A RESPONSIBLE AND SUSTAINABLE CHEMISTRY

GRI Standards :

301-1, 301-2 : Materials

EXECUTIVE SUMMARY

Green chemistry focuses on making industrial chemistry safer and cleaner, and on giving more consideration on how energy could be used more efficiently while generating economic benefits.

In order to reduce our environmental footprint, Sanofi teams work on optimizing its processes from the design of R&D synthetic pathways to the production of active pharmaceutical ingredients, making greener choices in its consumption use of solvent and reagents, as well as promoting green chemistry 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 impacts on the environment and on human health, and also 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 industrial chemistry safer and cleaner, and on giving more consideration on how energy could be used more efficiently while generating economic benefits. 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 it’s 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 so that it minimizes the impact on the environment.

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 a number of tangible steps 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. Optimizing raw material use and processes

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.

Sanofi uses a KPPI (Key Process Performance Indicators) analysis tool for all its projects to guide chemists in the selection of synthesis routes, evaluate the critical parameters in terms of cost and HSE performances and allow a more targeted process improvement.

3.2. Tracking the greenness of our processes

Medicines are often produced using large amounts of input materials to obtain very small amounts of active ingredients, which corresponds to low mass efficiency. Developing and producing drugs this way is not only costly, but harmful for the environment.

Since 2019, Sanofi has relaunched its efforts at the development process level to implement:

- Biocatalysis The expected positive impact is to design benign chemicals, and better prevent accident use of renewable feedstocks and reduce derivatives,
- Flowchemistry (continuous chemistry). The expected positive impact is ot have less hazardous synthesis, design benign chemistry, including benign solvents and auxilairies, design for energy efficiency, reinforce real time analysis for pollution prevention.

The engagement of Industrial Affairs in digital should allow Sanofi better monitoring in real-time.

Benchmarking shows that the pharmaceutical industry typically uses about 100 kg of raw material to produce 1 kg of active pharmaceutical ingredient. This 1% mass efficiency compares to about 20% for fine chemicals and 50% for bulk chemicals.

We also face the trend of shifting towards biotechnologies, i.e. processes based on fermentation with micro-organisms for the synthesis of active molecules. This evolution means that fewer chemical steps are necessary, but fermentation processes have other environmental impacts (mainly biological chemical oxygen demand, or COD, load to wastewater treatment).

Experts from within the industry, as well as health authorities such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), recommend that drug companies focus greater attention on this issue. To this end, it is essential to adopt a common metric to measure progress toward more sustainable manufacturing.

To meet these requirements, the American Chemical Society-Green Chemistry Institute-Pharmaceutical Roundtable (ACS-GCI-PR) implemented, among other indicators, the Process Mass Intensity (PMI) indicator. PMI measures the mass (weight) of the produced API compared to the mass (weight) of substrates, reagents, solvents, and process water used to manufacture the API. As a member of ACS-GCI-PR, Sanofi uses PMI as a key metric for process greenness.

The initial PMI assessments of our products reveal that our figures are clearly within the pharmaceutical industry range.

However, the PMI alone does not enable a detailed view of process improvement.

In order to remedy to this limitation, a working group from Process Development has met several times since 2013 to investigate appropriate qualitative and quantitative indicators including process efficiency as well as economic and environmental criteria at different development stages, such as:

- Design of industrial synthesis pathways at laboratory scale
- Process development and optimization
- Continuous process improvement at industrial level

The aim of this investigation is to give better guidance to the operating teams, based on relevant KPIs, and focus on the key sustainable activities.

The key process performance indicator (KPPIs) tool and our solvent selection guide were some of the deliverables of this working group.

The amount of solvent and the amount of water used in the process are also considered to be important environmental metrics.

In 2018 most of our commercial products were evaluating using KPPIs tool and action plans for process improvement identified. For instance, for Apomorphine, process improvement should lead to a cost of goods decrease of 50% and a capacity increase of 270%

In each case, the process improvement program was oriented by the outcome of the study.

In parallel, within the framework of our continuous process improvement program we were able to achieve a remarkable reduction of either solvent or water consumption for some of our industrially manufactured products (APIs or intermediates).

For example:

Product	Index	Initial	Optimized
Fexinidazole (API)	SI	88	15
Irbesartan (Intermediate-1)	SI	Total suppression	
Irbesartan (Intermediate-2)	PMI	12.1	7.9
Lasamide (API)*	WI	64.50	25.7

* implemented in production in 2017

The solvent index (SI) calculates the ratio of the total solvent consumed in the process to the mass of the isolated product.

The water index (WI) calculates the ratio of the total process water consumption to the mass of the isolated product.

In 2017, the process improvement in Ankleshwar (India) won the golden award at Sanofi Industrial Affairs Innovation Awards for their project “Environment Protection by reducing wastewater of Lasamide”.

In 2018, a new working group has been initiated with the objective to develop a complete assessment based on raw data already available in our KPPI tool, and to provide an easy-to-understand visual representation that quantifies improvements throughout the development process. This global evaluation of the performance of our processes will not be only based on economic or overall yield aspects but also on all HSE considerations. 15 key metrics were identified and scored. Among these parameters, we can mention, productivity, solvent recycling, HSE scores of solvents and reagents used, potential air emission, PMI, Hazardous substances in water, solvent index, energy, etc…

A color code was also assigned automatically to each metric, and a Scorecard with a global score is generated for each process. This data visualization is now available and allows us to compare different processes performance with the ability to see details at step level. This powerful tool dedicated to R&D teams allows to evaluate environmental performance of any process very early in development cycle till Life cycle management and helps developers to focus on the most critical tasks all along development and production.

3.3. Solvents

3.3.1. Making choices when it comes to solvent use

From the earliest stages of product development, teams are encouraged to use reagents and solvents that pose the least possible hazard. 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.

The vast majority of energy, chemical reagent, and solvent reduction occurs during scale-up and the manufacturing of medicines, rather than during the drug-research phase. Even after an active ingredient is in the production phase, industrial development teams continue to optimize chemical and biochemical processes whenever possible. Choices made during the industrial development phase are often difficult to change later on, which is why it is important to make sustainable decisions early in the development process, taking into account future manufacturing and scale-up.

To choose substances and materials with the least environmental impact, the company has established processes designed to:

- Select the least toxic solvent
- Reduce the quantities of solvents used in industrial processes
- Recycle solvents whenever possible

The guide that was developed, "Sanofi's solvent selection guide: a step toward more sustainable processes[1]," was published in November 2013 and is available at http://pubs.acs.org/doi/abs/10.1021/op4002565. An update of the Sanofi's solvent guide is ongoing and will be available by mid 2021.

3.3.2. Optimizing solvent consumption

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

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

- Process optimization
- Recycling (when possible)
- Incineration with energy recovery

Sanofi has initiated a solvent management plan in 2015 to improve solvent reporting. Thanks to this action plan, we have improved the accuracy of our solvent figures ever since.

For example, in 2020 we prevented 110,126 tons of solvent waste by regenerating solvents and feeding them back into our industrial processes.

[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

	2020	2019
Solvents used (tons)	178,381	184,472
Percentage of regenerated solvents (%)	62	62

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 humans and environment, or that are not very safe to use and that can also generate large amount of waste. For example, this is the case of oxidation reactions, reductions, fluorinations, formation of amides.

The best choices of reagents are studied during the development of the processes and the 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 the 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 very regularly used. In order to not impact the 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. Development work will follow in the coming months.

3.5. Promoting green chemistry within the pharmaceutical industry

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) and the American Chemical Society (ACS), among others. Since 2011 Sanofi has taken an active part in a workshop organized by the Union des Industries Chimiques (UIC) on “Chemistry and Sustainable Raw Materials,” which focuses on the importance of designing green processes.

3.5.2. Our partnership with the ACS-GCI Pharmaceutical Roundtable (ACS-GCI PR)

Sanofi has joined the ACS-Green Chemistry Institute (GCI)-Pharmaceutical Roundtable, which aims to catalyze the implementation of green chemistry and engineering throughout the pharmaceutical industry globally.

Sanofi has launched various collaborative initiatives in line with these general objectives, including:

- Assessment of PMI improvements for the production of key active pharmaceutical ingredients
- Contribution to the training program developed by the GCI-Pharmaceutical Roundtable in Europe
- Contribution to the current review of the solvent guide with members of the GCI-Pharmaceutical Roundtable

For more information about the ACS-GCI-Pharmaceutical Roundtable, see:
http://portal.acs.org/portal/acs/corg/content?nfpb=true&pageLabel=PPTRANSITIONMAIN&node

3.5.3. 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 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 625000 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 valorize 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, 4 july 2018)*

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 of 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.