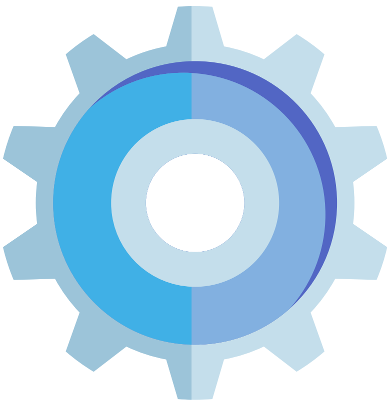
EUROPEAN FINE CHEMICALS GROUP

THE IMPORTANT ROLE OF SOLVENTS

IN THE PRODUCTION OF PHARMACEUTICALS AND FINE CHEMICALS

Solvents play a crucial role in the fine chemicals industry, which includes pharmaceuticals, agriculture, cosmetics, biotechnology, and other sectors[1]. They are used in various stages of the manufacturing process for developing, manufacturing, and formulating active ingredients or excipients.

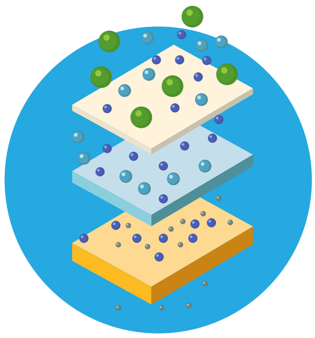
The choice of which solvent to use in the various stages of the manufacturing of fine chemicals is carefully considered to ensure the safety, efficacy, and quality of the final product. This is extremely important especially in the case of highly regulated applications, such as the synthesis of Active Pharmaceutical Ingredients (APIs). Many fine chemicals are produced under the scrutiny of Regulatory authorities who provide strict guidelines and standards for the use of solvents to ensure compliance with safety and quality standards (Good Manufacture Practice or GMP[2]).



KEY USES OF SOLVENTS IN FINE CHEMICALS

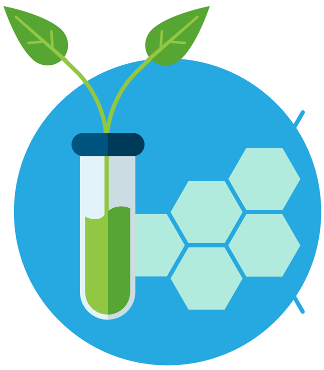
DRUG AND ACTIVE SUBSTANCE SYNTHESIS

Solvents are often used in the synthesis of fine chemicals, including API and other active substances. They help dissolve reactants, promote chemical reactions that lead to the formation of the desired drug compound and help control reaction conditions such as temperature.



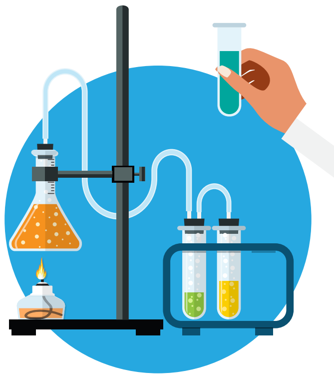
EXTRACTION AND PURIFICATION

Solvents are employed in the extraction of desired compounds from natural sources, such as plants or microorganisms. This is a common method for obtaining bioactive compounds that serve as the basis for many pharmaceuticals. After synthesis or extraction, solvents are used in purification processes to isolate the desired substance from impurities.



CRYSTALLISATION

Solvents are essential in the crystallisation process, where the substance is precipitated and formed into pure crystals, thus isolating the ingredient in a highly purified form, crucial for the effectiveness and safety of the drug or for performance of the fine chemical.



FORMULATION

Solvents are essential in formulation, where they are used to dissolve the fine chemical and other necessary components such as excipients. In the case of pharmaceuticals, this facilitates the creation of pharmaceutical dosage forms such as tablets, capsules, and liquid formulations.

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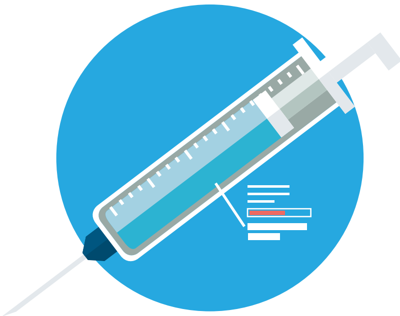
[1] https://efcg.cefic.org/fine-chemicals/applications/
[2] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice;
https://single-market-economy.ec.europa.eu/single-market/european-standards/harmonised-standards/cosmetic-products_en

COATING

Solvents are used in the preparation of coating solutions, which are often applied to tablets or capsules to control the release of the drug. Many coating technologies exist and, like other process steps that are critical for the final function of the pharmaceutical or crop protection product, the coating process is carried out under GMP.

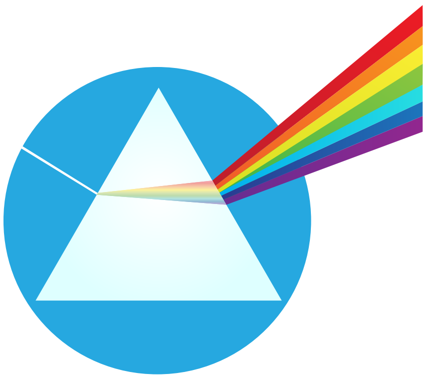
CLEANING AND STERILISATION

Solvents are used for cleaning and sterilising equipment and containers in fine chemical manufacturing. This is crucial to maintain aseptic conditions, prevent contamination and ensure the quality of the final product.



DRUG DELIVERY SYSTEMS

In some cases, solvents are used as carriers in drug delivery systems. For example, they may be used in the formulation of parenteral (injectable) drugs to improve solubility and bioavailability. The active substance is dissolved within the formulation.



ANALYTICAL TECHNIQUES

Various analytical techniques, such as chromatography and spectroscopy, essential for quality control and characterisation of fine chemical products frequently make use of solvents. These are also used in dissolution tests to assess how quickly a substance dissolves – a crucial information for formulating dosage forms with optimal bioavailability. The analytical methods used are often controlled by agreed test guidelines (such as OECD guidelines for testing of chemicals)[3], these methods can stipulate the solvents that must be used for a particular test method, or the dissolution test may be required as part of the approval with the regulatory authorities. This means the solvent cannot be readily changed without requalification of a new test method.

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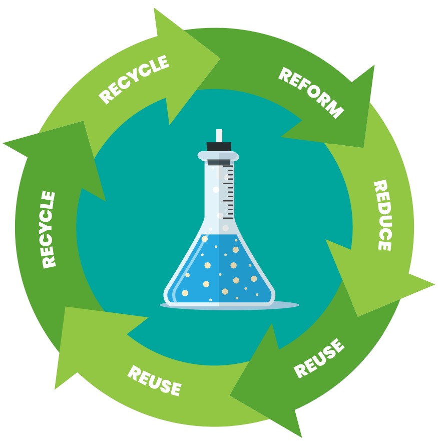
[3] https://www.oecd.org/env/ehs/testing/

TRENDS IN THE USE AND CHOICE OF SOLVENTS

The pharmaceutical and fine chemical industry place the strongest emphasis on the selection of solvents based on safety, environmental impact, and regulatory compliance. The use of solvents in the production of fine chemicals, especially in active ingredients, is a carefully regulated aspect of manufacturing to ensure the safety and efficacy of the final drug, crop protection and cosmetic products.

Nowadays, the choice and use of solvents is increasingly dictated by the need to minimise the environmental impact of chemical processes and streamline the use of solvents. Companies in the pharmaceutical supply chain are continuously exploring solvent alternatives to enhance the sustainability of their processes.



CIRCULAR ECONOMY DEVELOPMENTS

focus on recycling, re-using and minimising the use of solvents already in the design phase, leading to significant economic benefits by reducing raw material costs and waste disposal expenses and reducing the environmental impact of chemical processes.

GREEN CHEMISTRY PRINCIPLES

encourage the design of chemical processes that minimise the use of solvents. Techniques such as solvent-free reactions, use of alternative solvents (e.g., water, supercritical CO_2), and catalytic processes are promoted.

PROCESS INTENSIFICATION

involves redesigning chemical processes to make them more efficient and reduce the need for solvents. Examples include using continuous flow reactors instead of batch reactors and integrating multiple process steps into a single unit, leading to a reduction of the energy consumption, the amount of solvent needed and safer reactions.

APPENDIX – CASE STUDIES AND EXAMPLES

Case study 1 : Development of a Second generation (2-GEN) Process for an analgesic

The efficiency of the original process was markedly increased by designing a three-step domino sequence to an advanced intermediate. Using this approach, several aqueous workup steps and solvent exchanges could be eliminated, which had a significant impact on cycle times and waste amounts. Moreover, switching to a phase transfer catalytic system allowed the reduction of the reaction temperature from 105°C to 25°C, leading to a decrease in energy consumption. Furthermore, it was possible to combine two hydrogenation steps into a one-pot sequence, leading to the final API in excellent quality. The process was not only superior in terms of sustainability, but also in terms of cost; in comparison to the previous route there was an approximately 50% cost reduction. A summary of the achievements is outlined below:

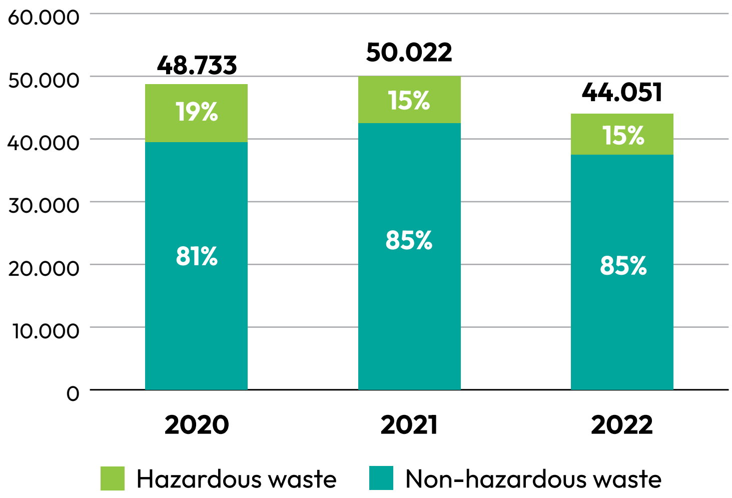
Increase of overall yield	From 24% to 42%
Cost reduction	More than 50%
Total weight of raw materials and solvents used	Reductoin of approx. 50%
Operator hours	Reduced by 40%
Equipment hours	Reduced by 50%
Reduction of waste	Reduced to 55% compared to previous process
Reduction of isolated steps	From 17 to 11

The above example demonstrates that reduction or replacement of solvents is often substantially incentivised by the associated reduction in costs and/or cycle times, as well as increases in process efficiency and safety. Therefore, these intrinsic benefits will drive industry to streamline their processes further without the need to put additional regulations in place.

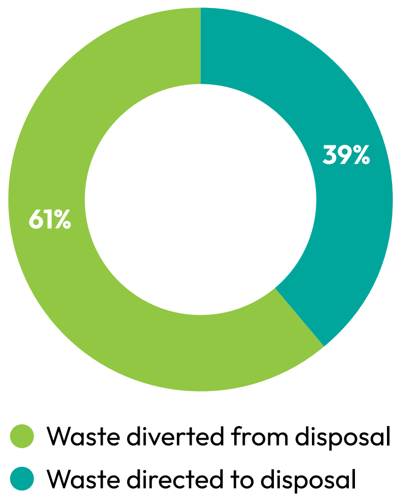
Case study 2 : Re-use and recovery of solvents as part of the circular economy

Circular economy is one of the most important pillars for the environmental strategy of EFCG members. One of them, a major innovative API manufacturer in Europe, has implemented a comprehensive programme for recovering and reusing solvents during the production cycle or sending them to external recovery sites. Their aim is to combine a responsible use of natural resources and raw materials with a responsible waste management approach. Moreover, this Company promotes and develops solutions aimed at recycling and reusing materials (among them solvents), energy and waste.

Generated waste (ton)

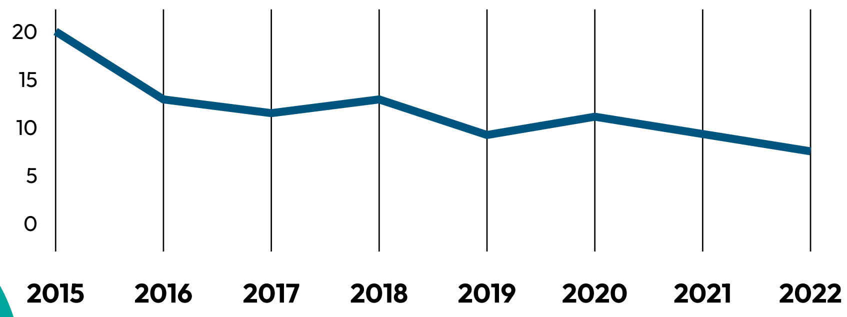


Waste management in 2022 (%)



-12%
of waste generated in 2022 vs 2021

Total waste
Per ton of manufactured product (Ton / Ton)



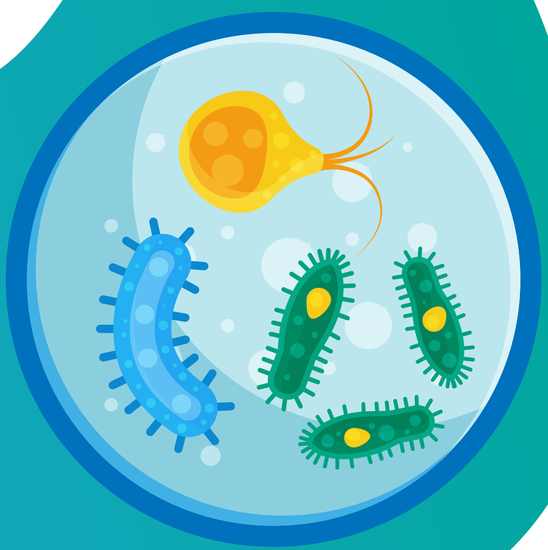
GRI 306-3: Waste generated					
Waste by composition	**u.m.**	**2022**	**2021**	**2020**	**2022 vs 2021**
Mother liquors and solvents	ton	36.685	41.496	38.431	-12%
Production solids		354	379	422	-7%
Packaging		1.491	1.525	1.496	-2%
Sludges		4.769	5.248	7.611	-9%
Others		752	1.374	774	-45%
Total Waste generated		44.051	50.022	48.733	-12%

In 2022, this company generated 44.051 tons of waste with a reduction of about 12% compared to 2021; 61% of the waste generated was recycled or recovered. Waste generated consists mainly of mother liquor containing solvents, organic and inorganic salts, and traces of active pharmaceutical ingredients. Other types of waste include uncleaned empty packaging – which originally contained raw materials used in production processes – used filtration materials, waste coming from laboratories and from construction, demolition, and maintenance activities. The company makes sure that all systems guarantee and provide for the safe handling, movement, storage, recycling, reuse, or management of waste and materials and prevent and mitigate accidental spills and release of fuels, waste, chemicals, intermediates, products, and other hazardous materials into the environment.

This company's circular initiatives focus on increasing the manufacturing processes efficiency; they strive to optimise plant performances, in order to reduce the amount of energy, materials, solvents and natural resources they need. In particular the Company has equipped itself with innovative technology for the enhancement of materials, such as the introduction of distillation columns for solvent recovery which allow the reduction of waste generated, reusing solvents which would otherwise be diverted to disposal. Green Chemistry projects are also a focus of this Company for the replacement of most toxic chlorinated solvents and the reduction of critical substances which could be particularly toxic, especially on new manufacturing processes. One such example is the replacement of 1,2-Dichloroethane with Dichloromethane.

Continuous manufacturing processes

To increase efficiency and reduce the energy required for production, especially in the functioning of reactors, the same company is implementing several continuous manufacturing processes, investigating both the flow chemistry approach and the continuous stirred tank reactors (CSTR). These approaches entail leaving no batch reactors with loading and unloading phases but keeping constantly active production units – either microreactors or small classical reactors. The outcome is that, at the same levels of production, continuous manufacturing processes can reduce the footprint of the manufacturing process in comparison to standard methods. This innovative production technique enables a double positive impact in terms of sustainability. Indeed, it allows the use of smaller amounts of material per unit time, therefore resulting in increased local temperature control and in the possibility to avoid extreme temperatures, making the manufacturing process less energy intensive. It also provides greater safety for operators and along the process itself, due to the possibility of using limited quantities of products that react together at any given time. Advanced processes can dramatically reduce the use of energy and solvents.



Biotechnology

Since the 1960s, the same company has developed a specific Biotech division focusing on microbial fermentation and manufacturing. In the first applications this technique was used to produce antibiotics and many other molecules, including cancer drugs. Today, fermentation is applied to manufacturing processes for life-saving treatments. Microbial fermentation is an eco-friendly and highly sustainable process that uses almost only water, renewable nutrients, and microorganisms, therefore reducing the need for chemical solvents, whose use is already significantly limited in all of the company's biotechnology centres.

To support ongoing innovation, this Company, as a majority of others in the sector, is firmly committed to further reducing its environmental impact by limiting the use of chemical solvents in all its manufacturing processes.

Biocatalysis

Today the urgency for more cost-effective, robust and selective chemical transformations is increasing. Biocatalysis, which could be defined as the use of microorganisms or enzyme preparations to catalyse chemical transformations, meets these requirements for an increasingly growing number of reactions.

The use of biocatalysis in industrial processes is extremely attractive thanks to its several advantages, such as:

- synthesis of products that are not always accessible by standard chemical reactions;
- use of alternative raw materials that are often less complex and less expensive;
- high selectivity of biocatalysts, resulting in the synthesis of high purity and, therefore, high quality products;
- eco-sustainability thanks to the use of water as a reaction solvent, potential virtual elimination of organic solvents and reaction temperature close to room temperature.

Production containment

Most of the EFCG companies have and continue to introduce technologies to increase the degree of production containment, in order to protect workers and the environment.

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