

GSK Public policy positions

Pharmaceuticals in the Environment

The Issue

Pharmaceuticals are designed to cure and treat disease, and to help people be healthy. However, 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 (i.e., metabolites) may be excreted as part of normal biological processes. Sewage treatment systems are not always able to completely remove these substances meaning the residues sometimes pass through treatment facilities and enter rivers, streams or lakes. To a lesser extent pharmaceutical actives may also enter the environment from unused medical products or via discharges from manufacturing facilities. Animal husbandry can also be a source of pharmaceuticals entering the environment.

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

By the same token, stakeholders generally agree that the levels of PiE are significantly below those which would result in acute (short-term) effects in environmental species, including aquatic life. There are however concerns that chronic (long-term) exposure to these levels could result in a potential risk to organisms. Others have focused on the potential developmental and reproductive effects of endocrine active chemicals in aquatic vertebrates, as well as on the role that the environment, which receives antibiotics and antibiotic resistance genes from many different sources, has in driving antibiotic resistance.

This paper sets out how GSK is responding to stakeholder concerns regarding pharmaceuticals in the environment (PiE). It includes our commitment to assessing the evolving science behind PiE; to minimising its occurrence and impact relating to GSK products; and to sharing our environmental data with key stakeholders.

GSK's Position

- GSK acknowledges that PiE is an area of concern for some parties.
- GSK is committed to ensuring that our compounds do not adversely affect people or the environment. We carry out state-of-the-art environmental testing on all our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to human health and the environment.
- GSK performs environmental risk assessments to meet current regulatory requirements for all new pharmaceutical and consumer healthcare 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; they are therefore exempt from any ERA requirements.
- Our assessments indicate 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 Environmental Risk Assessments were to indicate areas of concern with a particular Active Pharmaceutical Ingredient (API), GSK would work with appropriate stakeholders, such as regulators, patient groups and others, to find ways of addressing the concerns in a way that ensures 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.
- GSK places a priority on minimising the risk of any APIs entering the environment as a result of our manufacturing processes. To this end, we have implemented an ERA programme across all our manufacturing sites to ensure safe discharge to the receiving environment.
- GSK has made a commitment to minimise antibiotic discharge in our supply chain and to ensure that factory discharges from all third party antibiotic manufacturers are negligible by 2020.

- We place a premium on being transparent about our approach to PiE. We make information on the environmental hazards and impacts of our products (including Safety Data Sheets and Product ERAs) readily accessible to interested parties on gsk.com. We also publish environmental data, assessments and related topics in scientific literature.
- GSK supports voluntary and responsible programmes dealing with safe disposal of unused medicines.

Background

The Size of the Problem

The presence of APIs in the environment is increasingly being 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 too low 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 typically well below 50 ng/L (50 parts per trillion). This is an extremely low level; if this concentration of paracetamol (the active ingredient in the GSK product Panadol) were present in drinking water one would have to consume eight Olympic sized swimming pools of water (equivalent to 25,000 years of water consumption at 2L/day) to receive just one adult dose (1,000 mg) of the drug.

PiE and Environmental Health: Questions have been raised about the potential for long-term (chronic) effects on aquatic life from multiple compounds or certain classes of compounds. Current scientific information suggests that the release of pharmaceuticals into the environment does not appear to have a significant impact on wildlife populations or ecosystems. Nonetheless, there are some key areas of concern for some stakeholders. Most notably:

- *PiE & Endocrine Disruption:* Some studies suggest that certain classes of pharmaceutical, such as endocrine or hormonally active substances, may be linked with impacts on fish populations at environmentally relevant concentrations. 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 and, where appropriate, GSK conducts bespoke fish studies to understand the impact of our potentially endocrine active medical products.
- *PiE and 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.
- *PiE and Diclofenac:* Diclofenac has been linked to the decline of the vulture population on the Indian sub-continent due to the excessive use of an unlicensed veterinary product containing diclofenac in cattle. This veterinary use has resulted in "atypical" or unusual exposure to high levels of diclofenac by the vultures who directly feed on cattle carcasses. Recent evidence, however, from peer reviewed articles, suggests that diclofenac is unlikely to be a risk to human or animal health or on the environment at levels typically found in surface water. Therefore, while the vulture scenario highlights how unusual routes of exposure can have severe and unforeseen consequences, a proportionate response is required.

Regulatory Oversight

The potential impact of PiE, though often presented as an emerging issue, is not new. However, 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 in place and a specific ERA process for pharmaceuticals is under development.
- In Europe the Water Framework Directive (WFD) is the European Commission's legislative instrument for achieving good water quality status throughout the EU. Significantly, pharmaceuticals are currently not listed on the priority substance list for identifying chemical substances presenting a risk to the aquatic environment. However, some pharmaceuticals, including diclofenac, have been placed on the WATCH list whereby targeted EU-wide monitoring of substances of possible concern is undertaken.

Industry's Response

In 2015, GSK became part of a 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 on delivering the following objectives:

- A Research Programme for developing a methodology to prioritize 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.

Environmental Risk Assessments (ERA)

Medicine regulatory bodies have mandated that all prescription drug submissions in the US and EU require an Environmental Risk Assessment (ERA) of the API. This involves conducting 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.

GSK's Portfolio

We 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. The risk assessments that have been carried out to date using currently available human and environmental "fate and effects" data indicate that GSK pharmaceuticals do not present an appreciable risk to humans or to the environment.

GSK and Manufacturing Discharge

Factory discharges are widely recognised as a minimal route for pharmaceuticals to enter the environment. GSK routinely conducts site effluent risk assessments of our products, supported by training and web-based tools, which provide PNEC values for GSK and non-GSK APIs against which discharges from our manufacturing sites are assessed to ensure they do not harm the receiving environment.

Third Party Facilities: While manufacturing emissions are well managed across all GSK sites, external stakeholders have expressed concern about the performance of supply chain (third party) manufacturers in regions of the world where there is less regulation.

As a multinational organisation with global outreach, often exercising substantial influence over those with whom we conduct business, GSK recognises that we have a role to play in driving best practice in key areas such as environmental protection. We therefore expect third parties with whom we work to adopt similar environmental standards as GSK in their operations.

That said, the diversity and nature of our supply chain relationships is extensive and complex. The process for embedding our environmental standards in all relevant third party contracts will therefore take time and will be subject to a risk based approach, initially focussing on third party suppliers of antibiotics.

The link between manufacturing discharges and antibiotic resistance patterns is not well understood; however GSK recognises the importance of managing effluent discharges responsibly and establishing clear expectations of our third party partners. Where third party standards are found lacking, remediation steps will be taken. By 2020, we will have established science-led, risk-based targets for discharge concentrations of antibiotics. These will inform our PNEC standards, which we will expect all our suppliers to meet. Our commitment is to ensure that factory discharges from all third party antibiotic manufacturers are negligible by 2020.

GSK and Scientific Collaboration

The science underpinning PiE concerns is still under active development.

In addition to GSK's regulatory and stewardship obligations, we work with external stakeholders, including leading Universities, to develop and understand the scientific basis of PiE. For example, in 2012, GSK co-sponsored and participated in a workshop hosted by the Canadian Society of Microbiologists to review the state of the science of Antimicrobial Resistance (AMR).

We have also entered a four year multi-stakeholder collaboration 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 is on developing in silico tools to predict environmental risks of pharmaceuticals in our developmental pipeline. These tools will also 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. This IMI project represents an unprecedented opportunity for the pharmaceutical industry to work with stakeholders from academic, regulatory and environmental agencies to address key concerns associated with PiE.

GSK's Commitment to Transparency

Transparency is one of GSK's four core values. Examples of our commitment in this area include disclosing clinical trial data, details of our financial support for patient groups and details of our engagement with healthcare professionals. Specific examples relating to disclosure of 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.



GSK and Unused Medicines

Husbandry¹ and patient excretion are recognised as the primary sources of pharmaceutical residues in the environment; however, improper disposal of unused or expired medicines is also 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.

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¹ GSK does not have any veterinary products in our portfolio.