A Responsible and Sustainable Chemistry

GRI Standards:

301-1, 301-2: Materials

EXECUTIVE SUMMARY

Sustainable chemistry focuses on making industrial chemistry safer and cleaner by preventing and optimizing environmental pollution while generating economic and health benefits to a growing world population.

In order to reduce our environmental footprint, Sanofi teams work at optimizing its processes from the design of R&D synthetic pathways to the production of active pharmaceutical ingredients, by taking actions to identify green chemistry alternatives, as well as changing mindsets by promoting green chemistry principles within the pharmaceutical industry.

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1. Background

Chemistry is an integral part of our pharmaceutical business. Green chemistry is understood to have minimal impact on the environment and human health, and to be cost effective.

Over the past decade, the pharmaceutical industry has been moving toward the application of green chemistry principles, mainly by introducing new production and analytical technologies, using greener solvents, and emphasizing catalysis and enzymatic chemistry.

Green chemistry focuses on making safer and cleaner industrial chemistry and giving more consideration to innovative actions to prevent and reduce waste, optimize energy consumption, consider sustainable resource demand and replace hazardous substances. This concept is driven by efficiency combined with environmental responsibility, to offer enhanced chemical-process economics.

To quote the words of Paul Anastas, who introduced the term "green chemistry" in 1991: "It's more effective, it's more efficient, it's more elegant, and its simply better chemistry!"

To discover the 12 Principles of Green Chemistry, visit the ACS Green Chemistry Institute® website: http://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/principles/12-principles-of-green-chemistry.html

2. Policy

With a long history in active ingredient manufacturing, Sanofi is committed to improving its drug manufacturing processes to minimize environmental impacts.

Each development team involved in the design and improvement of our chemical and biotechnical processes for producing our active ingredients is intently focused on this goal. In support of our corporate commitment, we have taken several tangible actions to reduce our environmental footprint — from the design of our R&D synthetic pathways to the production of active pharmaceutical ingredients (APIs) in our plants.

3. Actions

3.1. TARGETING ACTIONS ON ENVIRONMENTAL HOTSPOTS

Throughout the chemical and biochemical product development stages that are part of manufacturing drugs, Sanofi teams make decisions about the processes they use based on criteria designed to protect the health and safety of employees while preserving the environment.

In 2019, we started classifying our process raw materials (solvents, reagents, etc.) according to their hazardous properties for human health and the environment. This classification is used to replace and avoid substances of concern used in our new products & industrial manufacturing processes.

Since 2015, Sanofi uses a process performance analysis tool for all its projects to guide chemists in the selection of synthesis routes, evaluate critical parameters in terms of cost and environmental performances and to allow specific targeted process improvement.

Various parameters are monitored from earliest stages of product development to the industrial development phase. Product mass intensity (PMI), solvent & water indexes and reagents' scoring are tracked from R&D synthetic pathways to the production of active pharmaceutical ingredients (APIs) in our plants. Energy & safety work-up efficiency are also part of the monitoring to deliver a sustainable and optimized drug manufacturing process at launch.

Furthermore, since 2016, Sanofi is performing environmental life-cycle assessments (LCA), an international standardized (ISO: 14040 & 14044) and multicriteria methodology to quantify the environmental impacts of several commercialized medicines through their entire value chain, including drug substances. Our goal

is to optimize our commercial medicines environmental profiles and learn from these environmental analyses to better improve the environmental impacts of future medicines.

For more information, see in our Document Center: Eco-design factsheet.

3.2. GREENING OUR PROCESS ACTIONS

Medicines are often produced using large amounts of resources to obtain very small amounts of active ingredients, which corresponds to low mass efficiency.

Benchmarking shows that pharmaceutical industries typically use about 100 kg of raw materials to produce 1 kg of active pharmaceutical ingredients. This 1% mass efficiency compares to about 20% for fine chemicals and 50% for bulk chemicals.

Developing and producing drugs this way is financially inefficient and environmentally unsustainable. As an alternative, since 2019, Sanofi has relaunched its efforts at the development process level to implement:

- **biocatalysis:** by shifting from the usage of rare metals for catalysis, the expected positive gains are to design benign chemicals, prevent and reduce accidents, promote use of renewable feedstocks and reduce undesirable derivatives;
- **actions example**: inspired by nature and biomimicry, we are using innovative technologies to improve our synthesis routes;
- **flowchemistry** (continuous chemistry): by moving from batch unit operations, the expected positive impact is to reduce hazardous waste generation, design benign chemistry, utilizing benign solvents and reagents, design for energy efficiency, reinforce real-time analysis for pollution prevention;
- **actions example**: by shiftting from batch to flow/continuous process on feasible processes, we can optimize by nearly 30% on most sustainability metrics (PMI, energy, greenhouse gas) by reducing solvent quantities usage, increasing yield and quality, which has a direct impact on medicine environmental profiles;
- **biotechnologies:** requires fewer chemical steps thanks to processes based on fermentation with micro-organisms for the synthesis of active molecules. As fermentation processes have other environmental impacts (mainly biological chemical oxygen demand – COD - load to wastewater treatment), comparative environmental life-cycle assessments (LCA) are performed to take the best decision on the most environmental-friendly technology;
- **actions example**: at one of our industrial sites, we are using a tailor-made enzyme that enables eco-designed insulin production. A new highly selective trypsin variant for insulin production increased final yield by 50% at industrial scale. The number of batches per year can be reduced significantely in the future. For each batch, environmental savings are: 2,000 m^3 purified water, 22 tons of raw materials, and 61 tons CO_2e.

3.3. SOLVENTS

3.3.1. Solvent environmental profile selection

From the earliest stages of product development, teams are encouraged to use reagents and solvents with the least possible hazardous properties for human health and the environment. To help teams make decisions on a daily basis, Sanofi has developed an internal guide on the appropriate use of solvents for the design of drug-manufacturing processes.

"Sanofi's solvent selection guide: a step toward more sustainable processes[1]," was published in November 2013 and made publicly available at http://pubs.acs.org/doi/abs/10.1021/op4002565. The guide was a success based on its 15,408 views (reference date: March 24, 2022). An update of Sanofi's solvent guide was performed in January 2021.

Choices made during the industrial development phase are often difficult to change later, which is why it is important to make sustainable decisions early in the R&D development process, considering future manufacturing and scale-up.

3.3.2. Optimizing solvent consumption

Most of the energy, chemical reagent, and solvent reduction occurs during scale-up and manufacturing, rather than during the drug-research phase. Even after an active pharmaceutical ingredient is in the production phase, industrial development teams continue to optimize chemical and biochemical processes whenever possible.

Solvents used in the production processes are either purchased ("consumed" quantities) or recycled at Sanofi sites or at partner company sites.

To decrease the use of non-renewable raw materials, the Company focuses on three areas:

- reduce solvents quantities used in scale-up and industrial processes;
- recycle solvents (when possible); and
- incineration with energy recovery.

Sanofi initiated a solvent management plan in 2015 to improve solvent reporting. Thanks to this action plan, we have continually optimized quantities of solvent use.

In 2021, we prevented 93,243 tons or 57% of our total quantities of solvent use in our industrial processes by on-site regeneration and reuse in a closed-loop approach.

[1] Prat, D., Pardigon, O., Flemming, H., Letestu, S., Ducandas, V., Isnard, P., Guntrum, E., Senac, T., Ruisseau, S., Cruciani, P. and Hosek, P. (2013). "Sanofi's solvent selection guide: a step toward more sustainable processes," in *Organic Process Research and Development*, 17(12), pp.1517-152.

Weight of solvents used and percentage of regenerated solvents

Reference	2021	2020	2019
Solvents used (tons)	164,938	178,381	184,472
Percentage of regenerated solvents (%)	57	62	62

For more information, see in our Document Center: Waste Management factsheet; Protection of the Atmosphere factsheet.

3.4. REAGENTS

3.4.1. Change for greener reagents

Depending on the type of chemical conversion to be carried out, the choice of reagents is often limited to products that are toxic to human health and the environment, are not very safe to use and generate large amounts of waste. This is the case for oxidation reactions, reductions, fluorinations and formation of amides.

The best choices of reagents are studied during the process development stage thanks to an internal classification of our process raw materials (solvents, reagents etc.) according to their hazardous properties in which stoichiometries are optimized.

3.4.2. Promote catalytic transformations

Even if reagents generate less waste compared to solvents, it is our duty, as recommended by the 12 Principles of Green Chemistry, to implement as much as possible catalytic chemical or enzymatic transformations.

For example, Palladium catalyzed Suzuki type C-C bond formation reactions are commonly used. In order not to impact the Cost Of Goods (COGs), the recycling of catalysts is studied.

More recently, based on work published in the literature, the application of different reagents for catalytic amidation on our products has been successfully tested.

We lead a long-term program collaboration with universities to improve the environmental impact of synthetic routes by replacing non-sustainable biocatalysts.

3.5. SHIFTING MINDSET BY PROMOTING GREEN CHEMISTRY

3.5.1. Membership of learned societies

Sanofi is a member of several learned societies in the chemistry field, including the *Société Française de Chimie* (SFC), *France Chimie*.

3.5.2. The Innovative Medicines Initiative (IMI)-CHEM21 project in Europe

The discovery of green and sustainable synthesis methodologies is a long-term endeavor. Today, collaborations between academia and pharmaceutical companies provide an opportunity to develop green, safe, and more effective processes to deliver medicines for the 21st century.

The Innovative Medicines Initiative (IMI) is a pan-European public-private partnership supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA). It was created in 2007 to bolster the development of better and safer medicines for patients in the European pharmaceutical industry. *To find out more about IMI, visit www.imi.europa.eu*.

Sanofi makes the largest contribution of all EFPIA member companies and has contributed more than €5 million over the course of the program.

Sanofi participated as co-coordinator of the IMI-CHEM21 project, which aims to generate a range of technologies to manufacture medicines that are demonstrably more sustainable than existing methods. Six work packages were developed covering chemistry, biochemistry, synthetic biology and education. Each work package has a Sanofi lead scientist and two packages, WP2 and WP4, are co-led by employees from Sanofi Chemistry & Biotechnology Development.

The aim of WP5 of IMI-CHEM21 was to influence the next generation of chemists by exemplifying low environmental impact chemistry, through the preparation and delivery of high-quality training and educational materials. In working package No. 5 (WP5), Sanofi contributed to "medicinal and process chemist education," with the goal of augmenting employee awareness, as well as setting up a "green chemistry index."

By taking part in the achievements of the CHEM21 project, Sanofi again played an important role in this platform in terms of structure, training on process safety, and solvents.

3.5.3. Sustainable chemical process application

The aim of the Working Package No.2 (WP2) of IMI-CHEM21 was to develop more sustainable chemical process for important chemical transformations.

One objective of this consortium was to use these sustainable methodologies in order to contribute to the development of more efficient and greener process for Essential Medicine molecules manufacture. A decrease in the manufacturing cost was expected, making Essential Medicine more accessible to African Continent. Flucytosine was identified as good target molecule. In Sub-Saharan Africa, around 625,000 mortalities per annum (20% of HIV/AIDS related deaths) result from Cryptococcal meningitis (CM) fungal infection. WHO recommends Flucytosine in combination with Amphotericin B for first line treatment of C. Meningitis.

Sanofi studied a new fluorination methodology based on the use of elemental Fluorine gas as electrophilic reagent and continuous process using flow conditions as technology (milli-reactor). As a great achievement, a new, readily scalable method for the direct synthesis of Flucytosine from cytosine using fluorine gas has been developed. A full process to manufacture Flucytosine API has then been designed and pre-industrial studies have been achieved successfully (kg scale) in order to demonstrate the potential of this new methodology.

In 2018, Sanofi proposed to share these results through Corporate Social Responsibility program. A tech transfer to Inicio/Pelchem, a South African startup that has confirmed interest in the project, would be proposed.

These important results have been partly communicated to scientific community through one publication and two talks (*Alain RABION & al, Org.Proc.Res. Dev*, 2017, *21*, 273; *Alain RABION, Flow chemistry symposium - Barcelonna Nov 14-16th, 2017*; *Alain RABION, Congress Societé Française de Chimie – Montpellier, July 4th, 2018)*