Quantifying trace levels of effluents from the production of 30 Sanofi products

Within the scope of this program, launched in 2012, Sanofi drew up an initial list of 30 compounds based on potential environmental hazard properties and annual production tonnage. The list includes compounds for the treatment of cardiovascular, inflammatory and central nervous system conditions as well as antibiotics and painkillers. We analyzed the effluents from chemistry sites where these compounds are produced using specific analytical methods devised by our Aramon, France, environmental laboratory to quantify the compounds at very low concentration levels. To date, 75% of relevant Sanofi chemical active pharmaceutical ingredient (API) plants worldwide have been reviewed and we have determined target values for 23% of the 30 selected compounds.

In 2013, we launched a pilot program at a pharmaceutical manufacturing site in collaboration with a leading water company, as we began to consider ways to adapt this initiative to pharmaceutical manufacturing sites.

In addition, we plan to test and compare different monitoring tools and strategies, as well as wastewater treatment technologies, to limit potential discharge of pharmaceuticals and other chemicals into the environment. Several advanced oxidation, adsorption or retention techniques are currently being implemented and/or tested at our sites. In line with risk assessments, we evaluate practices and technologies for risk reduction and mitigation, taking into account each site’s specific characteristics.
Our challenge

Pharmaceuticals found in the environment due to human activity, such as patients’ use of medicines, raise concerns about their potential impact on human health and the planet. This is a challenge that Sanofi takes seriously.

OUR PROGRESS

<table>
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<tr>
<th>Our objectives</th>
<th>2013 progress and actions</th>
<th>Status</th>
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<tbody>
<tr>
<td>By 2015: Implement an effluent assessment plan at 100% of chemistry sites where 30 active pharmaceutical ingredients (APIs) are manufactured</td>
<td>• Effluents reviewed at chemistry sites and one pilot pharmaceutical site</td>
<td></td>
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<tr>
<td>• Review completed of the effluents of 75% of chemistry sites where 30 selected APIs are manufactured</td>
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<tr>
<td>• Updated monitoring of the environmental impact of our Vertolaye site in France</td>
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<tr>
<td>• Exploration of ways to adapt this initiative to pharmaceutical manufacturing sites</td>
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<tr>
<td>Conduct voluntary environmental risk assessments for drugs already on the market</td>
<td>Voluntary environmental risk assessment completed for 26 marketed medicines</td>
<td></td>
</tr>
<tr>
<td>By 2015: Define environmental target values for the 30 selected APIs</td>
<td>Defined environmental targets for 23% of selected APIs</td>
<td></td>
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<tr>
<td>Develop our knowledge of pharmaceuticals impact in the environment</td>
<td>Take part in scientific research programs with Poitiers University, Montpellier University, Technion Institute of Technology, Al-Quds University, and Health and Environmental Sciences Institute (HESI) Animal Alternatives</td>
<td></td>
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<tr>
<td>Support programs to take back unused and expired medicines</td>
<td>To date, we contributed to the implementation of take-back programs in Belgium, Brazil, Canada, Colombia, Ecuador, France, Greece, Mexico, Portugal, Saudi Arabia, Spain, and Taiwan</td>
<td></td>
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<tr>
<td>• Largest contributor to the Cyclamed take-back program in France</td>
<td></td>
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<tr>
<td>• Support for Punto Azul take-back scheme in Colombia</td>
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<tr>
<td>• Support for French program for the safe disposal of sharps (DASTRI)</td>
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OTHER INITIATIVES

Photo credit: Sanofi Brazil

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The Punto Azul take-back scheme in Colombia

Photo credit: Sanofi Israel

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A safe sharps disposal program in France: DASTRI

Photo credit: Sanofi

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Managing the use of biological techniques for the treatment of wastewater

Photo credit: Sanofi

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Monitoring the environmental impacts of our sites: the Dore River (France)
Strategic approach

Sources of pharmaceuticals in the environment (PIE)

Trace amounts of pharmaceuticals may end up in the environment in various ways. When patients ingest medicines, pharmaceuticals are excreted or they are transformed by the body into metabolites, which may be released into the environment through sewers and sewage treatment plants.

Other sources of discharge include emissions from drug production plants and discharge resulting from the inappropriate disposal of unused medicines (e.g., by an end-user disposing of unused medicine directly into a sewage system).

What is Sanofi doing to address this challenge?

In light of growing public concern about pharmaceuticals in the environment and relatively limited knowledge, Sanofi has developed a multi-faceted approach in line with the Group’s HSE Policy and requirements:

- HSE Policy
- Health, Safety and Environmental Management System factsheet

We are improving our knowledge of the environmental fate and potential impact of Sanofi products by conducting both mandatory and voluntary environmental risk assessments of new and marketed products under the guidance of an internal group of experts, the ECOVAL Committee.

The ECOVAL Committee addresses stakeholder concerns surrounding the potential impact of our products on the environment. Members include environmental experts and representatives of product stewardship, science and medical affairs, regulatory affairs, and other Sanofi departments. The committee’s role is to:

• help Sanofi to protect the environment through the best possible knowledge on the environmental fate and effects of our products; and
• address external requests, in particular those linked to regulatory requirements, and to anticipate for the development of new requirements.

We are working in close collaboration with academia through public/private initiatives to develop general knowledge about PIE.

We are evaluating and limiting discharge from our manufacturing plants.

We are supporting take-back programs for unused medicines to facilitate their proper disposal. In addition, we provide guidance about how to dispose of medicines.

The current state of research on the potential impact of PIE

In terms of potential impact on the environment, current studies suggest that short-term effects on aquatic ecosystems are unlikely, considering the low concentrations of pharmaceuticals found in water. Concerns, however, have been raised about potential long-term environmental effects, especially for certain classes of pharmaceutical products, such as hormonal substances and antibiotics.

Thanks to improved analytical methods, today it is possible to detect the presence of an increasing number of pharmaceuticals in the environment. Depending on the substances and where they are found, they may be present in very low concentrations – measured in nanograms or micrograms per liter – even in drinking water.

Further research is necessary to improve our understanding of the potential long-term effects on the environment and human health of such concentrations, in addition to more extensive research into the potential impact of combinations of pharmaceuticals, metabolites and other chemicals that may be present in low concentrations in the environment.

According to the World Health Organization (WHO)¹, current analyses of available data indicate a substantial margin of safety between the very low concentrations of pharmaceuticals that potentially could be consumed in drinking water and the minimum therapeutic doses, suggesting a very low risk to human health.

¹ WHO “Drinking Water” report in English: http://apps.who.int/iris/bitstream/10665/44830/1/9789241502085_eng.pdf
Highlights

Supporting initiatives to take back unused medicines

To date, we have contributed to the development and implementation of take-back programs for unused medicines by Sanofi affiliates in many countries, including Belgium, Brazil, Canada, Colombia, Ecuador, France, Greece, Mexico, Portugal, Saudi Arabia, Spain, and Taiwan.

We are the largest contributor to the Cyclamed take-back program

French patients are accustomed to returning unused medicines to their local pharmacies, which are required by law to collect unused and expired drugs. To preserve the environment and protect consumers’ health, Cyclamed works with dispensing pharmacies, wholesalers, dispatchers, and drug companies to oversee the safe elimination of unused tablets, capsules, syrups, and ointments.

The Cyclamed program only collects take-back products from households (not waste from hospitals or healthcare professionals), which are put through a clean disposal process with energy recovery. This non-profit organization is financed entirely by drug manufacturers, based on the number of boxes they market. As one of the largest pharmaceutical companies in France, Sanofi makes a large financial contribution to the program. In 2012, a total of 14,271 tons of unused medicines were collected. In 2013, Sanofi’s contribution amounted to €1,231,333.

The Punto Azul take-back scheme in Colombia

The Punto Azul (Blue Point) program helps prevent the release of pharmaceuticals into the environment by providing an easy way to dispose of unused and expired medicines. This take-back program has set up collection points for used medicines across 15 Colombian states, representing 37% of the country’s population. Developed by the National Association of Colombian Enterprises (ANDI), this program was launched in 2010 with 26 founding members, including Sanofi and Genzyme, and Genfar subsidiaries. It is 100% funded by manufacturers and importers of medicines.

To date, 592 containers have been installed in pharmacies and large supermarkets. Approximately 76 tons of used medicines have been collected since the program’s inception, and this volume is expected to grow as the initiative is expanded to include more states, with a goal of 70% national coverage by 2017. The collected unused and expired medicines are incinerated by licensed operators.

The Ministry of Environment and Sustainable Development is organizing education and awareness-raising initiatives in connection with the Punto Azul program. Campaigns have already reached an estimated 38 million people.

This initiative follows the example of a pioneering program implemented in 2010 in Brazil and exclusively sponsored by our affiliate Medley. By year end 2013, 231 collection points have been set up at points of sale of Droga Raia, a major pharmacy chain in Brazil, thanks to which 22 tons of unused and/or expired medicines were collected in 2013. Consumers can go online to track the fate of their unused medicines that are incinerated. This experience significantly served as a basis for measuring the financial impact and logistics of such an initiative on a larger scale in the context of debates about the Brazilian solid waste policy.

Photo credit: Sanofi, Brazil

MORE in our Download Center

- Implementation of REACH legislation factsheet
- Green Chemistry factsheet
- Waste management factsheet
- Packaging factsheet

MORE online

- http://www.cyclamed.org/en
A safe “sharps” disposal program in France

A new program called DASTRI was founded in late 2012 to help ensure the safe disposal of “sharps” (needles, lancets, infusion sets, etc.) after use by individual patients, primarily people with diabetes. Sanofi has been a driving force in this organization, alongside 40 other members: pharmaceutical companies, manufacturers and distributors of medical devices, etc. This initiative has three primary focuses:

• providing special “sharps” containers free of charge;
• collecting and disposing of the containers; and
• improving communication and awareness among all stakeholders.

DASTRI aims to collect an estimated 360 tons of “sharps.” Collection points will be set up every 15km, for a total of 15,000 points across France.

The organization complies with French regulatory requirements concerning manufacturers’ role in the responsible management of their products’ end-of-life cycle. Sanofi’s contribution represents 20% for a total annual cost of €10 million.

HOW THE FRENCH TAKE-BACK SCHEME DASTRI ORGANIZES THE COLLECTION AND DISPOSAL OF “SHARPS” IN FRANCE

1. Regulatory obligation for all pharmacies to provide a box where patients can dispose of sharps.
2. Sharps disposal container provided to auto-treated patient.
3. Each time patient uses a sharp, it is disposed of in the container – ensuring patient safety.
4. Full containers are taken to collection points.
5. Sharps waste is weighed and administration formalities undertaken.
6. Full containers are collected and replaced with empty containers.
7. Containers are transported to a ‘pre-treatment’ site for disinfection or incineration.
8. Sharps are destroyed along with containers – containers are disposable (never re-used).

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Introduction
Outreach
Patient
Ethics
People
Pharmacological in the environment
Working in close collaboration with academia to learn more about PIE

Sanofi participates in scientific research to improve our understanding of pharmaceuticals in the environment (PIE).

- From 2008 to 2011, we took part in two scientific projects conducted by French universities:
  - Poitiers University analyzed the efficiency of various oxidative treatments (ozonation, H₂O₂/UV, chlorination) to remove pharmaceuticals from water. The results revealed differences in the efficiency of different oxidative treatments. For some compounds, an increase in toxicity was observed during and after treatment. These results confirm the need to assess other wastewater treatment technologies.
  - Montpellier University studied the environmental fate of some pharmaceuticals in coastal waters, with a particular focus on bioaccumulation in mollusks, which are used in biomonitoring programs. Results showed different bioconcentration profiles depending on the compounds. Further research is needed to better understand these processes in mollusks.

Findings from both projects were published in scientific journals and were presented at scientific meetings in 2012 and 2013.

- Since 2008, Sanofi has been an active participant in the work of the Health and Environmental Sciences Institute (HESI) Animal Alternatives in its Environmental Risk Assessment Committee to develop and promote high-quality and efficient alternatives for animal testing in environmental risk assessments. Several scientific papers and conference presentations have been developed based on findings to date.

Managing the use of biological techniques for the treatment of wastewater

Since 2012, we have supported a Palestinian-Israeli research program managed by the Peres Center for Peace, an NGO that brings together Israeli and Palestinian researchers and graduate students from the Technion Institute of Technology in Haifa and Al-Quds University near Jerusalem. It aims to assess the efficiency of different biological treatments, adsorption and membrane techniques (reverse osmosis/nanofiltration) to remove active pharmaceutical ingredients from wastewater from both domestic and industrial sources. Some of the team’s results have been published or are forthcoming, and other articles are planned, among them a publication co-authored by both teams. These results could potentially be used to enhance treatment of effluents from pharmaceutical sites and may also contribute to improving the quality of drinking and irrigation water across the Middle East, an area of high water stress.
Evaluating and reducing discharge from manufacturing sites

In line with our objective to minimize our industrial sites’ impact on the environment, in particular the aquatic environment, we have developed a program to evaluate our manufacturing activities’ potential contribution to the overall discharge of pharmaceuticals in the environment.

Monitoring the environmental impact of our sites: The Dore River (France)

The Vertolaye site in France was the focus of media attention in 2011 after endocrine disruption was observed in some fish living in the Dore River, located near Vertolaye. Questions were raised about a potential connection to wastewater from the factory. Sanofi worked closely with the authorities, water agencies, ONEMA, INERIS, ecological associations, and others to understand the cause of the observed effects. We developed a specific analytical method that has been implemented to monitor the potential presence of substances responsible for the effects observed in the fish. In cooperation with a leading water treatment company and following preliminary treatment studies, we set up pilot equipment on site to test a dedicated technology based on activated carbon adsorption. Encouraging results have shown that this technology is appropriate as a final treatment of on-site discharge to the Dore River.

In 2013, Sanofi began installing the equipment using activated carbon technology. It should be fully set up by mid-2014, making it the largest such system in the world using this innovative wastewater treatment technology. The investment was subsidized by the regional basin authority (Agence de Bassin Loire-Bretagne) as its third largest industry project for water improvement. Sanofi will continue to support future environmental studies to monitor the situation and the improvement of the local aquatic habitat.

Environmental risk assessments of our products

The environmental fate and effects of drugs’ properties are investigated during the drug development phase. In Europe (since 2006) and the United States (since 1987), as well as other countries, full environmental risk assessments are required as part of the marketing authorization application for new drugs. They are also required for marketed drugs if, for example, sales of an existing drug are expected to rise due to a new disease indication.

Sanofi is also evaluating our existing products that were brought to market prior to the enactment of these regulations. To date, 26 compounds have undergone voluntary environmental risk assessment by Sanofi. These evaluations, which focus on pharmaceuticals in the environment following use by patients, have not shown any significant environmental risk at the expected environmental concentration.

Number of compounds that have undergone voluntary environmental risk assessment by Sanofi

26

Photo credit: Sanofi