environments may not necessarily be transferable to marine environments. The differences in physico-chemical conditions including salinity, pH and organic matter between freshwater and seawater can impact on the environmental fate of pharmaceuticals [41]. The environmental fate of ionizable pharmaceuticals may be altered by the increased pH of seawater. Photodegradation may be a less important removal



mechanism in coastal waters compared with more shallow freshwater environments due to light attenuation. Indirect photodegradation mechanisms may differ to those occurring in freshwater due to differences in water composition [42,43]. There is some evidence to suggest that the environmental fate of pharmaceuticals can differ between fresh and saline environments. The transformation behaviour of ibuprofen differed between freshwater and seawater [44] and prochlorperazine was more stable in seawater than freshwater [43].

### 3. Current state of knowledge of pharmaceutical concentrations in marine environments

#### (a) Seawater

The assessment of the concentrations of pharmaceuticals in coastal environments has been limited. Forty-nine studies have reported concentrations for individual pharmaceuticals and metabolites detected in estuarine and coastal waters. Only studies published since 2000 are considered. Seventy per cent of these studies have been published since 2010. The geographical breakdown for the studies is Europe (20), Asia (21), North America (6), South America (1) and Oceania (1). The studies included those investigating the presence of 30 or more pharmaceuticals over a wide spatial area [45] studies targeting specific classes of compounds, for example, sulfonamide antibiotics [34] and method validation studies screening only a limited number of 'real' samples [46].

To date, 113 pharmaceuticals and pharmaceutical metabolites have been detected in coastal waters at concentrations ranging from 0.01 to 6800 ng l<sup>-1</sup> with the maximum concentrations for 69 of these compounds exceeding the European Medicines Agency threshold for predicted environmental concentrations for surface waters of 0.01 µg l<sup>-1</sup> [47] (electronic supplementary material, tables S1–S3). Data were most frequently reported for antibiotics (41 compounds) followed by non-steroidal anti-inflammatories (8) and analgesics (8). Twenty compounds were reported in five or more studies (table 1) including acetaminophen, atenolol, carbamazepine, clarithromycin, diclofenac, 17α-ethinyloestradiol, erythromycin-H<sub>2</sub>O, gemfibrozil, ibuprofen, ketoprofen, naproxen, norfloxacin, oxafloxacin, propranolol, roxithromycin, sulfadiazine, sulfadimidine, sulfamethoxazole, tetracycline and trimethoprim. The higher frequency of reporting for concentrations of antibiotics and painkillers for the marine environment are consistent with Hughes *et al.* [1] synthesis of pharmaceutical data for freshwater environments.

Current methodologies targeting the dissolved fraction of pharmaceuticals may be underestimating the environmental concentrations and the potential impacts on aquatic ecosystems [49]. The majority of the studies published to date have reported pharmaceutical concentrations in seawater for the dissolved fraction only with filtering being the first step in sample extraction methods. Two studies have investigated pharmaceutical concentrations in SPM. Mean concentrations of pharmaceuticals in SPM (more than 0.7 µm) from the Long Island Sound Estuary ranged from 7 to 44 ng g<sup>-1</sup>. The pharmaceuticals detected in the SPM were either hydrophobic, for example, tamoxifen, or positively charged, for example, clarithromycin, and up to 47% of the total concentration was sorbed to the SPM [19]. Yang *et al.* [19] compared concentrations of pharmaceuticals in the sediment, SPM and the

colloidal and soluble phases in the Yangtze River Estuary and adjacent coastal areas. SPM concentrations were up to 5 times higher than that in the sediments. The colloidal phase had sorption affinities of 2–4 orders magnitude greater for pharmaceuticals than the SPM and contributed up to 45% of the target pharmaceuticals in the Yangtze system.

Pharmaceutical metabolites and transformation products can be more persistent and more toxic than the parent compound [50]. Twenty-one studies reported data for pharmaceutical transformation products in coastal waters with erythromycin-H<sub>2</sub>O the most commonly reported transformation product. Transformation products can be present in WWTP effluents and surface waters at concentrations equivalent to or exceeding the parent compound. For example, concentrations of metabolites of carbamazepine (carbamazepine epoxide), diclofenac (4'- and 5-hydroxy diclofenac) and atorvastatin (o- and p-hydroxy atorvastatin) in wastewater discharged into the Oslofjord were present at higher concentrations than the parent compounds [51]. Similarly the concentrations of sulfonamide metabolites measured in Liaodong Bay, China were comparable to those of the parent compounds [34].

Pharmaceuticals have been detected significant distances from their source(s). Pharmaceuticals were detected at a reference site approximately 9 km downstream from the WWTP outfall in Halifax Estuary [52]. Similarly, pharmaceuticals in the Baltic Sea were detected 17 km downstream of WWTP outfalls [53]. Zhang *et al.* [54] detected antibiotics including erythromycin-H<sub>2</sub>O, sulfamethoxazole and trimethoprim (0.1–16.7 ng l<sup>-1</sup>) 400 km offshore of the coast of China.

#### (i) Seasonal trends

Identifying seasonal trends for pharmaceutical concentrations in marine and coastal waters is crucial for determining time periods during which sensitive ecosystems may be at greater risk from exposure [55,56]. To date only a handful of studies have investigated seasonal trends for pharmaceutical concentrations in the marine environment. Pharmaceutical concentrations in the Yangtze River and Pearl River Estuary were higher in the dry season than in the wet season [57]. Similarly, heavy rainfall events reduced pharmaceutical concentrations in Jamaica Bay, a wastewater impacted estuary [20]. Conversely, Zheng *et al.* [58] and Qi *et al.* [21] reported increased river water concentrations of antibiotics in China during the wet season and attributed the increased concentrations to increased runoff of veterinary medicines and decreased efficiency of WWTPs due to increased wastewater flow. Temporal trends in pharmaceutical concentrations were not observed in Southern California coastal waters with relatively constant year-round temperatures [59]. By contrast, Hedgespeth *et al.* [55] reported higher probability of detecting acetaminophen in seawater from Charleston Harbor, South Carolina during winter. Pharmaceuticals were transported further downstream when the Aura River (Finland) was covered by snow and ice with the spring snowmelt increasing the speed of transport [60].

Seasonal trends in WWTP effluent pharmaceutical concentrations have also been reported which will in turn influence seawater concentrations. For example, total concentrations of NSAID drugs and bezafibrate were 3–5 times higher in effluent in winter than in summer [60]. Reduced removal rates in WWTPs and in surface seawaters can occur during colder months due to lower temperatures and



**Table 1.** Summary of seawater and biota concentrations and marine ecotoxicology data for the human and veterinary pharmaceuticals most frequently detected in seawater (ww, wet weight; dw, dry weight).

pharmaceutical	class <sup>a</sup>	seawater		marine biota		marine ecotoxicology data		
		no. studies	concentration range [ng L <sup>-1</sup> ]	no. studies	concentration range [ng g <sup>-1</sup> ] dw      ww	no. studies	organisms tested	most sensitive endpoint reported [µg L <sup>-1</sup> ]
acetaminophen	analgesic	7	1.9–1952	1	65–115		mussels	feeding rate LOEC = 23
ibuprofen	analgesic	18	0.01–2370				algae mussels	biochemical responses 0.25
carbamazepine	anticonvulsant	18	0.4–1400	4	1.3–11		algae amphipods	21d <sup>geotaxi</sup> NOEC = 1
erythromycin-H <sub>2</sub> O	antibiotic metabolite	9	0.1–1900	2	0.1–2			
clarithromycin	antibiotic	8	0.3–17.6					
norfloxacin	antibiotic	8	2.3–6800	3	370	2.7–255		
ofloxacin	antibiotic	7	3.5–5100	3	5–242			
roxithromycin	antibiotic	8	0.1–630					
sulfadiazine	antibiotic	10	0.4–71.8	3	2.7	3.0–5.2		
sulfadimidine	antibiotic	9	0.2–219	3	29.8–430	3.9		
sulfamethoxazole	antibiotic	18	0.6–765	2	20.1	2.3		
tetracycline	antibiotic	7	2.4–313	1		1.9	1	bacteria diatom growth EC50 = 16000
trimethoprim	antibiotic	20	0.2–870	1	<4–9			
atenolol	anti-hypertensive agent	5	3.8–293	2	0.3–13			
propranolol	anti-hypertensive agent	5	0.3–142	1	19–52		3	mussels Feeding rate NOEC = 11
gemfibrozil	hypolipidemic agent	11	1–758					
diclofenac	NSAID	11	0.6–843				7	algae amphipods copepods decapods diatoms mussels biochemical responses 0.25
ketoprofen	NSAID	7	0.6–805					
naproxen	NSAID	8	1.1–130					
17α-ethinylestradiol	SERM	9	0.1–38	2	7.2–38	2.7–3.4 <sup>b</sup>	2	copepod echinoderm development EC50 = 30.3

<sup>a</sup>Class descriptors as used in DrugBank [http://www.drugbank.ca/; [48]].

<sup>b</sup>Units are ng g<sup>-1</sup> lipid.



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resulting in lower rates of biological activity enhancing the persistence of pharmaceuticals in marine ecosystems [43]. Reduced sunlight levels during winter can inhibit removal of pharmaceuticals susceptible to photodegradation [60]. Snowmelt reduced pharmaceutical concentrations in effluent in Norway [61]. Seasonal trends in pharmaceutical usage should also be considered [62]. Antibiotic use patterns can be influenced by a number of factors. High antibiotic use in winter can be due to the inappropriate use for treating respiratory tract infections including the common cold and viral infections [63]. Anti-allergenic medicines may also have a seasonal profile. Wastewater concentrations of over-the-counter anti-allergenic cetirizine peaked in summer and followed the pollen season [64]. Certain disease-specific pharmaceuticals, such as antiviral drugs, will peak during disease outbreaks, as has been demonstrated for oseltamivir (Tamiflu) during the recent influenza A(H1N1)pdm09 outbreak in Europe [65].

### (b) Sediment data

Sediments are a reservoir for the accumulation of pharmaceuticals in marine ecosystems and can act as a secondary pollution source from which pharmaceuticals can be released by changes in environmental conditions such as salinity and pH [57]. Sediments can be resuspended during tidal changes and during storm events exposing marine biota to sorbed pharmaceuticals. Twenty-two studies reporting sediment concentrations of pharmaceuticals for estuarine and marine environments have been published since 2000. In total, 62 pharmaceuticals and transformation products have been detected in marine sediments at concentrations up to 2 615 000 ng g<sup>-1</sup> wet weight (electronic supplementary material, tables S4 and S5). Excluding the extremely high concentrations of antimicrobials measured in marine shrimp aquaculture pond sediments [32], 17 $\alpha$ -ethinyloestradiol was the pharmaceutical measured in sediment at the highest concentration (129.8 ng g<sup>-1</sup>). 17 $\alpha$ -ethinyloestradiol was also the pharmaceutical most frequently detected with sediment concentrations reported for nine studies. All other pharmaceutical compounds were reported in a maximum of three studies. Data were most frequently reported for antibiotics (26 compounds) followed by anti-hypertensive agents (6). Marine sediment data for pharmaceutical transformation products and metabolites are currently almost non-existent with only four studies reporting concentrations of pharmaceutical metabolites in marine sediments. Langford & Thomas [51] reported concentrations of  $\alpha$ -hydroxy metoprolol (1–3 ng g<sup>-1</sup>) and simvastatin hydroxy carboxylic acid (2–4 ng g<sup>-1</sup>) in sediments collected from Oslofjord in Norway. Erythromycin-H<sub>2</sub>O was reported in San Francisco Bay (3.4 ng g<sup>-1</sup> dw) [66] and in the Pearl River Estuary, China (0.7–14 ng g<sup>-1</sup> dw) [57]. Only nine of the 22 studies analysed both seawater and sediment samples.

### (c) Factors influencing pharmaceutical concentrations in seawater and sediment

Factors reported to increase concentrations of pharmaceuticals in seawater and sediment include proximity to WWTP outfalls [67,68], higher effluent outflows [69], size of the urban area and population [11,70,71], the number of rivers discharging into coastal waters [70], the type of wastewater treatment [19], low mixing and dilution rates for WWTP

effluents [72], the hydrodynamic flushing and residence time for confined water bodies [61,73,74], the type, scale and density of animal husbandry [34,58] and proximity to aquaculture [74,75]. Higher concentrations of pharmaceuticals have been measured in estuaries during low and incoming tides [76]. Re-suspension of sediments during weather events including monsoons and during incoming tides can increase surface water concentrations of pharmaceuticals. Stratification of pharmaceuticals in the water column with higher concentrations being measured at the surface has been reported in the Long Island Sound Estuary [19] and in Victoria Harbour, Hong Kong [77]. Local conditions may inhibit wastewater treatment resulting in higher surface water concentrations. For example, Arctic permafrost conditions reduce the efficiency of WWTPs [78].

### (d) Marine biota

Data for accumulation of pharmaceuticals in marine biota are scant most probably because of the lack of reliable analytical methods for these challenging analytical matrices [66]. Fourteen studies were identified reporting data for concentrations of pharmaceuticals in finfish, crustaceans and shellfish (electronic supplementary material, table S6). Ten of these studies reported results for filter-feeding marine shellfish and five for marine finfish. Tissue concentrations of 60 pharmaceuticals and seven metabolites have been reported with antibiotics being the most frequent class reported (38) followed by anti-hypertensive agents (6). Carbamazepine, ciprofloxacin and enrofloxacin were the most frequently reported compounds each being reported in four studies. Only three studies reported concentrations for pharmaceutical transformation products including erythromycin-H<sub>2</sub>O, salicylic acid and metabolites of venlafaxine [62,66,79]. Higher concentrations of venlafaxine metabolites than parent compound were detected in mussels (*Mytilus galloprovincialis*). As some marine organisms also metabolize pharmaceuticals [80], a wide range of metabolites could potentially be present.

Marine organisms can be exposed to pharmaceuticals over widespread geographical areas. The anti-depressant sertraline was detected at 43 of 68 mussels sampling stations along the California Coast [81]. Antibiotics were detected in 142 out of 190 mollusc samples collected from nine cities along the Bohai Sea in China [82]. Detectable concentrations of pharmaceuticals were measured in wild seafood samples purchased from Czech supermarkets including squid caught in the Eastern Central Pacific, herring from the Atlantic Northeast and shark from the Eastern Central Atlantic [83].

Pharmaceuticals have been detected in marine organisms despite not being detected in water or sediment. Ranitidine, sertraline and enalapril were detected in mussels from San Francisco Bay but not in seawater [66]. Diazepam was detected in all liver samples of hornyhead turbot but only infrequently detected in sediments near wastewater outfalls in the Southern Californian Bight [84]. Fluoroquinolone antibiotics were detected less frequently in water than in fish from six sampling sites in two marine aquaculture regions of the Pearl River Delta, China [74].

Pharmaceutical uptake in marine organisms is compound, species and body-tissue specific. Oxytetracycline preferentially accumulated in the viscera and oxolinic acid in the gills of *Mytilus edulis* [85]. Concentrations of fluoroquinolones antibiotics in fish from marine aquaculture regions of the Pearl River Delta were higher in liver tissue than in muscle tissue



[74]. Fluoxetine tissue concentrations in *Mytilus galloprovincialis* followed the order digestive gland > gills > mantle/gonads [86]. Li *et al.* [82] reported differences in uptake of antibiotics between mollusc species harvested from the Bohai Sea, China. In some situations, gender may also influence uptake of pharmaceuticals by marine organisms. Higher concentrations of diazepam were measured in male than female *Pleuronichthys verticalis* (hornyhead turbot) [84]. These preferential uptakes have implications for ecotoxicological impacts and human exposure to pharmaceuticals via consumption of seafood.

Field data for bioaccumulation of pharmaceuticals in marine organisms is limited. Field-derived bioaccumulation factors (BAFs) for pharmaceuticals in mussels from San Francisco Bay included dehydronifedipine (290–764), carbamazepine (90–322), diphenhydramine (118–218), triamterene (57–71) and erythromycin-H<sub>2</sub>O (11–54). The BAFs varied between sites by up to a factor of 7 [66]. Bioconcentration factors (BCFs) ranged from 1300 to 1500 for uptake of 17 $\alpha$ -ethinyloestradiol by mussels (*M. galloprovincialis*) harvested from Venice Lagoon, Italy [87]. Field-derived BAFs for antibiotics ranged from 0 to 11 000 in shellfish collected from the coastal environment of Dalian in China. Based on the average BAFs, the authors concluded that sulfamethazine, sulfamethiazole, sulfamonomethoxine and doxycycline are potentially bioaccumulative and that sulfadiazine, sulfameter, sulfamethoxyppyridazine and chloramphenicol are bioaccumulative in shellfish [88].

The uptake of pharmaceuticals by marine bivalves has been investigated using laboratory assays. Maximum BCF values in mussels of 100 were reported for tetrazepam and 51 for diazepam [89] and ranged from 200 to 800 for fluoxetine [86]. BAFs for diclofenac and propranolol in mussels (*Mytilus edulis*) ranged between 10 and 180 [90] and from 0.12 to 2 for oxytetracycline and from 0.27 to 0.55 for oxolinic acid [85]. No studies could be found reporting BCFs or BAFs for the uptake of pharmaceuticals by marine finfish.

Only one study has reported pharmaceutical concentrations in higher trophic level marine organisms. Federova *et al.* [83] reported a flumequine concentration of 2.9 ng g<sup>-1</sup> in an Eastern Central Atlantic shark sample. It is probable that trophic transfer of pharmaceuticals to top level predators including sharks, dolphins and whales is occurring in coastal ecosystems. Six anti-depressants and ethinyloestradiol were measured at trace concentrations (below quantitative limit to 4 ng ml<sup>-1</sup>) in plasma from bull sharks (*Carcharhinus leucas*) caught in the Caloosahatchee River, a wastewater impacted freshwater tributary of Florida's Charlotte Harbour [91]. The personal care product triclosan has been detected in plasma from wild Atlantic bottlenose dolphins (*Tursiops truncatus*) [92] and UV filters have been detected in Franciscana dolphins (*Pontoporia blainvillei*) [93]. Coastal avian species that feed on fish and shellfish may also be chronically exposed to pharmaceuticals.

## 4. Biological impacts in marine organisms

### (a) Marine ecotoxicology studies

While the body of work on the aquatic ecotoxicology of both human and veterinary pharmaceuticals is steadily growing, there is currently minimal data on the toxicity of pharmaceuticals to marine organisms. Only one study reporting field ecotoxicity data for marine organisms could be found. Exposure of benthic microalgal communities in the North Inlet Estuary (USA) to the antimicrobial tylosin in sediments

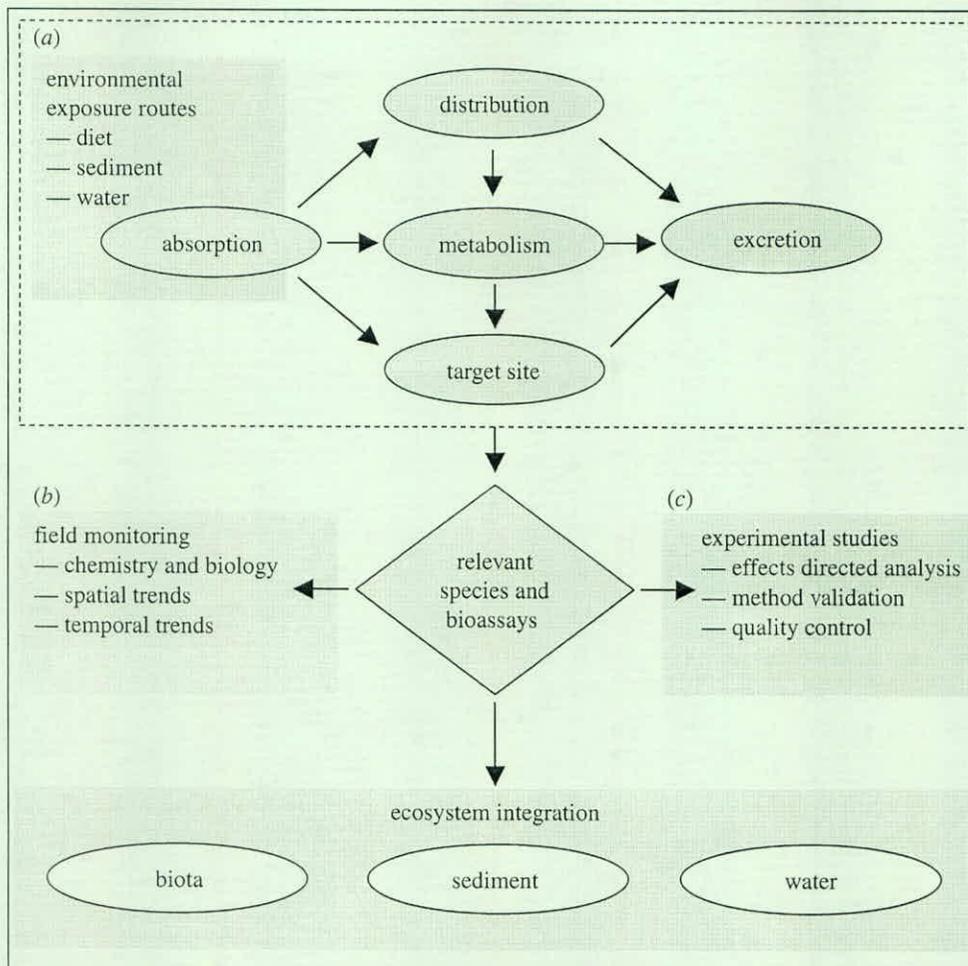
resulted in reduction of microalgal biomass and primary productivity and retarded diatom growth [94]. Laboratory ecotoxicity data could be found for 22 compounds and for the majority of compounds only one or two studies have been undertaken using marine organisms (electronic supplementary material, table S7). Fluoxetine was the exception, with marine ecotoxicity data reported in seven studies. Marine ecotoxicity laboratory data could be found for only seven of the 20 pharmaceuticals most frequently reported in seawater highlighting the current gap between researchers focusing on environmental presence and researchers focusing on ecotoxicity (table 1). Only one of these studies investigated the toxicity to sediment dwelling organisms [95]. A limited range of marine organisms have been tested to date including primary producers (e.g. microalgae and diatoms), primary consumers (e.g. bivalve molluscs and copepods) and consumers (e.g. crustaceans and fish). It is of great concern that in most studies nominal rather than measured pharmaceutical exposure concentrations were used.

Despite the limited number of studies, a wide variety of adverse effects have been reported for marine organisms with the effects being both test species and pharmaceutical specific. Examples of reported adverse effects for analgesics include reduced feeding rates [96], impacts on survival [97], reduced mussel byssus strength [90] and changes in immune response [96] and biochemical markers [98]. Studies have tended to focus on endpoints related to the therapeutic mode of action of the pharmaceutical. For example, reduced survival and developmental effects have been reported for anti-cancer drugs whereas studies on anti-depressant drugs have focused on neurobehavioural endpoints and spawning [99,100]. The reported no observable effect concentrations (NOECs) and lowest observable effect concentrations (LOECs) ranged from several orders of magnitude above environmental concentrations to comparable to reported environmental concentrations. For example, despite the NOECs for diclofenac for effects on byssus strength and oxidative stress in mussels of 1000  $\mu\text{g l}^{-1}$  [101], transient tissue-specific changes were reported after a 7 day exposure to 0.25  $\mu\text{g l}^{-1}$  diclofenac [98], a concentration well within the range reported in seawater (table 1).

Pharmaceuticals are present in marine ecosystems as mixtures complicating risk assessments. These complex mixtures may contain a wide variety of pharmaceuticals and other contaminants as well as a number of compounds from the same class (e.g. quinolone antibiotics) or with similar modes of action (e.g. non-steroidal anti-inflammatories) [102]. Additive effects have been reported for mixtures of pharmaceuticals on marine organisms. DeLorenzo & Fleming [103] investigated the toxicity of six pharmaceuticals and personal care products to the marine phytoplankton species *Dunaliella tertiolecta* both singly and in binary mixtures and reported additive toxicity for a mixture containing simvastatin and clofibrac acid. As mixture toxicity effects including synergistic effects have also been reported for freshwater organisms and cell lines [104,105], NOECs and LOECs derived from single substance testing may not be sufficient for deriving environmental quality standards [106].

There is a need to assess the impacts of pharmaceuticals on marine food webs. Marine food webs could either be directly affected through bioaccumulation of pharmaceuticals in the food chain to toxic levels or indirectly through the loss of a key species particularly sensitive to pharmaceuticals. The impacts of pharmaceuticals on primary producers such as phytoplankton is a key concern for marine ecosystems due





**Figure 1.** Adverse outcome pathways of chemicals fundamentally reflect patterns of absorption, distribution, metabolism, excretion and target sites in either acute or chronic exposure scenarios pertinent to marine contaminant monitoring. (Adapted from Hutchinson *et al.* [113].)

to the potential follow on effects on nutrient cycling and availability of food for other organisms [103]. Similarly, endocrine disrupting compounds which impact growth and reproduction in fish have the potential to affect predator and prey species [107].

### (b) Antibiotic resistance

Exposure of microorganisms to sub-lethal concentrations of antimicrobial compounds including antibiotics can induce antibiotic resistance. The rapid development of antibiotic resistance in bacteria is considered to be a global health security emergency and attention is being focused on mechanisms of transfer of antibiotic-resistant bacteria between species and identifying aquatic environmental reservoirs [108]. As high rates of horizontal gene transfer have been reported for marine bacteria [109], the contribution of contaminants in the marine environment to induction of antibiotic resistance and pathways for dispersal of clinically relevant antibiotic-resistant pathogens warrant further investigation. The development of antibiotic resistance in marine bacteria has been linked with wastewater discharges and the use of antibiotics in aquaculture [33,58]. Widespread antibiotic resistance has been reported in fish, marine mammals and seabirds living in coastal waters including in the North Eastern United States [110]. Higher prevalence of antibiotic-resistant strains of bacteria has been reported for marine wildlife populations exposed to sewage [111] and there is evidence to suggest that the antibiotic-resistant bacteria present in seabirds are of human origin [112]. The presence of antibiotic resistance

genes in marine ecosystems may be an indicator of ecological shifts occurring due to the presence of pharmaceuticals [113].

## 5. Data gaps and priorities for future research

This review has highlighted that human and veterinary pharmaceuticals and their transformation products (including metabolites) are present in coastal ecosystems. Occurrence data for the marine environment are only available for a tiny fraction of the large number of pharmaceuticals currently in global use. There are extremely limited laboratory ecotoxicology data for the impacts of pharmaceuticals on marine organisms and a marked lack of field data. As for other ecosystems, a forward-looking prioritization approach is needed for the marine risk assessment of both generic and novel prescription pharmaceuticals. For example, such an approach has been successfully used for Tamiflu that involved defining both the predicted exposure concentration ( $PEC_{\text{marine}}$ ) and predicted no-effect concentrations ( $PNEC_{\text{marine}}$ ) to provide a prospective risk assessment [8]. For the  $PNEC_{\text{marine}}$  to be reliable, it is important to consider the mode of action of the pharmaceutical, for instance, through the evaluation of Adverse Outcome Pathways in freshwater organisms and to extrapolate this to marine species [114] (figure 1). An Adverse Outcome Pathway is a conceptual framework for the link between exposure, the interaction of a contaminant at the molecular level within a cell and an adverse outcome or toxicological endpoint at the individual or community level.

Mechanisms for the increased sharing of data also need to be developed and a number of schemes have been developed in Europe (see the Swedish scheme [www.fass.se](http://www.fass.se) and <http://www.lif.se/default.aspx?id=29916> and the Norman network's EMPODAT Database [www.norman-network.net/empodat](http://www.norman-network.net/empodat)) and by individual companies through their Material Safety Data Sheets for specific pharmaceuticals. More widely, Daughton [56] recently proposed the development of a database on pharmaceutical occurrence in the environment, contributed to and curated by the wider science community.

The monitoring of prioritized pharmaceuticals and relevant metabolites in coastal environments should be considered as complementary to prospective risk assessments and include both dissolved and particulate fractions. In Europe, the Water Framework Directive (WFD; Directive 2000/60/EC) covers both freshwaters and transitional waters (the estuarine and coastal area up to one nautical mile, or 1.85 km, from the shore). Two hormones (17 $\alpha$ -ethinyloestradiol and 17 $\beta$ -oestradiol) and diclofenac have been placed on a watch list for emerging pollutants under the WFD. In a global context, it would be prudent to develop a monitoring suite of priority pharmaceuticals and transformation products that can be used in conjunction with biological assays to identify marine environments at risk from major centres of pharmaceutical inputs (e.g. WWTPs from megacities, intensive areas of aquaculture and pharmaceutical manufacturing industries).

As highlighted in reviews for pharmaceutical concentrations in freshwater [1] there is a marked absence of data for pharmaceuticals in marine environments in many regions (notably Africa, South America and small island nations in Oceania). These data gaps could easily be overcome by collaboration between well-resourced groups, with access to appropriate technology and validated analytical methods in developed countries, and local scientists in developing countries, at the same time providing valuable scientific and technical training.

The majority of data reported to date for pharmaceutical concentrations in marine organisms are for antibiotics used in aquaculture. In contrast, there are limited data for the accumulation of other classes of pharmaceuticals, their metabolites and transformation products in marine organisms. Further research is required to identify appropriate analytical methods for risk assessments for fish and shellfish to ensure that potentially reversible pharmaceutical metabolite conjugates are accounted for.

There are insufficient data on the potential for impacts on higher trophic levels, either through trophic transfer of pharmaceuticals or indirect effects, such as limited availability of food, due to impacts on lower trophic levels including algae. For high priority pharmaceuticals, it would be desirable to extend the environmental assessment to include fish-eating birds and mammals as recently illustrated by Murray Smith *et al.* [115].

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## IMPACT OF PHARMACEUTICAL WASTES ON HUMAN LIFE AND ENVIRONMENT

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### ABSTRACT

Now days, concerns about the occurrence and fate of active pharmaceutical ingredients, solvents, Intermediates and raw materials that could be present in water and wastewater including pharmaceutical industry waste water have gained increasing attention. Traditional wastewater treatment methods, such as activated sludge, are not sufficient for the complete removal of active pharmaceutical ingredients and other wastewater constituents from these waters. Environment and health are directly or indirectly affected by pharmaceutical effluents especially in the vicinity of pharma industrial zones. Though untreated or partially treated effluents released by pharma industries, drinking water sources are being polluted. Different classes of pharmaceutical compounds like analgesic, antidepressant, antihypertensive, contraceptive, antibiotic, steroids and hormones etc. have been detected in water samples from mg/L to µg/L range. Though the detected amounts are very minute but highly toxic for human, animal and aquatic lives. There is a need of regular monitoring of concentration of pharmaceutical compounds in pharmaceutical effluents entering into drinking water sources in order to save environment as well as living form of lives from health hazards. The present paper highlights such toxicity, health risk and assessment of environmental hazards due to pharmaceutical pollutants.

**Key words:** Pharmaceutical effluent, Industrial wastewater, Health Hazards.

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### INTRODUCTION

Pharmaceutical compounds are being used for several beneficial purposes in modern society but simultaneously pharma industries are releasing very toxic contaminants in the environment directly or after chemical modifications.<sup>1</sup> Moreover, pharmaceutical compounds may enter the environment by different routes such as discharge of treated wastewater, seepage from landfills sites, sewer lines, runoff from animal wastes etc.<sup>2,3</sup> Even though various physical and biological processes occurring in aquatic ecosystem may cause reduction of many pharmaceutical compounds, trace concentrations of human and veterinary pharmaceutical compounds as well as their metabolites have been detected in different water bodies like surface water, groundwater and drinking water sources.<sup>4-6</sup> The pharmaceutical industry in India is the world's third-largest in terms of volume and stands 14th rank in terms of value. It is growing at about 8 to 9 percent annually and is estimated to be worth 4.5 billion dollar. Different industries including pharmaceuticals, chemicals, paints etc. are speedily growing in India which disposes off their effluents into the streams either directly or after partial treatment.<sup>7</sup> It has been found that the pharmaceutical compounds reach the environment and can be considered as environmental pollutants. Several pharmaceutical production facilities were found to be sources of much higher environmental concentrations than those caused by the applications of drugs.<sup>8</sup> Generally, pharmaceutical industries generate a huge quantity of wastes during manufacturing and maintenance operations. Pharmaceuticals have been detected in wastewater treatment plant effluents and drinking water sources. Trace amount of pharmaceuticals in drinking water for longer duration may cause considerable adverse effects to human health and aquatic life, though concentrations of pharmaceuticals detected in drinking water (in nano gram per liter range) are several orders of lower magnitude than the minimum therapeutic dose.<sup>9</sup> There is currently no Bureau of Indian Standards (BIS)/ regulations limiting the levels of pharmaceuticals in wastewater or drinking water. However, the United States Environmental Protection Agency<sup>10</sup> has added four pharmaceutical compounds, which extensively used by human, to the most recent contaminant



candidate list (CCL 3) including three birth control substances and one antibiotic. The present paper highlights and reviews the impact of pharmaceutical effluents on nearby drinking water sources.

### General Environmental Pollutants i.e. Pharmaceutical Compounds

Pharmaceutical drugs being used for human as well as veterinary medicines are emerging as environmental pollutants. Different pharmaceuticals have been classified as Analgesics, Antibiotics, Antiepileptic, Antiseptics, Beta-blockers, Antihypertensive, Hormones, Contraceptives, Psychotherapeutics and Anti Virals.<sup>11</sup>

### Pharmaceuticals in the Environment

The environmental exposure routes of pharmaceuticals into the environment are manufacturing units and hospital effluents, land applications (e.g., bio solids and water reuse) etc.<sup>12</sup> However; sewage treatment services are not always successful in removing the active chemicals from waste-water. Consequently, pharmaceuticals find their way into the aquatic environment, where they directly affect aquatic organisms and can be incorporated into food chains. In a recent study, the extraordinarily high levels (mg/L) of several drugs were found in the effluents from local wastewater treatment plant near Visakhapatnam in India.

### Toxicity due to Some Pharmaceutical Compounds

Studies on antibiotics have shown that up to 95% of antibiotic compounds can be released unaltered into the sewage system. Moreover, higher concentrations of antibiotics can lead to change in microbial community structure and ultimately affect food chains. Non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, naproxen and diclofenac are widely being used and consequently are frequently detected in sewage, surface water and may be found in ground water system. Ibuprofen, ketoprofen, naproxen, indomethacin, diclofenac, acetyl salicylic acid and phenazone have been found in surface water system. However, diclofenac, ibuprofen and propyphenazone are the most commonly found drugs in the water bodies after clofibrac acid. Moreover, diclofenac has been proven to be highly toxic for vultures and cattle's.<sup>13</sup> NSAIDs like ibuprofen, naproxen and aspirin are the most commonly used drugs, which are usually found in effective quantities in municipal effluents.<sup>14,15</sup>

### Properties of Pharmaceutical Effluents

Many pharmaceutical industries are responsible to generate toxic effluent as a consequence of their operation. The waste water generated from these industries possess solids, biodegradable and non degradable organic compounds etc. Pharmaceutical effluents offer basic information about the reliability of the aquatic habitat in rivers and streams, into which they are discharged. The physico-chemical analysis of the effluents should indicate that most of these industries obey the standard guidelines of Federal Environmental Protection Agency (FEPA).<sup>10</sup> An important pollution index of industrial wastewaters is the oxygen content in chemical oxygen demand (COD) and biological oxygen demand (BOD), where the nutrients status are measured in terms of amount of nitrogen and phosphorus in waste water. Besides this, other significant water quality parameters include pH, temperature and total suspended solids (TSS).<sup>16</sup> However; pharmaceutical effluents are also categorized by their unusual turbidity, conductivity, COD, TSS and total hardness.

### Pharmaceuticals Analysis in Drinking Water

The mystery of pharmaceutical occurrence in drinking water has particularly concerned the public health. While unpleasant human health results from the existing levels of drugs and pharmaceuticals in drinking water are highly unlikely, the resulting impacts to aquatic ecosystems are more dangerous. Moreover, pharmaceuticals have been detected in waters for more than four decades. In the past decade, the number of papers on the analysis of drugs or pharmaceuticals in drinking water sources has increased considerably.<sup>2-5</sup>



In a monitoring study, out of fourteen pharmaceutical drugs analyzed, some pharmaceuticals like acetaminophen (detection frequency 0.32%), codeine (0.16%), p-xanthine (0.08%), sulfamethoxazole (0.41%), caffeine (0.24%), carbamazepine (1.5%) and trimethoprim (0.08%) have been detected at concentrations more than or equal to detection limits of selected methods. Besides, detection frequencies of pesticides (33%) and trihalomethanes (28%) in the same sources were reported considerably higher<sup>17</sup>. The pharmaceuticals have been identified in water cycle at trace levels by advanced analytical techniques and instrumentation. Several reports have confirmed the presence of pharmaceuticals in effluents of pharma industries and in municipal wastewaters and these have been recognized as a major source of drugs and pharmaceuticals in drinking water. Most of the research work has been performed on the analysis and detection of pharmaceutical in drinking water samples in developed countries including USA, Japan, the Republic of Korea and some countries in Europe.<sup>9</sup>

### Health Risk of Pharmaceutical Effluents

The long term exposure of lower concentration of complex pharmaceutical mixtures on stream biota may result in acute and chronic damages<sup>18,19</sup>, behavioral changes<sup>20,21</sup>, accumulation in tissues<sup>22</sup>, reproductive damage<sup>23</sup> and inhibition of cell proliferation.<sup>24</sup> Several studies have demonstrated that fish exposed to wastewater effluents can exhibit reproductive abnormalities. Moreover, fish exposed to trace levels of birth control pharmaceuticals in the range of concentrations found in the environment show dramatic decreases in reproductive success, suggesting population level impacts are possible.<sup>25</sup>

### Assessment of Environmental Hazard

Globally, the detection of waste pharmaceuticals in the environment creates the risks, which are associated with their introduction into human, aquatic life and wildlife and is becoming a serious problem equally for both regulators and the pharma industry. Significant success on this issue is simply not achievable with the currently limited state of knowledge on environmental transport, fate, and effects of pharmaceuticals. There is need to take into consideration the possible growing effects of different drugs affecting the same receptors<sup>12</sup>. Risk assessment of the pharma chemicals involves the detection of the inherent hazards at each stage and an estimation of the risks due to these hazards.

### CONCLUSION

Currently, pharmaceutical compounds are being merged into the environment in extremely large quantities regularly and present system of regulations of their release is not able to control the untreated or partially treated pharma effluents. The impacts of drugs are entering into and occurring on ecosystems, biota and humans. The side effects on human, aquatic and animal health need to be investigated through thorough safety and toxicological studies. Sincere efforts are required to reduce the problem along with some adequate regulations to monitor or to control them. Water quality guidelines enforced in India needs to include analysis of most commonly used pharmaceutical compounds in drinking water sources. Moreover, the latest remedial measures need to be adopted at large in effluent treatment plants of pharmaceutical industrial units to check long term environmental and health hazards.

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ANALYSIS

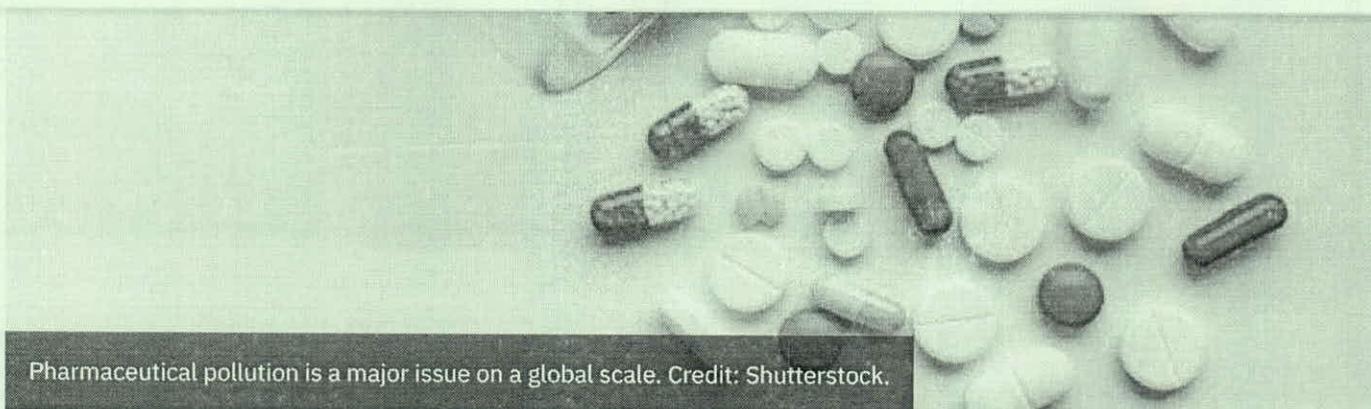
# Pharma and the environment: pollution continues despite public pressure

By Allie Nawrat | 02 Oct 2018 (Last Updated January 27th, 2020 05:10)

The negative impact of the production of pharmaceutical products on the natural environment is well known. However, this remains largely unregulated, meaning the extremely toxic impact it has on both animals and humans continues with no clear end in sight.



## PHARMACEUTICAL TECHNOLOGY



Pharmaceutical pollution is a major issue on a global scale. Credit: Shutterstock.



Over the past 30 years, international organisations and the pharmaceutical industry have begun to notice that the detrimental impact pharma products have on the environment on a global scale.



Pharmaceutical products enter the environment at various stages of their life-cycle, but particularly during the production phase. One of the main threats is that discharging antibiotics into the environment can promote the natural development of antibiotic-resistant pathogens that are harder to treat. Lord Jim O'Neill noted this trend in his 2016 UK government-funded independent Review on Antimicrobial Resistance.

Although it is a global issue, like other environmental issues, pharma pollution more directly and seriously affects those living near production plants whose water and food sources are contaminated with waste pharma products.

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## &A: SmartSense Sales Director Josh Griggs

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Backed by global internet of things (IoT) leader Digi International, SmartSense delivers IoT solutions for leaders in the retail pharmaceutical

Health Care Without Harm (HCWH) Europe runs the Safer Pharma campaign to raise awareness of the negative relationship between pharma and the environment and challenge the healthcare industry to clean up its production.

“The production of both active pharmaceutical ingredients (APIs) and finished dose antibiotics is concentrated in specific locations so the resulting point, source pollution, is in incredibly high concentrations and encourages the development of drug resistance,” says HCWH Europe pharmaceuticals policy officer Dr Adela Maghear. “This practice has a detrimental impact on vulnerable populations living near manufacturing facilities and wastewater treatment plants in these countries.”



The pollution of pharma products into the environment also adversely affects animals, particularly fish living in contaminated water. For example, a report published in science journal Nature in 2009 noted that ‘many of Europe’s rivers are home to male fish that are ‘intersex’ and so display female sexual characteristics, including female reproductive anatomy. Some males also produce vitellogenin, a protein normally found in eggs that can be induced in males by hormone exposure’.

Another large study of this problem in 2004 by the UK government’s Environment Agency found that 86% of male fish sampled at 51 sites around the country were intersex.” This phenomenon is blamed upon pollution of the contraceptive pill and its API, ethynyl oestradiol.

## Reforming the relationship between pharma and the environment

This awareness has led to a number of initiatives to try to better understand the consequences of pharma production on the environment and how this can be mitigated.



Poll |

**In your opinion, which of the following is a potential barrier to widespread adoption of sustainability principles in tourism activities?**

*Please rank, with 1 being the most and 5 being the least relevant factor*

	1- Most relevant factor	2	3	4	5- Least relevant factor
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Awareness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Next

An early initiative was the European Commission's environmental risk assessment of pharma products (ERAPharm). Between 2004 and 2007, ERAPharm tracked the fate and effect of pharma products in the environment in order to educate and inform legislators. It primarily focused on three compounds: the  $\beta$ -blocker atenolol, fluoxetine, an anti-depressant, and the veterinary parasiticide ivermectin.

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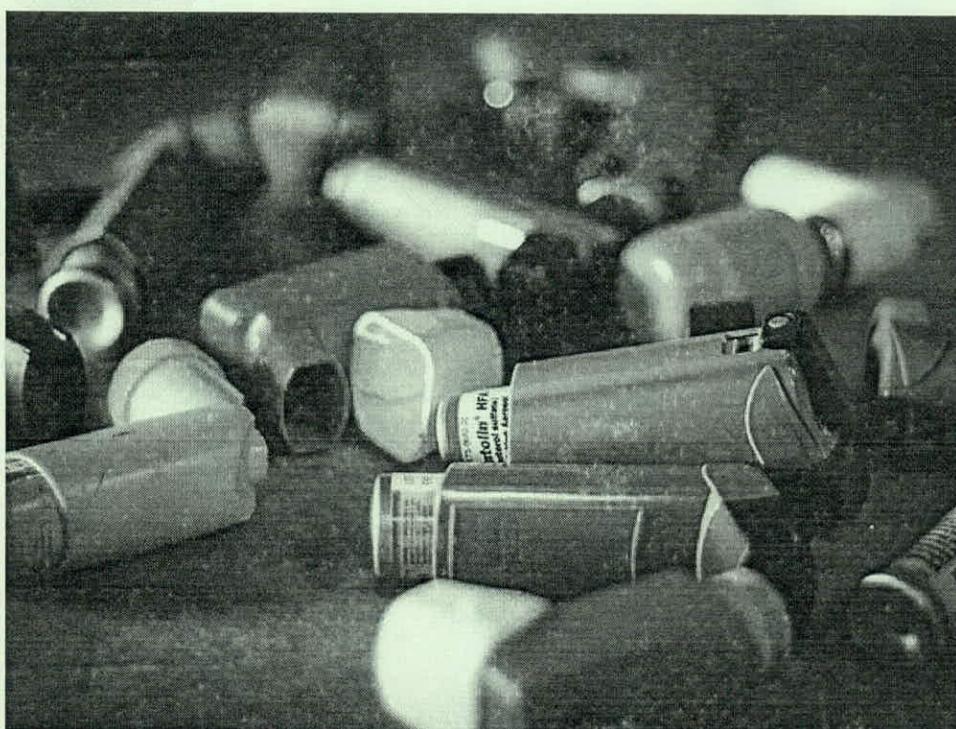
## &A: SmartSense Sales Director Josh Griggs

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Backed by global internet of things (IoT) leader Digi International, SmartSense delivers IoT solutions for leaders in the retail pharmaceutical

In Europe, this was followed by, among others, commitments by the European Federation of Pharmaceutical Industries and Associations (EFPIA) to reduce the presence of pharmaceuticals in the environment.

Must Read



### World Asthma Day: can fevipiprant revolutionise asthma treatment?

Unfortunately EFPIA’s primary course of action seems to be to push the burden of responsible pharma disposal to patients, according to Maghear, ‘This moves focus away from the fact that pharmaceutical companies should be cleaning up their own production and supply chains and investing in biodegradable pharmaceuticals’.

She believes: “Solely focusing on one pathway, as the EFPIA declaration suggests, will not ensure long-term



protection of the environment.”

However, despite recognition of the destructive impact the pharma industry has on the environment, the US Food and Drug Administration and European Medicines Agency have not moved to include environmental standards in their good manufacturing practices guidelines.

In addition, there is a lack of legislation and regulation on a local, regional and global level focusing on reducing the negative impact of the pharmaceutical industry on the environment; for example, Maghear explains there is no legislation requiring pharma companies to report environmental incidents.

Non-governmental organisation (NGO) Changing Markets, which has organised awareness campaigns on the issue of pharmaceuticals in the environment agreed, telling The Bureau of Investigative Journalism in January: “There is a crying lack of transparency about pharmaceutical supply chains which means that we know practically nothing about where our drugs are made. This is a scandal and pharmaceutical companies will face increasing calls to do something about it.”

The main role of HCWH Europe’s Safer Pharma campaign, according to Maghear, is ‘to push the EU to be the first region to legislate on pharmaceutical pollution – leveraging health professionals’ leadership role in tackling this issue’. They have made some progress, however, there is a long way to go and environmental breaches continue to occur across the world.

## Case study: contaminated water in Hyderabad, India

In November 2016, German scientists found that all of the specimens collected from sampling sites in the direct environment of bulk drug manufacturing facilities in



Hyderabad and nearby villages, known as the Patancheru-Bollaram zone, India, were contaminated with antimicrobials.

They also found 95% contained worryingly high levels of bacteria and fungi resistant to antibiotic drugs.

These findings led the researchers to conclude: “Insufficient wastewater management by bulk drug manufacturing facilities leads to unprecedented contamination of water resources with antimicrobial pharmaceuticals, which seems to be associated with the selection and dissemination of carbapenemase-producing pathogens.” The findings were published in the *Infection* journal in August 2017.

Hyderabad is where 50% of India’s drug exports are produced – there are approximately 170 companies operating in the area – and India is the world’s fifth largest producer of generic drugs.

A contributor to the study, German media company NDR, found that 19 companies operating in the area were suppliers of antibiotics to the European market.

This grievous level of pharma pollution exists despite NGO, governmental and judicial pressure on companies operating in the area to clean up their act. In 2009, the Patancheru-Bollaram zone was classified in India’s national pollution index as ‘critically polluted’ and in 2016, the country’s Supreme Court ordered pharma companies to implement a zero liquid waste policy.

Safer Pharma notes that ‘contamination of water sources with antimicrobial drugs (combined with mass misuse of antibiotics and poor sanitation) has had grave consequences in India, where an estimated 58,000 newborns die from multidrug-resistant infections every year’. These figures are based on a research project by



Laximnarayan, Duse, Wattal et al published in The Lancet in November 2013.

The immense scale of the pollution problem from drug manufacturing has pushed Indian public health professionals, campaign groups and local people to call on the European Union (EU) to revise good manufacturing practices and include these considerations during factory inspections. The letter follows the EU's announcement that it had scrapped plans to clampdown on pharma pollution.

Campaigners hope that pressure from local groups directly affected by the pharma industry's pollution will persuade the EU to reverse its earlier decision and, along with the industry and other governments, fulfill its unmet promises to mitigate the environmental consequences of drug manufacturing.

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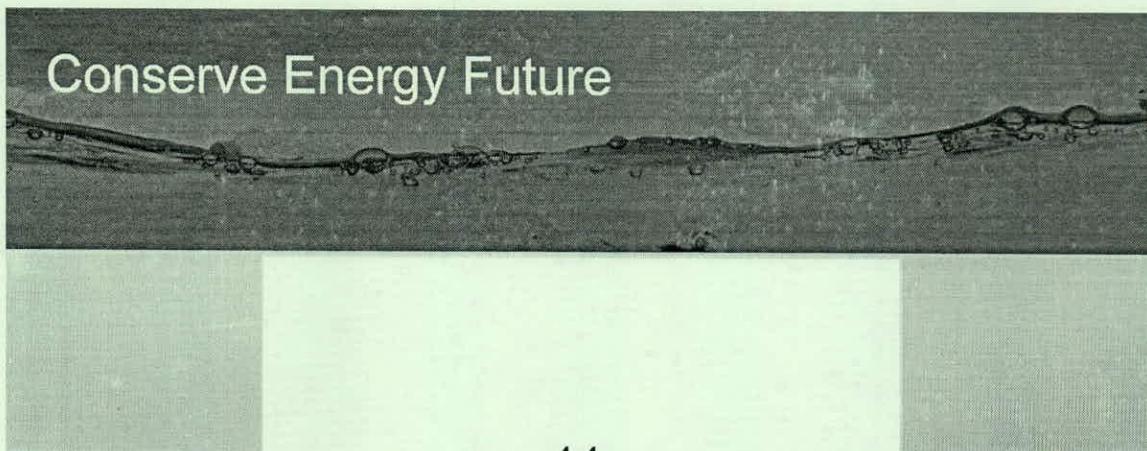




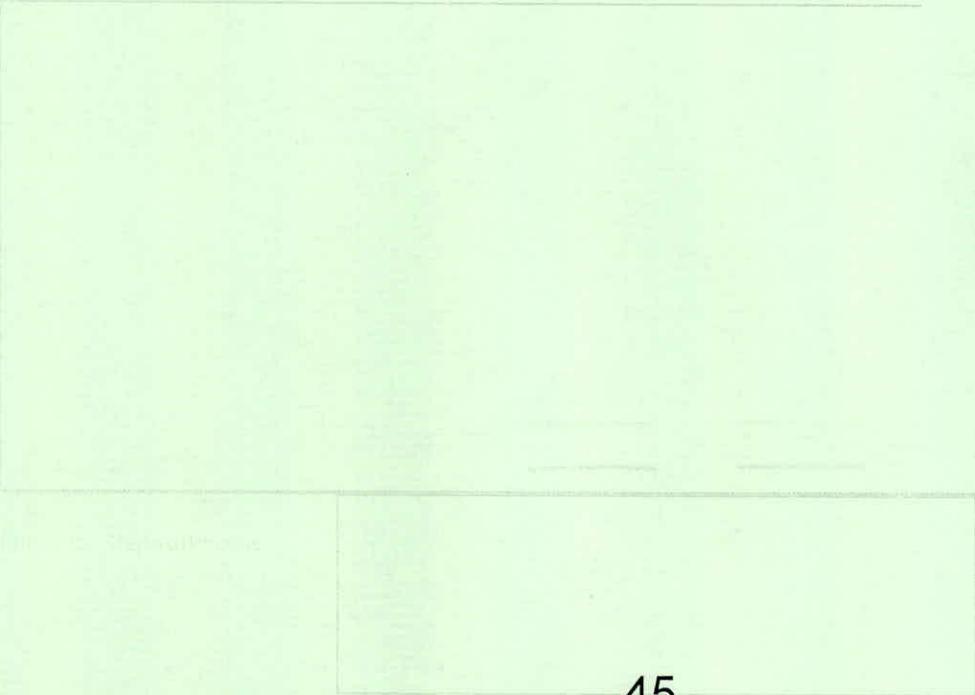
## What is Pharmaceutical Pollution?

As the world’s population continues to expand, pharmaceutical products – generally drugs and chemical-based care products have continued to become more prevalent. Their significance in modern life cannot be underestimated, but then again, their use and disposal is bringing about massive concerns in regard to environmental pollution.

A great example is the pollution of water systems, where pharmaceuticals are released into the environment and reach aquatic systems such as lakes, oceans, rivers, and groundwater. Pharmaceutical plants are often incapable of filtering out all the chemical compounds used in their manufacturing process and as such, the chemicals will seep into the surrounding freshwater systems and eventually into the oceans, lakes, streams, and rivers.



# SOURCES AND CAUSES OF WATER POLLUTION



Many urban and rural sources of groundwater, although clean and pure enough to drink, for example, contain trace amounts of pharmaceutical ingredients, from birth control pills, antidepressants, painkillers, shampoos, anti-epileptics, caffeine, and many other pharma products.

Wastewater from pharmaceutical manufacturers is also sometimes discharged into open fields and nearby water bodies, thereby increasing the pharmaceutical waste or their by-product load in the environment, landfills, or dumping areas. **All this is basically known as pharmaceutical pollution, and this article looks at the causes, effects, and solutions to pharmaceutical pollution.**

**Contents** [show]

## Causes of Pharmaceutical Pollution

### 1. The Drugs We Use and How They are Ingested and Expelled!

Our bodies metabolize only a fraction of the majority of the drugs we swallow. The remaining part can be sweated out, but the large part is excreted from the body through urine or fecal matter, meaning the excreta will be part of the wastewater and eventually will be in the environment.



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## 2. Healthcare Institutions

Hospitals and nursing homes also contribute to pharmaceutical pollution. Hospitals, in particular, might be less of a problem as they have on-site pharmacies with arrangements to return the unused drugs to the manufacturers for credit or disposal.

Nursing homes, on the other hand, are particularly guilty of flushing medications down the toilet or drain, especially if a patient dies or is transferred to another facility, mainly because in most cases, they do not have a similar return policy with drug manufacturers as hospitals.

**See also** [Various Types and Serious Effects of Pollution You Can't Afford To Miss](#) 

The rule of getting rid of the opioid painkillers is to flush them down the drain as it is an acceptable option, encouraging them to flush down all their leftover medications.



### 3. Di

Althou Il guilty of  
contributing to pharmaceutical pollution. Some will dispose of the drugs  
in a landfill, and some will flush them, among many other ways of  
disposing of the drugs.

A US Geological Survey study revealed contamination levels downstream  
from two drug manufacturing plants in the state of New York, which were  
between ten and 1,000 times higher than those at comparable facilities in  
the country.

### 4. Agriculture and Agro-products

Like humans, not all the drugs fed to domesticated animals are  
metabolized by their bodies. For this reason, they excrete parts of the  
drugs that remain undigested. About 2 trillion pounds of animal waste,  
which is generated by large-scale poultry and livestock operations in the  
United States, was found to be laced with hormones and antibiotics fed to  
animals.

The drugs and horm rock and poultry  
grow faster as well s such, and  
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groundwater or get into waterways and contribute to pharmaceutical pollution.

## 5. Human Domestic Drug Use and Disposal Behavior

We as consumers are responsible for a significant amount of the pharmaceutical and personal care products that end up in streams, groundwater, lakes, and rivers. It is not uncommon to find a home cabinet full of unused and expired drugs. The problem is that out of all these drugs, only a fraction is disposed of properly.

For instance, data collected in 2007 from a medication collection program in California, suggested that only about 50% of all medications, prescription and over-the-counter, were discarded properly. Even if that figure is a huge estimate, and the real proportion could be lower, the conclusion is that there is a lot of unused and mostly expired medication that potentially gets into the water systems.

Effects of Pharm

1. Effects on F



A number of studies have indicated that Oestrogen and chemicals that behave like it, have a feminizing effect on male fish and can alter female-to-male ratios. Such Oestrogen can be found in birth control pills and postmenopausal hormone treatments.

The Potomac River, in the United States, is known to have several intersex fish, which are fish with both male and female characteristics, mainly because of the pollution of the river in different sections.

Because of the higher Oestrogen levels in the downstream water from the river, there are more female and intersex fish downstream from the plants that pollute it. Popular antidepressant medications have also been found concentrated in the brain tissue of fish downstream from wastewater treatment plants.

## 2. Disrupting the Normal Operations of the Sewerage Process

Antibiotics are widely used in medicine that can disrupt the

contain material microbial ecology



of surface water. Antibiotics present in the sewage treatment systems can, therefore, inhibit the activities of the sewage bacteria, and therefore seriously affect the organic matter decomposition. Antibiotics can also be toxic to nitrifying bacteria in the wastewater treatment process.

**See also** Causes, Effects and Solutions of Agricultural Pollution on Our Environment 

### 3. Effect on Drinking Water

The chemicals present in these pharmaceuticals, find a way into waterways, after being excreted from the body or after being flushed down the toilet. Most municipal sewage treatment facilities do not remove these pharmaceutical compounds from your drinking water and as such, we end up consuming the same compounds.

They are found in very minimal concentration in rivers and streams as compared to the normal dose, but there is a growing concern that chronic exposure to these compounds could result in serious health issues. It is

also speculated that... logistically to cause...  
...are healthy...



For instance, **endocrine disruptors**, which come from agricultural, domestic and industrial sources such as pharmaceuticals, disrupt biological processes like growth, development and reproduction, which are regulated by hormones. Also according to a 2006 research by Italian researchers, a combination of pharmaceutical compounds inhibits the growth of embryonic kidney cells in laboratory tests.

Researchers first identified trace amounts of pharmaceutical drugs in surface water and groundwater in the early 1990s, sounding alarm bells ever since.

#### 4. Long-term Effects on the Environment

Some pharmaceutical compounds last a long time in the environment and in water supplies. Once the concentration reaches a certain level, usually around one part per million, the chemicals begin to affect the environment. Some drugs, like antiepileptics, are persistent, with some being pseudo-persistent, meaning, they degrade eventually, but after quite some time.

This means they co  
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bioaccumulate, enter a cell and move up food chains, becoming more concentrated in the process.

Surveys in Europe and the US, have found hundreds of these compounds in groundwater, sewage, surface water, wastewater from treatment plants and of course tap water. Polluted water from streams, lakes, rivers and other sources, will therefore eventually make its way into our bodies

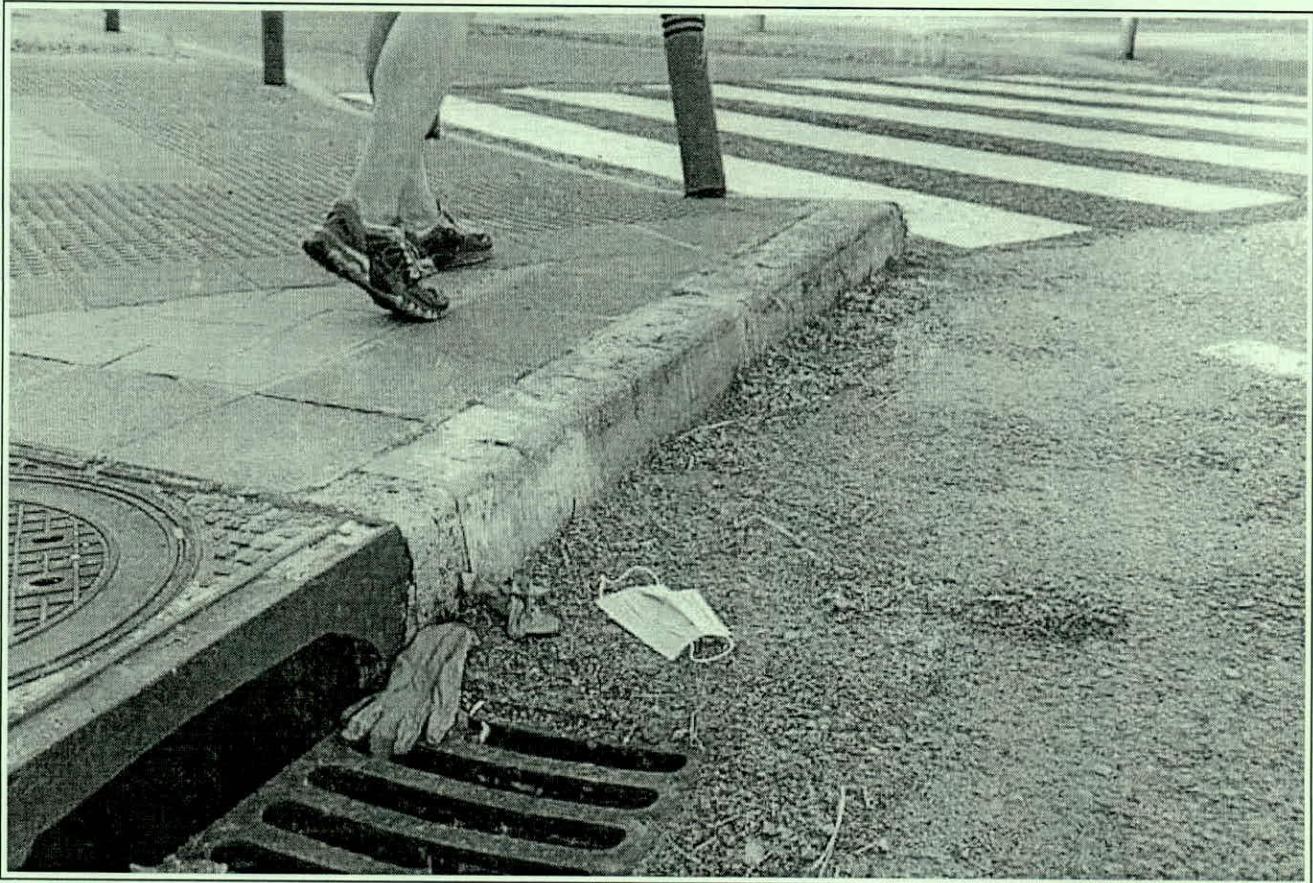


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### 5. Air

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Howe' caused by drug  
manufacturing pollution. This is the conclusion drawn from studies in 2016  
and 2017, focused on antibiotic manufacturing pollution in India and  
China.

### 6. Effects on Wildlife

Pharmaceuticals, flushed into the environment by humans, or through the  
sewage are also affecting wildlife. These animals are consuming water that  
contains these particles, or are preying on fish which swim in such waters.

Studies on the effects of pharmaceuticals on wildlife are little and have not  
led to conclusive results, but it is believed that these effects will soon  
affect the natural world massively. The little known results have shown  
that antidepressants reduce feeding in starlings and a contraceptive drug  
is decreasing fish populations in lakes.



See also [Air Quality Index: Categories and Types of Air Pollutants](#)



## Solutions to Pharmaceutical Pollution

### 1. Proper Drug Disposal

The easiest, cheapest, and most effective solution to pharmaceutical pollution is keeping the drugs from reaching the waterways in the first place. We should invest in public education on the proper disposal of drugs, as part of the drug take-back programs.

This way, people will know how to properly get rid of old or expired medicine without contributing to pharmaceutical pollution. awareness can also create initiatives that mitigate the effects already caused by pharmaceuticals on the environment.

### 2. Tougher Regulations

If tougher regulations are in place, they would help limit large-scale medicine flushing in hospitals, nursing homes and other healthcare institutions. Tougher regulations can be installed by the nation or state's department of health, or by the national body that handles health matters.



The institutions would restrict themselves from disposing of the drugs without proper procedure and would also ensure their relationship with drug manufacturers is in a way that they can return the drugs if they are expired.

### 3. Additional Research Pertaining to the Potential Dangers of Pharmaceutical Pollution

More research is desperately required to assess the potential human effects of pharmaceutical pollution. It will also address the best methods for removing the compounds at treatment plants in a way that is not hazardous or dangerous to the environment in general. If a significant long-term risk to public health is identified, more aggressive efforts can then be taken to control the problem as required.

### 4. Limit Bulk Purchases

Another solution is to limit the bulk purchases of pharmaceuticals. The majority of institutions and individuals purchase them in bulk since large volumes attract discounts, which makes the overall price more attractive.

However, it gives rise to a situation where there are large bottles of unused pills which ultimately end up being flushed or disposed of in the wrong way. Limiting bulk purchases will ensure only the required amount is supplied and therefore, less pharma pollution.



## 5. Trashing is Better Than Flushing

Throwing unused medication into the trash leads to them being incinerated or buried in landfills. It is a better way of disposing them than flushing or pouring them down the drain. However, if you are to trash them, do it properly. Remove them from their packaging, crush them, and seal them in a plastic bag with water.

More to that, add sawdust, coffee grounds, or cat litter or any other material that is unappealing. Although this is not for environmental reasons, it cuts down the chances that a child or animal might ingest the contents.

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### About Rinkesh

A true environmentalist by heart ❤️. Founded Conserve Energy Future with the sole motto of providing helpful information related to our rapidly depleting environment. Unless you strongly believe in Elon Musk's idea of making Mars as another habitable planet, do remember that there really is no



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Divi's Labs

Prasath Reddy | Hyderabad

Last Updated at March 22, 2017 02:14 IST



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In a big setback to Hyderabad-based active pharmaceutical ingredients (APIs) maker Divi's Laboratories Limited, the US Food and Drug Administration (USFDA) has issued an import alert on the company's Unit 2 facility at Visakhapatnam, Andhra Pradesh, though with certain exemptions.

The latest action comes after Divi's management had submitted a 700-page response in the light of Form 483 observations issued by the US drug regulator in December 2016. On December 7, 2016, the USFDA inspection team issued a Form 483 with five observations citing lack of proper control ...

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First Published: Wed, March 22 2017. 02:14 IST

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