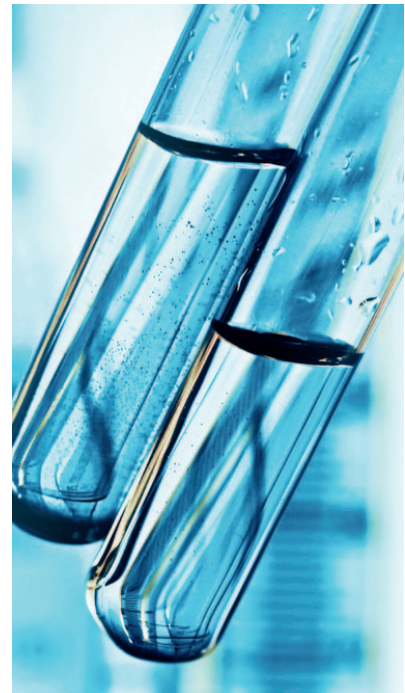


# Pharmaceuticals in the environment – the global perspective

## Occurrence, effects, and potential cooperative action under SAICM



## Imprint

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## Summary

Pharmaceuticals are a crucial element of modern medicine and confer significant benefits to society. About 4,000 active pharmaceutical ingredients are being administered worldwide in prescription medicines, over-the-counter therapeutic drugs, and veterinary drugs. Their active ingredients comprise a variety of synthetic chemicals produced by pharmaceutical companies in both the industrialized and the developing world at a rate of 100,000 tons per year. While pharmaceuticals are stringently regulated for efficacy and patient safety, the adverse side effects they may have in the natural environment have not yet been sufficiently studied and are not covered by an international agreement or arrangement.

Pharmaceutical residues have been increasingly measured in the environment over the past decade, mostly in surface waters, but also in groundwater, soil, manure, biota, and even in drinking water. Since pharmaceuticals are specifically designed to cause pharmacological effects in living organisms, it is not surprising that a growing body of literature has shown that pharmaceuticals are having adverse effects on wildlife and ecosystem health. It is challenging to assess the potential long-term health risks of trace amounts of pharmaceuticals in drinking water, especially given that drinking water is currently not systematically monitored for pharmaceutical residues. This situation has triggered public concerns about the aesthetic-hygienic quality of drinking water.

With better access to health care in developing nations and aging populations in industrialized countries, the production, use, and disposal of pharmaceuticals is expected to grow. As a result, unless adequate measures are taken to manage the related risks, pharmaceuticals will increasingly be released into the environment.

### Nomination as an emerging policy issue under SAICM

The Strategic Approach to International Chemicals Management (SAICM) has identified “Environmentally Persistent Pharmaceutical Pollutants” (EPPP) as a possible emerging policy issue for the International Conference on Chemicals Management (ICCM) to consider at its fourth session. An extended nomination dossier (SAICM/OEWG.2/INF/15) has been developed by the Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment for consideration at the second meeting of the Open-ended Working Group (OEWG2), to be held in Geneva on December 15-17, 2014.

A workshop held in Geneva on April 8-9, 2014 ([www.pharmaceuticals-in-the-environment.org](http://www.pharmaceuticals-in-the-environment.org)) concluded that SAICM could be used as a voluntary policy framework to address the issue of pharmaceuticals in the environment on a global scale. This could be done without compromising the effectiveness, availability, or affordability of medical treatment, especially in countries in which access to health care is still limited. Cooperative action under SAICM could initiate a multi-sectoral, multi-stakeholder, life-cycle approach to preventing, reducing, and managing pharmaceuticals in the environment.

# 1. Emission pathways of pharmaceuticals entering the environment

After passing through the body, pharmaceutically active ingredients are excreted either in an unchanged active form or as a metabolized substance (Figure 1). Municipal sewage collects a variety of human pharmaceuticals (and their metabolites) administered in households, hospitals, and for elderly care. Unused medicines that are improperly disposed in sinks and toilets also end up in municipal sewage. Conventional sewage treatment facilities, including activated sludge processes, do not fully remove pharmaceuticals from wastewater; indeed, removal efficiencies range from less than 20% to more than 80% for individual pharmaceuticals. Thus, residues are released into rivers, lakes, and groundwater aquifers. In addition, pharmaceutical manufacturing facilities have been shown to release active ingredients into nearby streams (Larsson et al. 2007).

Veterinary pharmaceuticals applied in animal husbandry are released into the soil environment where manure is used as fertilizer. Over time, residues from these drugs accumulate in the soil or drain into groundwater or surface water; they may also be taken up by plants (Carter et al. 2014). Veterinary pharmaceuticals used in aquaculture directly enter surface waters.

In the environment, transformation and degradation reactions alter the mobility, persistence, and fate of the pharmaceutical residues.

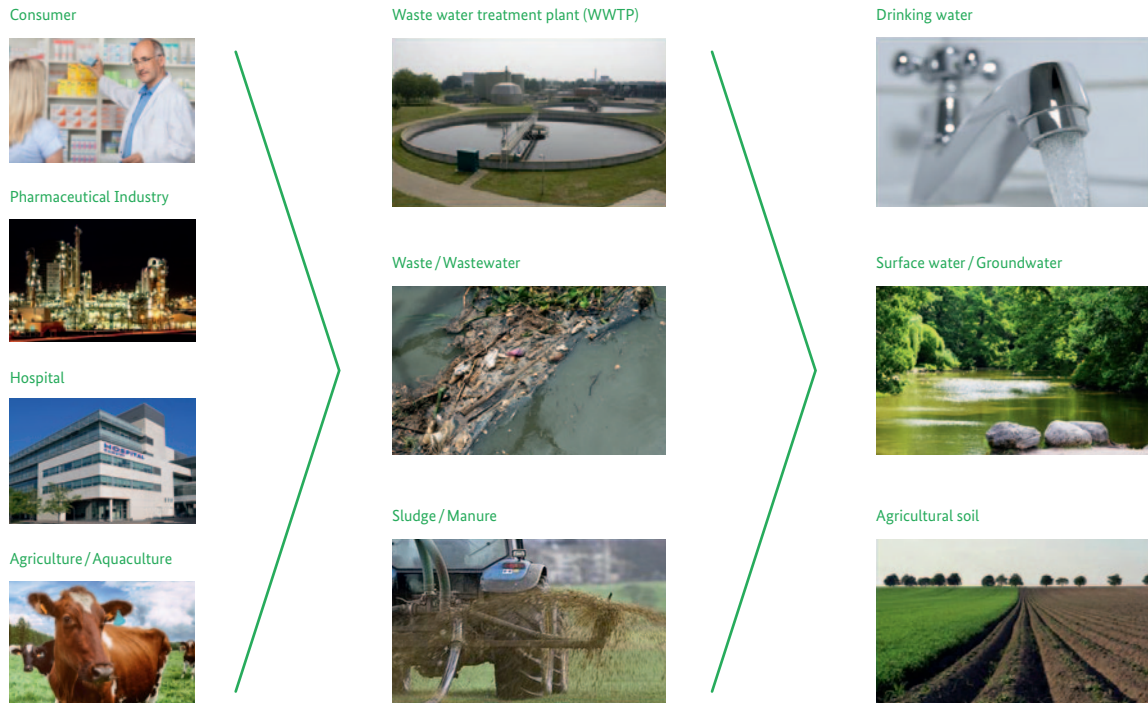


Figure 1: Main emission pathways of human and veterinary pharmaceuticals entering the environment.

## 2. Monitoring pharmaceutical residues in the environment

Advanced methods are required to monitor pharmaceuticals in different environmental matrices (e.g., surface water, groundwater, soil) at the relevant concentrations, in some cases down to nano-grams per litre. The required instrumental equipment – such as gas chromatography or liquid chromatography coupled to tandem mass spectrometry (GC-MS/MS or LC-MS/MS) – is quite expensive, both to acquire and maintain. While reliable methods have been established at laboratories worldwide, there is currently no internationally standardized analytical protocol for pharmaceuticals. Such a protocol could help to ensure both the quality and comparability of data.



Figure 2: Pharmaceuticals are found worldwide in surface water (Photo: IWW).

## 3. Global occurrence in the environment

A growing body of literature demonstrates that pharmaceutical residuals are found globally in the environment (IWW 2014; Hughes et al. 2013). Based on a review of more than 1,000 international publications, pharmaceutical residues have been detected in 71 countries worldwide in all five UN regional groups (Figure 3). Pharmaceuticals have mostly been detected in surface water and sewage effluent, but they have also been found in groundwater, manure, soil, and other environmental matrices. More than 600 active pharmaceutical substances (or their metabolites and transformation products) have been detected in the environment. These belong to a variety of therapeutic groups:

- antibiotics,
- analgesics,
- lipid-lowering drugs,
- beta-blockers,
- x-ray contrast media, and
- synthetic estrogens.

While most findings have been published in industrialized countries, monitoring campaigns are increasingly being conducted in developing and emerging countries; these have revealed the global scale of the occurrence of pharmaceuticals in the environment. For example, diclofenac, a non-steroidal inflammatory drug, has been detected in the aquatic environment in 50 countries worldwide (Figure 4). A number of globally marketed pharmaceuticals have been found in both developing and industrialized countries (Table 1). Regional differences in medicinal consumption patterns, access to health care, and sewage treatment help to explain the variation across countries.

In rivers and lakes that receive wastewater, pharmaceuticals are often found in concentrations of 0.1 µg/L to 1.0 µg/L. However, maximum concentrations in densely populated areas or downstream of sewage treatment plants may be considerably higher. Less data is available on pharmaceuticals in manure and soil, but residues have been detected in 28 countries, especially in the vicinity of intense animal husbandry.

**Number of pharmaceuticals detected in surface water, groundwater, tap water, and/or drinking water**

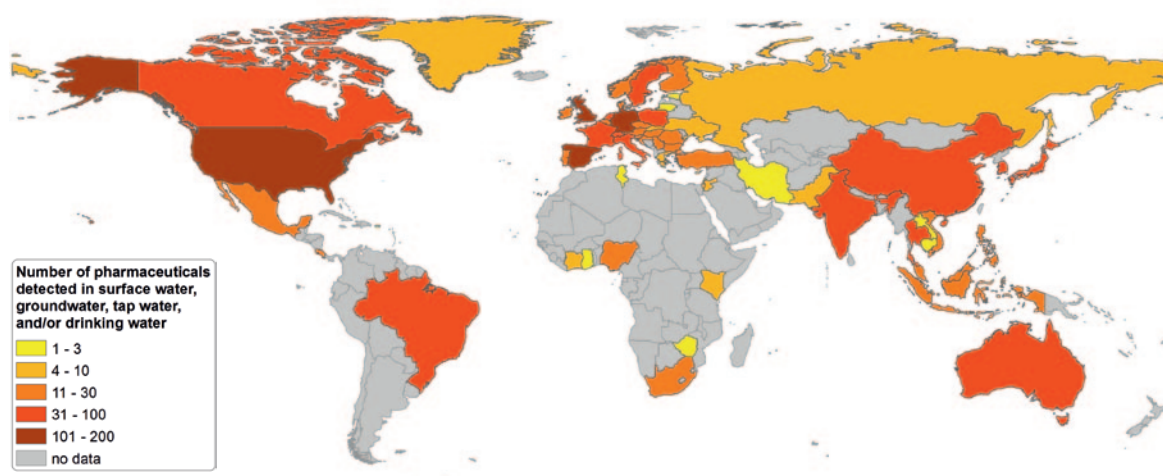


Figure 3: Global occurrence of pharmaceuticals: Pharmaceuticals have been found in the environment in all UN regional groups (IWW 2014).

Pharmaceutical	Therapy Group	Number of countries worldwide in which pharmaceuticals have been found in the aquatic environment
Diclofenac	Analgesics	50
Carbamazepine	Antiepileptic drugs	48
Ibuprofen	Analgesics	47
Sulfamethoxazole	Antibiotics	47
Naproxen	Analgesics	45
Estrone	Estrogens	35
17-β-Estradiol	Estrogens	34
17-α-Ethinylestradiol	Estrogens	31
Trimethoprim	Antibiotics	29
Paracetamol	Analgesics	29
Clofibric acid	Lipid-lowering drugs	23
Ciprofloxacin	Antibiotics	20
Ofloxacin	Antibiotics	16
Estriol	Estrogens	15
Norfloxacin	Antibiotics	15
Acetylsalicylic acid	Analgesics	15

Table 1: Several globally marketed pharmaceuticals have been found in the aquatic environment of all UN regional groups (IWW 2014).

## 4. Effects in the environment

Pharmaceuticals are biologically active substances that specifically affect control mechanisms in living organisms, for example by regulating metabolism, influencing hormonal balance, or alleviating signal transmission between cells. When released into the environment, this biological activity may adversely affect wildlife (so-called non-target organisms) and impair ecosystem health. This can occur through a variety of mechanisms, some of which have been demonstrated in laboratory and field observations (Table 2); others may yet be discovered.

Prominent examples of demonstrated ecotoxicological effects include (1) a near-extinction of vultures on the Indian subcontinent, which was caused by the birds' feeding on the carcasses of cattle treated with the anti-inflammatory drug diclofenac; (2) a lake experiment involving the synthetic estrogen ethinylestradiol, which is used in birth control pills, that resulted in feminized male fish; and (3) effects of veterinary use of the parasiticide ivermectin on dung decay, dung insect populations, and aquatic invertebrates.

To assess the environmental risks, predicted (or measured) concentrations of pharmaceuticals in the environment are compared with Predicted No-Effect Concentrations (PNEC), which are derived from standardized laboratory experiments with model organisms such as algae, daphnia, fish, or plants. In the European Union, an environmental risk assessment is mandatory for newly marketed drugs (EC 2001a, b), but most commonly used drugs were introduced before the regulation came into force and thus have not been assessed.

The anti-inflammatory drug diclofenac provides a telling example. Maximum concentrations of the drug in surface waters have been measured above PNEC levels in 34 countries (Figure 4). This suggests adverse ecotoxicological effects on organisms at these locations. The highest concentrations often occur downstream of sewage treatment plants in densely populated areas.

### Diclofenac in surface waters: Highest concentrations measured

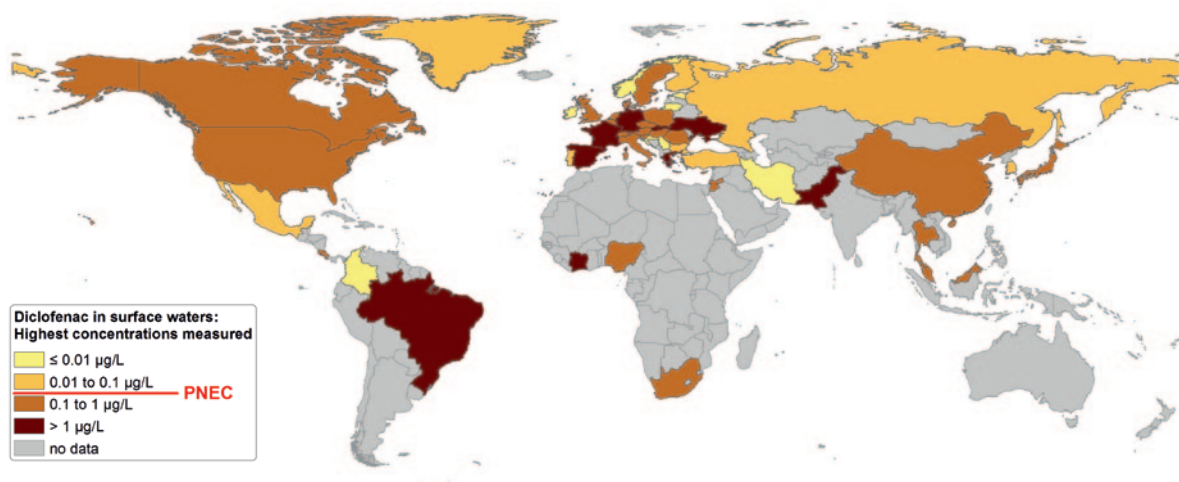









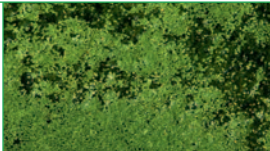
Figure 4: Highest diclofenac concentration in surface waters reported in comparison to the Predicted No-Effect Concentration (PNEC) of 0.1 µg/L.

## Antibiotic resistance

An alarming public health threat is the spread of pathogenic organisms that are resistant to antimicrobials. The presence of antimicrobials in the gut of humans and treated animals leads to the development of resistant bacteria and genes that can be excreted in faeces and spread to wastewater, sludge, manure, or soil. However, resistance genes can also develop in the environment if antibiotic residues are present; these genes can then be transferred to pathogenic bacteria (Allen et al. 2013). There is also evidence of an exchange of resistance genes between environmental bacteria and clinical isolates (Forsberg et al. 2012). Thus, strategies to reduce the introduction of antibiotics into the environment can also help to contain antimicrobial resistance (WHO 2014).

## Endocrine-disrupting pharmaceuticals

Some pharmaceuticals have an endocrine function, which means they affect the hormone system. Examples of these include contraceptives, some cancer treatments, medicines for thyroid and nervous system diseases, and several veterinary drugs. Some endocrine-disrupting pharmaceuticals have been found to have adverse effects on wildlife at very low concentrations, such as feminizing male fish, preventing reproduction, or triggering population collapse (Kidd et al. 2007). These pharmaceuticals are a subgroup of endocrine-disrupting chemicals (EDC), which the SAICM has addressed as an emerging policy issue since 2012 (UNEP & WHO 2013).

				
<b>Pharmaceutical</b>	<b>Diclofenac</b>	<b>17<math>\alpha</math>-Ethinylestradiol</b>	<b>Diclofenac</b>	<b>Sulfonamide</b>
<b>Therapeutic group</b>	Analgesics	Synthetic estrogen	Analgesics	Antibiotic
<b>Non-target organism</b>	Vulture ( <i>Gyps bengalensis</i> )	Fathead minnow ( <i>Pimephales promelas</i> )	Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Maize ( <i>Zea mays</i> ) Willow ( <i>Salix fragilis</i> )
<b>Effects</b>	Population collapse due to renal failure	Population collapse due to feminization of male fish	Strong reactions of liver, kidney, and gills	Adverse effects on root growth. Death of maize at high conc.
<b>Study type</b>	Wildlife	Whole-lake experiment	Laboratory	Greenhouse
<b>Reference</b>	Oakes et al. 2004	Kidd et al. 2007	Triebkorn et al. 2007	Michelini et al. 2012
				
<b>Pharmaceutical</b>	<b>Fluoxetine</b>	<b>Oxazepam</b>	<b>Ivermectin</b>	<b>Enrofloxacin, Ciprofloxacin</b>
<b>Therapeutic group</b>	Antidepressant	Anxiolytics	Veterinary parasiticide	Antibiotics
<b>Non-target organism</b>	Leopard Frog ( <i>Rana pipiens</i> )	European perch ( <i>Perca fluviatilis</i> )	Dung fly and beetle	Cyanobacterium ( <i>Anabaena flosaquae</i> ) Duckweed ( <i>Lemna minor</i> )
<b>Effects</b>	Delayed tadpole development	Altered behaviour and feeding rate	Mortality of eggs and larvae	Growth inhibition
<b>Study type</b>	Laboratory	Laboratory	Laboratory and field	Laboratory
<b>Reference</b>	Foster et al. 2010	Brodin et al. 2013	Liebig et al. 2010	Ebert et al. 2011

**Table 2:** Some selected examples of adverse effects of pharmaceuticals on non-target organisms in laboratory, field, and environmental observations.



## 5. Current knowledge of pharmaceuticals in drinking water

Pharmaceuticals have also been found in drinking water, largely at concentrations several orders of magnitude below the minimum therapeutic doses. The substantial margins of safety for individual substances suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking water (WHO 2012). However, at the local level, the production of pharmaceuticals has led to relatively high concentrations in well water that is used as drinking water (Fick et al. 2009). Systematic monitoring programmes are scarce, and there have been few comprehensive, systematic studies of the occurrence of pharmaceuticals in drinking water. This lack of data presents a key challenge to assessing the potential health risks of long-term, low-level exposure to pharmaceuticals in drinking water, especially for vulnerable sub-populations, including infants and the chronically ill.

In addition, if pharmaceuticals are repeatedly detected in drinking water – even at concentrations below what is considered harmful – the public may lose confidence in the overall quality of their drinking water. The precautionary principle calls for actions to minimize the occurrence of pharmaceuticals in drinking water.

## 6. Potential cooperative action

Cooperative action under SAICM could initiate a multi-sectoral, multi-stakeholder approach to prevent, reduce, and manage pharmaceuticals entering the environment on a global scale. Such action can be taken without compromising the effectiveness, availability, or affordability of medical treatment. To follow through on such an approach, the following stakeholders might need to be involved in taking coordinated, cooperative action:

- Intergovernmental organizations
- National governments, regulatory agencies and authorities
- Pharmaceutical companies, both innovative and generic
- Health care professionals, i.e. medical doctors, hospitals, and pharmacists
- Patients
- Veterinarians, farmers, and aquaculture operators
- Municipal sewage treatment plant operators
- Development cooperation
- NGOs
- Health insurance institutions
- Drinking water utilities
- Academia

In what follows, selected examples of work areas and associated activities are proposed for further discussion, each of which could help to reduce the occurrence and effects of pharmaceuticals in the environment. Suitable work areas may differ between countries and appropriate activities should be selected based on regional conditions. The work areas and activities are structured according to the five categories of objectives of the overarching policy issues under SAICM.

## A. Risk reduction

### □ **Prioritizing action**

Develop a work plan that builds on existing national and international activities.

### □ **Monitoring campaigns**

Conduct monitoring campaigns to identify affected watersheds to support decision-making process, prioritization of actions, guidance and training tools involving relevant expertise.

### □ **Cleaner production**

Promote the transfer and adoption of cleaner production technologies and pollution prevention policies, in particular best available techniques and best environmental practices (BAT/BEP). Extend Good Manufacturing Practice (GMP) to incorporate environmental quality guidelines.

### □ **Green procurement**

Strengthen green procurement in health-care sector, e.g., building on the Joint UN Programme of Green Procurement in the Health Sector.

### □ **Veterinary medicine**

Promote measures to reduce metaphylactic subscription in animal husbandry and aquaculture, including promotion of non-chemical alternatives.

### □ **Disposal of unused/expired pharmaceuticals**

Establish and promote Best Management Practices for collection and disposal schemes, e.g., drug take-back programmes.

Establish adequate facilities for management of pharmaceutical waste (e.g., incineration facilities).

### □ **Improve sanitation and sewage treatment**

Promote access to sewage connection and biological sewage treatment for sanitation and hygienic reasons, which – as a secondary effect – would help to reduce the amount of pharmaceuticals entering the aquatic environment.

## B. Strengthening knowledge and information

### □ Global awareness raising

Raise global awareness about the adverse effects of pharmaceuticals entering the environment, with the aim of affecting patterns of prescription, usage, and disposal (e.g., discouraging people from flushing unused drugs down the toilet).

### □ Scientific advice

Provide up-to-date information and support to decision makers, e.g., by creating an international network of scientists and risk managers to facilitate information exchange, and by requesting the International Programme on Chemical Safety (IPCS) to produce a state-of-science report.

### □ Classification and labelling scheme

Provide information on environmentally benign pharmaceuticals to guide procurement, prescription, purchase, and usage behaviour, in cases where alternative drugs with comparable effectiveness are available.

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## C. Governance: strengthening institutions, law, and policy

### □ Coordination and Synergies

Improve coordination and realize synergies of ongoing initiatives at the international, regional and national level (e.g., the Joint UN Programme of Green Procurement in the Health Sector; the WHO programme on quality and safety of medicines; relevant SAICM initiatives, such as EDC Strategy, as well as other existing regional and national initiatives).

### □ Industry consultation

Promote industry participation and responsibility.

### □ Environmental standards

Derive limits/thresholds for ecotoxicological-relevant pharmaceuticals in surface waters.

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## D. Enhance capacity building and technical cooperation

### □ Capacity building

Implement capacity building and technical cooperation to support developing countries and countries with economies in transition.

### □ Monitoring and analytics

Establish monitoring campaigns, standardized protocols, and analytical capabilities to measure pharmaceuticals in environmental matrices at relevant concentrations.

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## E. Illegal international traffic

### □ Addressing illegal traffic

Withdraw substandard, spurious, falsely-labelled, falsified, or counterfeit medical products from the world market.

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