



Our position on Pharmaceuticals in the Environment

What is the issue?

Pharmaceuticals help treat disease but, like many foods and nutritional supplements, they are not always completely absorbed or broken down by the body. Residues of the pharmaceutical or its breakdown products are mainly excreted by patients as part of normal biological processes. Sewage treatment systems do not always completely remove these substances, meaning that residues may sometimes pass into the environment. To a lesser extent, pharmaceuticals can also enter the environment from unused medical products or factory discharges.^{i,ii}

Some pharmaceutical residues have been detected in the environment at very low levels. But published studies, including ones from the World Health Organization (WHO), have concluded that pharmaceuticals in drinking water are very unlikely to affect human health at the levels detected.

It is generally agreed that the levels of pharmaceuticals in the environment (PiE) are significantly below those which would result in acute (short-term) effects in environmental species, including aquatic life. But there are concerns that chronic (long-term) exposure to these levels may pose a potential risk to organisms.ⁱⁱⁱ

This paper sets out how we are addressing potential risks of pharmaceuticals which may enter the environment.

What is GSK's view?

- We are committed to ensuring our compounds do not adversely affect people or the environment. We carry out state-of-the-art environmental testing on our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to human health and the environment.
- We perform environmental risk assessments to meet current regulatory requirements for all new pharmaceutical products before they are launched. We submit the resulting data to regulatory authorities as formal Environment Risk Assessment (ERA) reports. The PiE risk associated with vaccines is considered negligible, so they are exempt from any ERA requirements.
- Our current assessments show that adverse impacts to public health or the environment are unlikely to result from post-patient or manufacturing releases of GSK pharmaceuticals. However, we continue to work with industry groups and regulators to develop the science and methodologies to evaluate our products and management practices.
- If our ERAs were to indicate any areas of concerns, we would work with appropriate stakeholders, such as regulators and patient groups; and look for solutions that help protect patient access to innovative products, while safeguarding the environment. Any decision to limit release of a medicine on environmental grounds needs to be carefully balanced against the public health implications of restricting access for patients.
- We have implemented an ERA programme across all our manufacturing sites and key API third party sites.

- GSK is committed to zero impact API levels for all sites and key suppliers by 2030¹. This means working to keep any API manufacturing emissions below levels that may negatively impact human health or the environment.
- As part of our strategy to get ahead of antimicrobial resistance, we have committed to minimise antibiotic discharge in our supply chain. At the same time, we will seek to ensure that factory discharges from our third-party antibiotic manufacturers and our own sites conform to the AMR Industry Alliance Common Antibiotic Manufacturing Framework and wastewater discharge limits.
- We make information on the environmental hazards and impacts of our products (including Safety Data Sheets and Product ERAs) accessible on our website. We also publish environmental data, assessments and related topics in scientific literature.
- We support voluntary and responsible programmes dealing with safe disposal of unused medicines.

Background

The presence of APIs in the environment is increasingly reported in peer-reviewed scientific literature by scientists around the world. Improvements in analytical capabilities now allow extremely low levels of these materials to be detected. Some API residues are being detected in drinking water, surface waters (such as rivers and lakes), ground waters, sediments and soils.

PiE and human health: Current Predicted No Effect Concentrations (PNECs) for humans indicate that levels of PiE are very unlikely to pose any short-term (acute) or long-term (chronic) risk to people. Specifically, the WHO's 2012 Technical Report on Pharmaceuticals in Drinking Water concludes that concentrations of pharmaceuticals in treated drinking water are at trace levels, typically well below 50 ng/L (50 parts per trillion).

PiE and environmental health: Current scientific research suggests that the release of pharmaceuticals for human use into the environment does not appear to have a significant impact on wildlife populations or ecosystems.^{iv} But there are some areas of concern, including:

- **Endocrine active substances:** Overall, the contribution of human pharmaceutical products with endocrine activity appears to be relatively small compared to naturally sourced oestrogens from the human and animal population. The contribution of pharmaceuticals to this phenomenon however continues to be researched. To this end, where appropriate, GSK conducts bespoke studies to understand the impact of potentially endocrine active medical products.
- **Antimicrobial resistance:** The presence of antibiotics in the environment, and its impact on driving antibiotic resistance, is a growing concern for many stakeholders and an active area of research. While clinical and agricultural practices are generally recognised as the dominant sources of antibiotics entering the environment, unregulated manufacturing practices may also act as a potential hotspot for local development of resistance.

Regulatory oversight

In recent years, regulatory agencies have increased their scrutiny and activity in this area:

- The US Food and Drug Administration (FDA) has regulated PiE since 1977 through its environmental review process for New Drug Applications.
- At a European level, guidelines for Environmental Risk Assessments (ERAs) that accompany Marketing Authorisation Approval Applications for new drugs have been available since 1996, with the most recent update issued in January 2006.
- In Canada, a requirement for environmental assessment is being evaluated; and a specific ERA process for pharmaceuticals is under development by Health Canada.
- In Europe, the Water Framework Directive (WFD) is the European Commission's legislative instrument for achieving good water quality status throughout the EU. Currently, pharmaceuticals are not listed on the priority substance list for identifying chemical substances presenting a risk to the aquatic environment. But some pharmaceuticals have been put on the WATCH list, where substances of possible concern are monitored EU-wide. Should a risk be identified, this substance may be proposed as a candidate priority substance and be subject to regulation. The pharmaceutical industry is working with the European Commission to make sure that the development of safe water levels, known as Environmental Quality Standard (EQS), are based on scientifically robust data.

Environmental Risk Assessments

Medicine regulatory bodies have mandated that all prescription drug submissions in the US and EU require an ERA of the API. This involves studies to evaluate the environmental fate of the API and assess its potential toxicity to relevant environmental species. The data from these studies are captured in the ERA expert reports that are submitted in support of US/EU drug filings.

Our portfolio

We routinely test our products according to currently recognised and established procedures. The results of these tests are used to calculate Predicted No-Effect Concentrations (PNECs) which are compared to Predicted or Measured Environmental Concentrations (PECs or MECs) to assess risk. Our PEC calculations are based on very conservative worst-case scenarios in order to be protective of the environment.

Manufacturing discharge

Compared to other factors such as patient use and excretion through normal biological processes, factory discharges are generally recognised as a minimal route for pharmaceuticals to enter the environment. GSK routinely conducts effluent risk assessments of our products, supported by training and web-based tools, which provide PNEC values against which effluents from our manufacturing sites are assessed.

As a multinational organisation, we have a role to play in driving best practice in areas such as environmental protection. So, we expect third parties with whom we work to adopt similar environmental standards as GSK in their operations. The process for embedding our environmental standards on all



relevant third parties will take time and will be subject to a risk-based approach, initially focussing on third party suppliers of antibiotics.

In our environmental ambition, our business is committed to zero impact active pharmaceutical ingredient levels for all sites and key suppliers by 2030.

Working in partnership

GSK is a member of the governance team for the European based industry-wide Inter-Association Initiative (IAI), comprising the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and Medicines for Europe, to address issues relating to PiE. The resulting Eco-Pharmaco-Stewardship (EPS) framework is working towards the following objectives:

- A research programme for developing a methodology to prioritise legacy compounds based on risk.
- An evaluation of how to assess and control the potential impact of API residues in manufacturing effluents.
- An extended ERA model to help address PiE throughout the lifecycle of a medicine.

Scientific collaboration

The science underpinning PiE concerns is still in active development. In addition to GSK's regulatory and product stewardship obligations, we work with external stakeholders, including leading universities, to develop and understand the scientific basis of PiE.

We have worked with industry colleagues in the AMR Alliance to share environmental data of our pharmaceuticals and generate safe discharge standards for 120 antibiotics, which have been published.

In Europe, GSK has been an active contributor to the ground-breaking iPiE project (2015-2019) under the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative, aimed at speeding up the development of better and safer medicines for patients and the environment. The focus of the project has been on developing in silico tools to predict environmental risks of pharmaceuticals in our developmental pipeline. These tools are intended to help to evaluate the risk of legacy APIs which have been on the market for a long time and prioritise these for further evaluation where warranted.

Building on this work, we are now a partner in a project with IMI, focused on the Prioritisation and Risk Evaluation of Medicines in the EnviRonment (PREMIER). The project, which includes other pharmaceutical companies, regulators and research institutes, aims to deliver an innovative framework for assessing and characterising the environmental risks of APIs. This information may then be used to:

- Develop tools and models to identify potential environmental hazards and risks associated with APIs earlier in development.
- Screen and prioritise legacy APIs authorised for use prior to 2006 for a tailored environmental assessment.

- Explore the feasibility and practicality of greener drug design.
- Make environmental data on APIs more visible and accessible to all stakeholders.

Transparency

Our commitments to disclosing environmental data include:

- Safety Data Sheets (SDS): A Safety Data Sheet is a legally required document that provides information on the hazardous properties of any chemicals and potential effects on human health and the environment. Environmental fate and effects test results on all GSK APIs are detailed in our SDS and are available on gsk.com.
- ERAs: Since 2014 GSK has posted summaries of our Environmental Risk Assessments for our prescription medicines on gsk.com. We were the second pharmaceutical company to do so.
- Fass.se ERAs: GSK is an active participant in the voluntary Swedish Classification Scheme for pharmaceuticals where environmental data on all our medicines can be accessed by Healthcare Professionals and members of the Swedish public.

Unused medicines

Household and patient excretion are recognised as the primary sources of pharmaceutical residues in the environment but, improper disposal of unused or expired medicines may also be a contributing source. GSK encourages proper and safe disposal by patients and supports the use of approved voluntary 'take-back' programmes in the communities and countries where they are available.

We support the US Federal Guidelines on the Proper Disposal of Prescription Pharmaceuticals developed by the White House Office of National Drug Control Policy. We also support the SMARXT Disposal standard developed by the US Environmental Protection Agency (EPA), US Health and Human Services (HHS) and US FDA which is being promoted by leading US pharmaceutical and OTC industry trade associations. This is a public awareness campaign for safe disposal guidelines and is a unique public-private partnership between the US Fish and Wildlife Service, the American Association of Pharmacists and the Pharmaceutical Research and Manufacturers of America.

ⁱ Effects of Human Pharmaceuticals on Aquatic Life: Next Steps Environmental Science & Technology 2006 40 (11), 3456-3462 DOI: 10.1021/es063017b

ⁱⁱ Caldwell, D.J., Mertens, B., Kappler, K., Senac, T., Journal, R., Wilson, P., Meyerhoff, R.D., Parke, N.J., Mastrocco, F., Mattson, B., Murray-Smith, R., Dolan, D.G., Straub, J.O., Wiedemann, M., Hartmann, A. and Finan, D.S. (2016), A risk-based approach to managing active pharmaceutical ingredients in manufacturing effluent. *Environ Toxicol Chem*, 35: 813-822. <https://doi.org/10.1002/etc.3163>

ⁱⁱⁱ Boxall AB. The environmental side effects of medication. *EMBO Rep*. 2004;5(12):1110-1116. doi:10.1038/sj.embor.7400307

^{iv} Lina Gunnarsson, Jason R. Snape, Bas Verbruggen, Stewart F. Owen, Erik Kristiansson, Luigi Margiotta-Casaluci, Tobias Österlund, Kathryn Hutchinson, Dean Leverett, Becky Marks, Charles R. Tyler, Pharmacology beyond the patient – The environmental risks of human drugs, *Environment International*, Volume 129, 2019, Pages 320-332, ISSN 0160-4120 <https://www.sciencedirect.com/science/article/pii/S0160412019309493#bb0045>