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Life
**PHARMA
DETOX**

**Demonstration of an innovative method for the
detoxification of pharmaceutical wastewater
from pharmaceutical facilities**

**Deliverable B.5.4: Preliminary/draft Business Plan
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Disclaimer

The information included herein is legal and true to the best possible knowledge of the authors, as it is the product of the utilization and synthesis of the referenced sources, for which the authors cannot be held accountable.

Abstract

The LIFE PHARMA-DETOX project aims to address the environmental challenges posed by pharmaceutical wastewater by developing an innovative treatment system that detoxifies Active Pharmaceutical Ingredients (APIs) and promotes water recovery and reuse. The preliminary business plan shows that the feasibility of the business model is highly dependent on relevant policies and is directly influenced by water pricing and potential subsidies or other investment incentives. The business plan outlines the current state of the pharmaceutical industry in Europe, the current regulatory framework in Europe and in the partners' countries, provides the business model canvas of the PHARMA-DETOX system and refers to other related systems on the market.

Keywords

▪ APIs ▪ Wastewater ▪ Pharmaceutical Industry ▪ Business Plan ▪ Policies

Abbreviations and Acronyms

APIs	Active Pharmaceuticals Ingredients
IPR	Intellectual Property Rights
FDF	Finished Dosage Forms

CSTR	Continuous Stirring Tank Reactor
R&D	Research and Development
EMA	European Medicines Agency
AMR	Antimicrobial Resistance
SDGs	Sustainable Development Goals
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
WWTPs	Wastewater Treatment Plants
NCAs	National Competent Authorities
GMP	Good Manufacturing Practices
GCP	Good Clinical Practice
CTIS	Clinical Trials Information System
SPCs	Supplementary Protection Certificates
ICH	International Council for Harmonisation
WHO	World Health Organization
ECJ	European Court of Justice
SSbD	Safe and Sustainable by Design
POPs	Persistent Organic Pollutants
MSFD	Marine Strategy Framework Directive
EQSD	Environmental Quality Standards Directive
WL	Watch List
PNECres	PNEC for resistance selection
PNECeco	PNEC for ecological effects
ERA	Environmental Risk Assessment
STPs	Sewage treatment plants
BAT	Best Available Techniques
IED	Directive on Industrial Emissions
BREFs	BAT Reference Documents
LVOC	Large Volume Organic Chemicals
GHG	Greenhouse Gas
RES	renewable energy
EED	Energy Efficiency Directive
RED	Renewable Energy Directive

IED	Directive on Industrial Emissions
MBRs	Membrane Bioreactors
FTO	Freedom to Operate
BMC	Business Model Canvas
AOPs	Active Oxidation Processes
GAC	Granular Activated Carbon
COD	Chemical Oxygen Demand
MBR	Membrane Biological Treatment
ZLD	Zero Liquid Discharge

Table of Contents

ABSTRACT	3
ABBREVIATIONS AND ACRONYMS	3
EXECUTIVE SUMMARY	9
1. INTRODUCTION	10
1.1. Background and scope of this deliverable	10
2. THE LIFE PHARMA-DETOX PROJECT	12
2.1. PHARMA-DETOX System Design Technologies	12
2.2. Circular Economy Principles.....	15
2.3. Outputs	16
3. THE PHARMACEUTICAL INDUSTRIAL SECTOR IN EUROPE	16
3.1. Pharmaceutical Landscape in Europe	16
3.2. The AMR Industry Alliance.....	21
4. CURRENT LEGAL FRAMEWORK FOR PHARMACEUTICAL INDUSTRIAL SECTOR	25
4.1. EU-Wide Strategies and Action Plans	26
4.2. Current Legal Framework for Pharmaceutical Industries wastewater treatment – wastewater generation-wastewater streams in Europe	28
4.2.1. Core EU Water Regulations.....	28
4.2.2. Regulations Specific to Pharmaceutical Pollution and AMR Prevention	30
4.2.3. Industrial Emissions and Wastewater Treatment Regulations	33
4.2.4. Climate and Energy Framework Regulations	35
4.3. Current Legal Framework for Pharmaceutical Industries Wastewater Treatment in Partners' Countries	35
4.3.1. Cyprus.....	35
4.3.2. Denmark.....	37
4.3.3. Greece	38
4.3.4. Sicily.....	39
4.4. Coordinating beneficiary - MEDOCHEMIE Case Study.....	40
5. BUSINESS PLAN DEVELOPMENT PROCESS	41
5.1. Background	41
5.2. Freedom to Operate analysis.....	41

5.2.1.	Value Map	42
5.2.2.	Road map	44
6.	MEDOCHEMIE DEMONSTRATION CASE – LIFE PHARMA-DETOX BUSINESS MODEL.....	45
6.1.	Introduction	45
6.2.	Existing competitive to LIFE PHARMADETOX technologies	45
6.3.	LIFE PHARMADETOX Value Proposition – Comparative advantages	47
6.4.	Technological solution validation	48
6.5.	Draft Business Canvas	50
6.6.	Value Creation & Delivery.....	52
7.	VALUE CAPTURE	53
7.1.	Economic Assumptions	53
7.2.	CAPEX & OPEX.....	53
7.3.	Results-Revenues/Foregone Costs.....	57
8.	REPLICABILITY POTENTIAL	58
9.	CANDIDATE SECTORS FOR TRANSFERABILITY.....	58
10.	CONCLUSIONS	59
	REFERENCES.....	60

List of Tables

Table 3-1	Top Pharmaceutical Enterprises by Country EU[1]	17
Table 3-2	AMR Alliance Science-Based PNEC Targets for Risk Assessments[13]	25
Table 4-1	List of PNECres and PNECeco. [24]	32
Table 6-1	Comparison of PHARMA-DETOX with other conventional wastewater treatment technologies	47
Table 7-1	Estimated annual cost of operating the LIFE PHARMA-DETOX System (OPEX)	56

List of Figures

Figure 2-1:	The PFD of the prototype system	13
Figure 3-1	European Pharmaceutical Preparations Number of Enterprises by Country in 2023[1]	17
Figure 3-2	Map with European manufacturing with Finished Dosage Form of small molecules[2]	18
Figure 3-3	Roadmap of the Fight Against AMR: The Role of the AMR Industry Alliance[9] ...	21

Figure 3-4 Sources of antimicrobials in the environment. How pharmaceuticals (including antibiotics) can enter the environment from numerous sources[12] 22

Figure 5-1: Value Map template..... 43

Executive Summary

The present report was prepared in the framework of the co-financed European LIFE PHARMA-DETOX (LIFE20 ENV/CY/000615) during the implementation of Activity B.5.1.: “Business Plan and Investment Memorandum”.

Being the preliminary draft of the LIFE Pharma-Detox system business plan it presents an initial mapping of the pharmaceutical industrial plants market dynamics, the market gap the system aims to fill in, the Pharma-Detox pilot system components, process and operation, the cost components in terms of CAPEX and OPEX as estimated for the pilot unit and the draft business canvas on which the business plan will be drafted.

The Business Plan, Deliverable B.5.1 will lay down the market landscape (size, dynamics/trends, segments and regions, competitors and customer “needs and wants”), as well as the relevant IPR landscape. It will also be used as an Investment Memorandum, including a final chapter regarding the investment needed (Round A and Round B) for delivering the foreseen financial growth.

The business plan will define the most important costs: The investment cost, the supply of raw materials, the fees and cost of intellectual property and the salaries of the employees.

A SWOT (strengths, weaknesses, opportunities and threats), PEST (Political, Economic, Social and Technological) and “Porter’s Five Forces” type of analysis will be conducted by NEVIS, to identify the ways to achieve maximum exploitation of the project results, market replication and return on investment in Deliverable B.5.2: Market exploitation report.

The capital and operating expenditures (CAPEX and OPEX respectively) will be calculated by NEVIS and Medochemie for different full-scale solutions, based on the construction and operation costs of the prototype.

1. Introduction

The LIFE PHARMA-DETOX project aims to the detoxification of wastewater produced from pharmaceutical industry, through the development and implementation of an innovative, economically viable and cost-efficient system for the transformation of pharmaceutical compounds, present in wastewater, into non-toxic substances (novel detoxification process). The LIFE PHARMA-DETOX system will be able to treat the wastewater generated from production activities, ensuring that no Active Pharmaceuticals Ingredients would end up in the wastewater sewage system without being processed and detoxified by the system developed (PHARMA-DETOX Demo System). Furthermore, after detoxification, the reclaimed water could be used for cleaning, irrigation or other purposes.

1.1. Background and scope of this deliverable

Through the efficient implementation of the LIFE PHARMA-DETOX project. Consortium partners are committed to achieving the following objectives:

- Avoid APIs release in the wastewater sewage system.
- Convert and detoxify APIs from the Lead Beneficiary - Medochemie's 3 manufacturing facilities.
- Apply the system to pharmaceutical industries across Europe. The EU has 4000 pharmaceutical enterprises (Eurostat). If the system is adopted through the EU, plenty of APIs would be converted to non-toxic compounds before being discharged in the wastewater sewage system per year.
- Recycle and reuse water that would otherwise have been discarded in the sewage system. The reclaimed water can be used in non-critical applications, such as in heat exchanging (chillers/boilers, equipment to control the temperature of air entering the production area), cleaning procedures or irrigation.
- Save about 3 m³ of potable water daily (that means 990 m³ yearly). In its place the same quantity of reclaimed water will be used.
- Minimize the environmental footprint of the system using 100% renewable energy sources.
- Demonstrate an innovative, cost effective, low energy consumption industrial system for the treatment of wastewater effluent containing traces of APIs that will be detoxified so that it can be reused.

- Develop a new, innovative method for the treatment and detoxification of pharmaceutical compounds with the aim of commercialization and implementation in other pharmaceutical companies across Europe.

Within the framework of LIFE PHARMA-DETOX implementation, Action B.5 and sub-action 5.1 focuses on Business Plan aspects, closely related to action B.4 which will offer a thorough study on replicability and transferability potential. A preliminary business plan has been elaborated already at the proposal preparation stage, at this stage the business plan will be updated.

More specifically, within Sub-action B.5.1 Business Plan and Investment Memorandum:

(1) The Business Plan will lay down the market landscape (size, dynamics/trends, segments and regions, competitors and customer “needs and wants”), as well as the relevant IPR landscape. It will also be used as an Investment Memorandum, including a final chapter regarding the investment needed (Round A and Round B) for delivering the foreseen financial growth.

The business plan will define the most important costs; the investment cost, the supply of raw materials, the fees and cost of intellectual property and the salaries of the employees. The first estimation for the cost of the PHARMA-DETOX prototype system has been made to be EUR 440,000, which refers to the different prototype components of the whole system that will be constructed and installed.

(2) During Sub-Action B.4.1., the identification of stakeholders for potential replication sites in the EU will be established. Market reports will also be purchased by NEVIS to retrieve useful information.

(3) A SWOT (strengths, weaknesses, opportunities and threats), PEST (Political, Economic, Social and Technological) and “Porter’s Five Forces” type of analysis will be conducted by NEVIS, to identify the ways to achieve maximum exploitation of the project results, market replication and return on investment.

(3) The capital and operating expenditures (CAPEX and OPEX respectively) will be calculated by NEVIS and Medochemie for different full-scale solutions, based on the construction and operation costs of the prototype.

A reconsideration and recalculation of the following will be necessary:

- Investment analysis, to determine how the investment is likely to perform and how suitable it will be for a particular investor.

- Financial investment analysis, a study of the access to financing sources and the physical identification of sites for full commercialization /industrialization is necessary to start a business and ramp it up to profitability.
- Setting the strategy for licensing agreements negotiation for transfer of the proposed solution into other contexts between the owner of the patent and someone who wants to use it and include stipulations.

The initial output of the above-described actions is the present report, Deliverable B.5.4. Preliminary/Draft Business Plan. This deliverable will serve as a ground document for Deliverable B.5.1: Business Plan/Investment Memorandum (including pitch presentation) which is closely connected to Deliverables B.5.2 Market Exploitation Report and B.5.3 Policy reviews and recommendations, additional foreseen deliverables of Action B.5.

2. The LIFE PHARMA-DETOX Project

The PHARMA-DETOX system combines advanced engineering, cutting-edge technology, and renewable energy to deliver an economically viable and sustainable solution for treating wastewater generated by pharmaceutical manufacturing activities. This system is designed to transform Active Pharmaceutical Ingredients (APIs) and other compounds into non-toxic substances, ensuring compliance with environmental standards and reducing the ecological footprint of pharmaceutical facilities. The system will be able to treat the wastewater ensuring that no APIs would end up in the wastewater sewage system without being processed and detoxified by the developed system.

2.1. PHARMA-DETOX System Design Technologies

The system design was developed to meet Medochemie's specific requirements for wastewater treatment, ensuring the detoxification of APIs in an efficient and sustainable way. The prototype system includes various components, each having a crucial role in the overall performance of the system. These components work together to achieve the desired result: effective treatment of pharmaceutical wastewater using renewable energy sources.

As shown in Figure 2-1: The PFD of the prototype system The prototype system consists of the following parts:

- 1) Mixing Tank,
- 2) Reverse Osmosis Unit,
- 3) Catalytic Reactor,

4) Water Electrolysis Unit

5) PV Area

Operational parameters and capacity of the proposed innovative system, including:

- Wastewater output: 2.5 m³/day (312 L/h) for 8h operation
- RO Permeate: 2 m³/day (250 L/h) for irrigation
- RO Concentrate: 0.5 m³/day (62.5 L/h)
- Reactor effluent: 0.5 m³/day (62.5 L/h) for cleaning

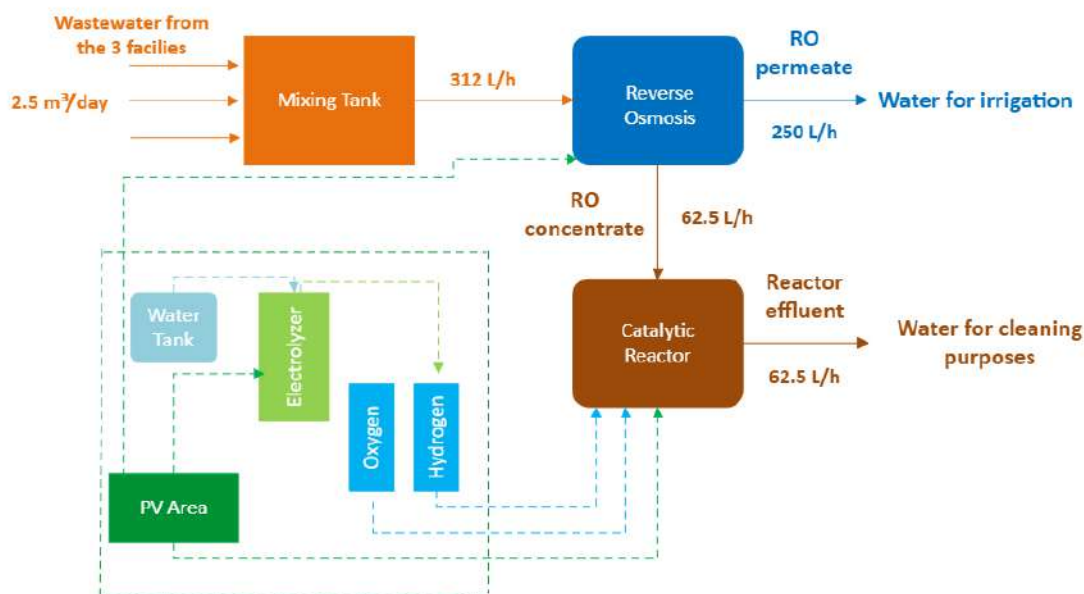


Figure 2-1: The PFD of the prototype system

Below is a detailed breakdown of the technologies and components that constitute the LIFE PHARMA-DETOX system:

1) Buffer Tank

The effluents from the three manufacturing plants of Medo B (Oral Penicillins Facility, Injectable Penicillins Facility, and Ampoules Injectables Facility Line 1 and 2) will be mixed in a Mixing Tank of 5 tn.

2) Reverse Osmosis

The Reverse Osmosis (RO) unit is designed to significantly reduce the volume of wastewater going through the catalytic reactor. By minimizing 80-90% of the volume of wastewater, the RO unit concentrates the stream containing pharmaceutical compounds, making the catalytic reactor more efficient and minimizing energy usage. The RO permeate stream, free from APIs, can be used for non-critical applications like irrigation, cleaning, and cooling purposes,

contributing to resource sustainability, in the frame of the social responsibility scheme of the company. The RO concentrate stream, estimated at approximately 62,5 L/h, will contain the pharmaceutical compounds and will be driven to and treated in the catalytic reactor. The RO unit ensures that only the most contaminated portion of the wastewater is processed in the catalytic reactor, reducing both operational time and the energy demands of the detoxification process. The operation of the RO system and the pumping of wastewater to and from the reactor will require an estimated 3-4 kWh/ m³ of treated wastewater. This energy demand will be covered through renewable sources, as the system is designed to rely on photovoltaics.

3) Catalytic Reactor

The concentrated stream from RO (about 62,5 L/h) will be driven to and treated in the reactor. At the heart of the detoxification process is the custom-designed catalytic reactor. This component is responsible for transforming pharmaceutical compounds into non-toxic substances through hydrogenation. The catalytic reactor is an autoclave Continuous Stirring Tank Reactor (CSTR), 100 L, constructed from SS316 stainless steel for corrosion resistance and durability. It uses hydrogen produced by the electrolysis unit as a reactant, and operates at room temperature and atmospheric pressure, minimizing energy consumption. The design and specifications of the catalytic reactor are derived from the outcomes of bench-scale tests that were conducted. The system will fully operate with renewable energy (solar).

4) Water electrolysis unit

The water electrolysis unit is integral to the system's energy and resource independence. It produces pure hydrogen, a critical reactant for the catalytic process, using renewable solar energy.

5) Photovoltaic Area

The PV system powers the entire LIFE PHARMA-DETOX system, providing an estimated 15 kW of renewable energy. This ensures that the system operates sustainably without relying on external power sources. Utilizing solar energy, the system will power the electrolyzer to produce pure hydrogen (H₂) during daylight hours. This hydrogen will serve as a reactant in the catalytic process. The sizing of the PV system has been optimized based on the energy demand of the wastewater system and the overall load, focusing on economic and efficient operation.

The unit will be installed in fully insulated new 20 ft, HC container suitably modified and separated in the middle with a 4 cm thick polyurethane panel with industrial floor for safety and durability. The container is split into two compartments to separate hazardous (ATEX Zone II) and non-hazardous areas. Safety was a top priority in the container design, critical components, including the catalytic reactor, electrolysis unit, reverse osmosis system, tanks, and gas cylinders, are in an ATEX Zone II area. To meet ATEX Zone II standards, components such as the stirring motor and mass flow controller are certified to prevent ignition, equivalent to Class I, Division 2 in US standards. Additional safety measures include gas detection systems, alarms, proper ventilation, and non-return valves, ensuring safe and compliant operations while minimizing risks. This separation and equipment selection guarantee reliable and secure wastewater treatment.

2.2. Circular Economy Principles

The LIFE PHARMA-DETOX system significantly contributes to the principles of the circular economy by transforming waste into resources, optimizing energy use, and reducing environmental impact. Its innovative design promotes sustainability in multiple ways. First, the system enables wastewater recovery and reuse. Through Reverse Osmosis unit, wastewater is separated into two streams: permeate and concentrate. The permeate, free from APIs repurposed for non-critical uses such as irrigation, cleaning, and cooling. This minimizes water wastage and supports the efficient reuse of resources. Second, the system addresses pollution prevention by detoxifying pharmaceutical wastewater. It converts hazardous pharmaceutical compounds into non-toxic organic matter, preventing harmful substances from entering natural water bodies. This aligns with circular economic principles by mitigating the environmental impact of pharmaceutical production and closing the loop on industrial waste. Third, the system utilizes renewable energy for its operations. Solar energy powers the entire system through a photovoltaic (PV) installation, eliminating reliance on fossil fuels and reducing carbon emissions. The hydrogen produced through electrolysis is used as a reactant in the catalytic process, further integrating renewable energy into the system's functionality. Fourth, the system minimizes material waste by employing durable and efficient components. Key parts, such as the catalytic reactor, are built with SS316 stainless steel to ensure longevity and reduce the need for frequent replacements. This extends the system's lifecycle and conserves resources. Additionally, the containerized and scalable design supports resource efficiency and adaptability. The modular structure allows the system to be transported and replicated at other pharmaceutical facilities, maximizing its impact and

enabling sustainable practices to spread across the industry. Finally, the system aligns with global sustainability goals by reducing the consumption of natural resources and mitigating environmental degradation.

2.3. Outputs

The LIFE PHARMA-DETOX system generates several valuable outputs that highlight its efficiency, sustainability, and alignment with environmental goals. The primary output is treated water, free from Active Pharmaceutical Ingredients and other hazardous substances, repurposed for non-critical applications such as irrigation, cleaning, and heat/cooling systems. This reduces the facility's reliance on freshwater resources, supporting water conservation efforts and promoting circular water use within the pharmaceutical industry. Another key output is the concentrated stream of detoxified organic matter, which ensures that pharmaceutical wastewater no longer presents environmental hazards. This system operates without chemicals or reagents and uses solar power to produce hydrogen through electrolysis of water, providing a clean and renewable source of energy. This hydrogen is used in the catalytic process that detoxifies pharmaceutical compounds, eliminating hazardous waste and reducing environmental impact. Using solar energy through a designed PV system, the PHARMA-DETOX system has no reliance on fossil fuels, no greenhouse gas emissions and a much smaller carbon footprint. The photovoltaic panels are designed to minimize energy consumption, ensuring efficiency and cost savings long-term.

3. The Pharmaceutical Industrial Sector in Europe

3.1. Pharmaceutical Landscape in Europe

The pharmaceutical industry is one of Europe's most dynamic and innovative sectors, numbering over 13,500 pharmaceutical companies.[1]

The sector represents a vital component of the region's economy and healthcare systems, contributing billions of euros annually to the economy while it provides millions of jobs directly and indirectly. Europe is a major exporter of pharmaceutical products, with key markets being the United States, Asia, and other parts of the world. The following figures show the leading countries within the EU and the number of pharmaceutical enterprise per country.

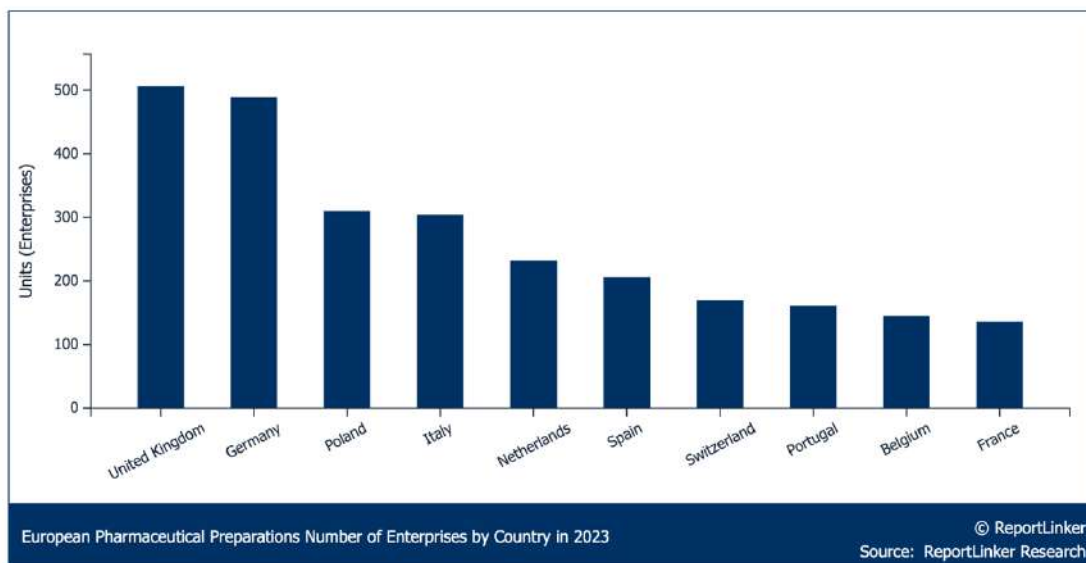


Figure 3-1 European Pharmaceutical Preparations Number of Enterprises by Country in 2023 [1]

Table 3-1 Top Pharmaceutical Enterprises by Country EU [1]

Country	Units (Enterprises)	Last Year	Year over Year	5-years Compound Annual Growth Rate
United Kingdom	506	2023	+2.22%	+2.42%
Germany	489	2023	-0.61%	+1.36%
Poland	310	2023	+2.31%	+1.7%
Italy	304	2023	-1.62%	-1.21%
Netherlands	232	2023	+2.65%	+2.71%
Spain	206	2023	-1.44%	+0.097%
Switzerland	170	2023	+1.19%	+2.53%
Portugal	161	2023	+3.87%	+4.86%
Belgium	145	2023	+1.4%	+0.56%
France	136	2023	-13.92%	-8.06%

In terms of segment, conventional drugs (small molecules) were the largest revenue generating molecule type in 2023. The infographic below highlights the countries which have the most facilities in Europe who develop and manufacture Finished Dosage Forms (FDF) of small molecules.

European Pharma CDMO Facilities 2025

Overview of countries with Finished Dosage Form (FDF) manufacturing of small molecules

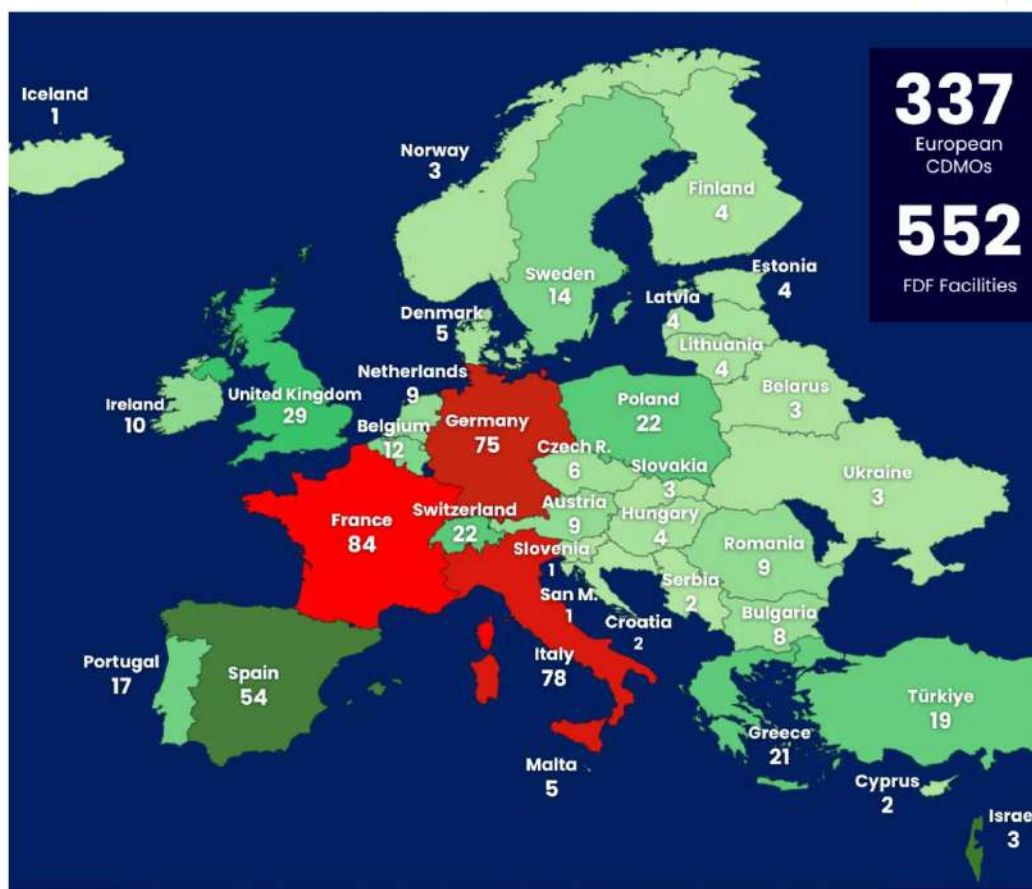


Figure 3-2 Map with European manufacturing with Finished Dosage Form of small molecules[2]

The country with the most contract manufacturing facilities is France (1st), followed by Italy (2nd) and Spain (3rd).

The pharmaceutical sector is characterized by its significant contribution to Research and Development (R&D) as it invests heavily in R&D, with billions of euros allocated each year to develop new treatments and improve existing ones. In closed cooperation with universities and institutions, such as the University of Cambridge, ETH Zurich, and the Max Planck Institute R&D is very well supported to Europe being a leader in pharmaceutical innovation.

Public-private partnerships, like the Innovative Medicines Initiative, foster collaboration between industry players, academic institutions, and governments and contribute to existing robust regulatory frameworks.[2]

The European Medicines Agency (EMA) plays a central role in evaluating, monitoring, and approving medicines for use across EU member states. Europe also maintains strong Biotech Clusters located in Basel (Switzerland), Cambridge (UK), and Medicon Valley (Denmark-

Sweden) as well as Life Sciences Hubs in Paris-Saclay, BioRN (Germany), and Flanders (Belgium).

Open to innovation, the sector has adopted AI, big data, and digital health technologies to continuously adjust and reshape the sector, aiding drug discovery and personalized medicine. Raised environmental concerns, including the management of pharmaceutical waste, are becoming increasingly important and to this end several hundreds of EU funded projects partly with the contribution of IMI are financed annually.

The sector also played an important role during the pandemic. As a response to the COVID-19 pandemic, the Commission launched several special actions for coronavirus research from Horizon 2020 and Horizon Europe, as part of a €1 billion pledge for coronavirus research. On 30 January 2020, the European Commission launched its first emergency call on Coronavirus research through which €48.2 million were awarded to 18 research projects. [3] On 19 May 2020, the Commission launched a second emergency call, through which €128 million were awarded to 24 research projects[4].

Projects funded via these two calls encompass the full spectrum of research and innovation to respond to the threat and better prepare for future outbreaks, from basic research, modelling, digital tools, epidemiology, the development of diagnostics, treatments and vaccines, to the understanding of behaviour and socio-economic effects during the outbreak, as well as the infrastructures and resources that enable all this research

Major hubs are mostly located in Western Europe and countries like Germany, Switzerland, France, and the United Kingdom. These are major pharmaceutical hubs, known for their strong research ecosystems and companies having global presence. Specifically, Germany is leader in manufacturing, with companies like Bayer and Boehringer Ingelheim while Switzerland is home to giants like Novartis and Roche. United Kingdom pharmaceutical industry emphasis is on biotechnology gene therapies, biologics and advanced pharmaceuticals, supported by companies like GlaxoSmithKline (GSK) and AstraZeneca. France has strong presence in R&D and generics, with companies like Sanofi. Rare Diseases and Orphan Drugs are focus areas on France and Belgium. [5], [6]

Northern Europe and in particular Scandinavia (Sweden, Denmark, Finland) is recognized for innovation in biotech innovations, such as gene therapies and biologics.

Denmark hosts Novo Nordisk, a leader in diabetes and hormone therapy. Sweden is characterized by AstraZeneca's R&D footprint and smaller biotech firms. Biotechnology: Scandinavia, the UK, and Switzerland lead in biotech innovations, such as gene therapies and biologics.[5], [6]

Southern and Eastern Europe are emerging markets with growing capabilities in manufacturing and generics. Italy is a leader in contract manufacturing. Poland, Hungary and Spain are countries with significant contribution to generic pharmaceuticals. [5], [6]

The pharmaceutical industry is strategically important for Cyprus as pharmaceutical products represent one of the key pillars in export in the overall export strategy for Cyprus. Around 30% of the country's total exports are medicines and a percentage of 39% of the exports to the EU are medicines.[7], [8] Additionally, the pharmaceutical industry in Cyprus provides more than 2000 workplaces for the local population. [8]

Therefore, the pharmaceutical industry in Cyprus plays a critical role in the island's economic development, particularly due to its strong export-oriented focus. Companies like Medochemie have propelled Cyprus onto the global stage by producing a diverse range of generic drugs that meet stringent international standards, including EU Good Manufacturing Practices (GMP). Cyprus benefits from its strategic geographic location, serving as a gateway to markets in Europe, the Middle East, and Africa. The sector's growth is supported by a highly skilled workforce, including pharmacists, engineers, and researchers, which allows for innovation and a focus on R&D.

R&D in Cyprus pharmaceutical sector has increasingly focused on new formulations and more efficient production methods. The regulatory framework in Cyprus, aligned with EU directives, ensures the safety and efficacy of pharmaceuticals produced and sold both locally and internationally.

The emphasis on high-quality, competitively priced generic medicines and expanding global markets positions Cyprus's pharmaceutical sector as one of the most significant contributors to the island's export economy, helping to bolster the country's reputation as a hub for reliable pharmaceutical production.

The European pharmaceutical industry has a dual focus on ensuring affordability for patients while maintaining incentives for innovation. Among the challenges the sector faces include the required regulatory alignment post-Brexit, addressing supply chain vulnerabilities and managing high costs of R&D and pricing pressures. However, pricing strategies vary across countries due to differing healthcare systems.

The information presented highlights Europe's strength as a global leader in pharmaceuticals and thus the significant contribution of pharmaceutical industry to the European economy and employment highlighting the importance of R&D to the sector's evolution, development and adaptation to emerging opportunities or critical situations affecting health.

3.2. The AMR Industry Alliance

Antimicrobial resistance (AMR) is recognized as one of the most serious health concerns worldwide. The WHO, G7, G20 and many world leaders have recognized the growing threat of AMR, which threatens the achievement of United Nations Sustainable Development Goals (SDGs). In 2016, the UN called on countries, companies and civil society to take broad, coordinated action to address the root causes of AMR, across multiple sectors including human and animal health, pharmaceuticals, food and agriculture, finance, environment and development. [9], [10]

In 2017, the AMR Industry Alliance, one of the largest private sector collaborations, was established to provide sustainable solutions to reduce antimicrobial resistance, bringing together more than 100 biotechnology, diagnostics, generic and research-based pharmaceutical companies and associations. [11]



Figure 3-3 Roadmap of the Fight Against AMR: The Role of the AMR Industry Alliance[9]

AMR is a direct threat to global public health. In 2019 alone, it was estimated that nearly 5 million deaths were associated with resistant bacterial infections—1.27 million of which were directly attributable to AMR. [12] There are several causes of AMR, including over and misuse of antibiotics in human and animal health in the agriculture and aquaculture sectors. Human health is closely linked to environmental health, and there is concern that the presence of antibiotics in the environment may also contribute to antibiotic resistance in humans through the development and subsequent spread of resistance in environmental bacteria. Active residues of antibiotics and resistant bacteria can find their way into the environment in four keyways. [10]

1. Human and animal use and excretion by people and animals (pets, horses and food animals) using antibiotics is by far the biggest source of antibiotics in the environment.
2. Agricultural applications include using manure or biosolids as fertilizer and the administration of antibiotics in aquaculture.
3. Inappropriate disposal of used or expired drugs.
4. Manufacturing emissions from both the production APIs and their formulation into drugs is another source of environmental emissions. In regions like Europe, only trace levels of antibiotics in the environment can be attributed to waste from production but in countries where discharges are not well controlled some studies have found very high levels of active residues in the discharge vicinity of antibiotic factories (for example, in China and India)

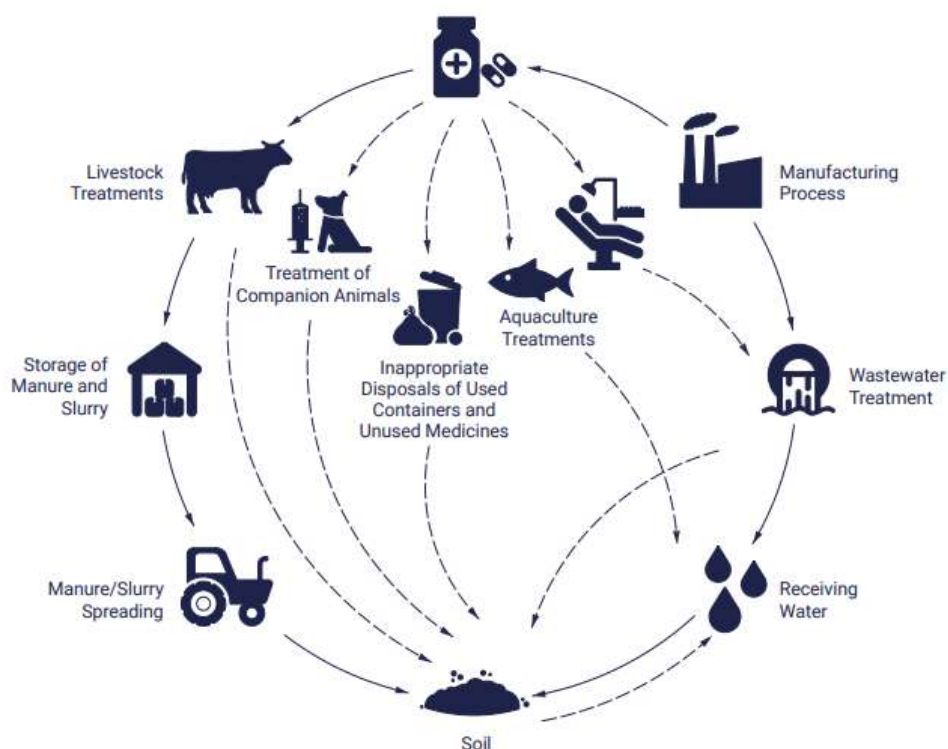


Figure 3-4 Sources of antimicrobials in the environment. How pharmaceuticals (including antibiotics) can enter the environment from numerous sources[12]

Releasing antibiotics into the environment in this way can increase the number of selection pressures that lead to the development of resistance. Other contaminants, such as biocides and heavy metals, can combine to add further pressure on bacteria to become resistant. Once

resistant bacteria are in the environment, they can persist and spread through waterways and soils. People and animals can be exposed to them through food, water and air, although more scientific studies are needed to understand the connection between the presence of antibiotics in the environment and the development of clinically relevant resistance in humans.

Even though manufacturing emissions are not the main source of antibiotics in the environment, pharmaceutical industries agree on the need for common responsible manufacturing practices to minimize their risk. The regulatory framework for waste and wastewater from antibiotic manufacturing varies widely from country to country. Active pharmaceutical ingredients are not specifically regulated in environmental laws. Inconsistent monitoring and enforcement of environmental regulations, particularly in certain emerging markets, makes it particularly important for manufacturers themselves to provide sufficient oversight of their antibiotic suppliers to ensure that responsible practices extend throughout the global antibiotic supply chain. Despite growing calls to reduce emissions from the manufacture of antibiotics, there is no simple process for developing a global standard to control and manage antibiotic residues in manufacturing.

However, to minimize the environmental impact of manufacturing production, many pharmaceutical companies set voluntary effluent targets for pharmaceuticals as part of their own environmental programs and recently the AMR Industry Alliance published science-driven, risk-based targets for discharges for approximately 120 antibiotics.[13]

The AMR Industry Alliance developed a common framework for managing antibiotic emissions. In early 2018, Alliance published the results of their work as a set of minimum environmental expectations for antibiotic manufacturers (the Common Antibiotic Manufacturing Framework[10]). The framework applied to all types of factories that make antibiotics, including those that produce active antibiotic pharmaceutical ingredients (APIs) and those that formulate those APIs into medicines. Following widespread dissemination of the Framework and the AMR Industry Alliance's members' progress in implementing the Framework's requirements, AMR Industry Alliance decided to formalize the Framework's requirements in this antibiotics manufacturing standard. The Antibiotic Manufacturing Standard provides a framework for managing antibiotic-containing wastewater to minimize the risk of AMR and aquatic ecotoxicity. The concentration of antibiotics in wastewater discharge must not exceed levels that could promote resistance in environmental bacteria.

The framework requires risk assessments to ensure that the Predicted Environmental Concentration (PEC) of antibiotic residues remains below the Predicted No-Effect Concentration (PNEC), a limit ensuring environmental safety.

Facilities must have permits for wastewater discharge, follow monitoring and reporting requirements, and use advanced treatment methods when needed. The guidelines highlight the importance of measuring API discharges, improving wastewater treatment systems, and using advanced treatments such as ozonation and oxidation processes. Facilities must also have emergency plans to deal with unexpected discharges, such as spills or firefighting water, to prevent environmental damage. Annex A offers practical guidance to minimize risks associated with antibiotic residues. Main recommendations focus on improving manufacturing processes to minimize waste, improving purification methods to reduce API losses and separating wastewater streams for more effective treatment. Advanced technologies, such as activated carbon adsorption and membrane separation, are suggested for pre-treatment, while modifications to existing Wastewater Treatment Plants (WWTPs) can enhance their effectiveness in removing antibiotics. The document also highlights the importance of ongoing risk assessments, data collection, and using scientifically established PNECs for environmental safety.

The LIFE PHARMA-DETOX project is closely related to the principles highlighted within the AMR Industry Alliance's framework. The main goal of LIFE PHARMA-DETOX project is to reduce the environmental impact of pharmaceutical waste by using advanced wastewater treatment technology. The detoxification using the catalytic reactor and reverse osmosis is in line with the recommended tertiary treatment methods, such as advanced oxidation, in the AMR standard. The LIFE PHARMA-DETOX project and the Standard Method both prioritize the Predicted No Effect Concentration (PNEC), ensuring that treated water is safe for reuse in non-critical applications such as irrigation and industrial cleaning. The integration of renewable energy in LIFE PHARMA-DETOX further complements the sustainability goals emphasized in the AMR guidelines.

AMR Industry Alliance has developed a science-based approach for establishing discharge targets in antibiotic manufacturing, grounded in PNECs, for environmental risk assessments. These targets are derived from two values: PNEC-Environment (PNEC-ENV), based on ecotoxicology data and standard risk assessment methodologies[14], [15] and PNEC-Minimum Inhibitory Concentration (PNEC-MIC), [16] to address resistance promotion. Manufacturers

are advised to use the low of these values, when available, to ensure robust protection of ecological resources and reduce the potential for AMR. If a substance is not listed, companies may read across to a similar antibiotic or use the default PNEC of 0.05 µg/L. The Alliance periodically updates this table as new reliable data emerges, and working toward these discharge targets helps protect both environmental ecosystems and human health. In the table below, they are presented only pharmaceutical substances expected to be found in wastewater from the 1st and 2nd line Ampoules injectable facility, the Oral penicillin facility, and the Injectable facility, reflecting the antibiotics most relevant for Medochemie manufacturing sites.

Table 3-2 AMR Alliance Science-Based PNEC Targets for Risk Assessments[13]

Active Pharmaceutical Ingredient	Facility	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Amikacin	2 nd line Ampoules injectable	18.7	16	16.0
Amoxicillin	Oral Penicillin	0.57	0.25	0.25
Ampicillin	Oral Penicillin	0.6	0.25	0.25
Cloxacillin	Oral Penicillin	20	0.13	0.13
Flucloxacillin	Injectable Penicillin	27	N/A	27.0
Gentamicin	2 nd line Ampoules injectable	0.15	1	0.15
Penicillin G	Oral Penicillin	1	N/A	1.0
Penicillin G Procaine	Oral Penicillin	16	N/A	16.0
Penicillin V	Oral Penicillin	3	N/A	3.0
Phenoxymethylpenicillin	Oral Penicillin	N/A	0.06	0.06

4. Current Legal Framework for Pharmaceutical Industrial Sector

The legal framework regulating the pharmaceutical industry in Europe ensures the safety, efficacy, and quality of medicines while promoting innovation and fair competition. It encompasses EU-wide legislation, national laws of member states, and international agreements.

At European Union level the EMA [17] is the centralized body responsible for scientific evaluation, supervision, and safety monitoring of medicines across the EU. The European Commission develops pharmaceutical legislation and policies and ensures harmonization across member states. The National Competent Authorities (NCAs), collaborate with the EMA and oversee specific regulatory processes in their respective countries.

Key regulations in place refer to authorization, manufacturing, and distribution of medicinal products and safety monitoring systems to ensure that medicines on the market remain safe for use. [18] Additionally, Good Manufacturing Practices (GMP)[19] set by EU guidelines ensure medicines are consistently produced and controlled. Good Clinical Practices (GCP)[20] set ethical and scientific quality standards for clinical trials. The aim of Clinical Trials Regulation is to harmonize clinical trial procedures across Europe, increasing transparency and streamlining authorization via the Clinical Trials Information System (CTIS). Pharmaceuticals are protected under national and EU patent systems for Intellectual Property and Market Exclusivity. Patents and Supplementary Protection Certificates (SPCs) extend patent protection for up to five years to compensate for the lengthy regulatory approval process.[20] Data generated for marketing authorization is protected for 8 years, with an additional 2 years of market exclusivity. A further 1-year extension is possible for significant new therapeutic indications. Pricing and reimbursement policies are determined by individual member states but must comply with EU rules, such as Directive 89/105/EEC, which ensures transparency.[20]

The EU aligns with international standards, including those set by the World Health Organization (WHO) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[20], [21]

Inspections and penalties for non-compliance are conducted by NCAs and EMA.[20]

The European Court of Justice (ECJ) plays a role in resolving disputes regarding EU pharmaceutical law.[22]

4.1. EU-Wide Strategies and Action Plans

The United Nations Agenda 2030, specifically SDG 6, along with the 2017 United Nations Environment Assembly Ministerial Declaration, represent important commitments to enhance water quality and prevent pollution[23]. The G7/G20 and the WHO have established policies to reduce AMR, promoting global efforts in this area. [24] The zero-pollution action is a cross-cutting objective contributing to the UN 2030 Agenda for Sustainable Development and complementing the 2050 climate-neutrality goal in synergy with the clean and circular economy and restored biodiversity goals. It is part and parcel of many European Green Deal and other initiatives, and the Commission will continue including the zero-pollution action in future policy initiatives. The LIFE PHARMA-DETOX project is in line with these wide strategies and action plans, promoting the implementation of these regulatory and environmental goals.

The EU has published the following directives aimed at protecting the environment and all forms of life:

- ❖ **Zero Pollution Action Plan**[25] minimizes and eliminates pollution, focusing on protecting human health, ecosystems, and biodiversity. One of its key areas of concern is water pollution, especially from hazardous substances, including pharmaceuticals. The action plan supports the work on Best Available Techniques (BAT) and innovation in clean technologies to reduce emissions from industrial facilities. The EU's Zero Pollution Hierarchy prioritizes pollution prevention at the source.
- ❖ **Biodiversity Strategy for 2030** [26] highlights pollution from chemicals, pharmaceuticals, and hazardous substances as a major driver of biodiversity loss. The strategy emphasizes the need to restore and protect freshwater ecosystems by improving water quality and preventing pollution. The strategy calls for better resource efficiency, water reuse, and reduced reliance on freshwater extraction.
- ❖ **Circular Economy Action Plan**[27] highlights the importance of reducing waste and pollution at the source, particularly in key sectors such as water, chemicals, and pharmaceuticals. One of its major goals is to establish a toxic-free, circular economy, ensuring that hazardous substances do not persist in the environment.
- ❖ **Europe's State of Water 2024**[28] report highlights the urgent need to improve water resilience due to increasing pressures from pollution, water scarcity, and climate change. It emphasizes the importance of zero pollution policies, advanced wastewater treatment, and sustainable water management. The report underlines that Europe's waters continue to fight chemical pollution, including pharmaceutical residues, which contribute to poor water quality and ecological degradation.
- ❖ **Indicator Framework for Chemicals**[29] aims to track and reduce chemical pollution, ensuring safer and more sustainable chemical management across industries.
- ❖ **Chemicals Strategy for Sustainability Towards a Toxic-Free Environment** [30] supports a toxic-free environment by reducing harmful substances in our daily lives and promoting safe, sustainable production and use of chemicals.

- ❖ **Strategic Approach to Pharmaceuticals in the Environment**[31] underlines that pharmaceuticals enter the environment through manufacture, use, and disposal, creating risks to ecosystems and potentially contributing to AMR.

The LIFE PHARMA-DETOX project supports key EU directives by treating effluents at the source avoiding pharmaceutical pollution and preventing harmful substances from entering water bodies and affecting aquatic life. Reuse of treated water in industrial and agricultural applications contributes to the Circular Economy Action Plan, reducing dependency on freshwater resources. The project contributes to zero pollution goals, reduces the risk of AMR, and supports compliance with EU water quality regulations. and resource recovery demonstrates a Safe and Sustainable by Design (SSbD) system, promoting circular economy principles. The use of renewable energy (solar energy) supports the EU Chemicals Strategy for Sustainability.

4.2. Current Legal Framework for Pharmaceutical Industries wastewater treatment – wastewater generation-wastewater streams in Europe

The legal framework for pharmaceutical wastewater treatment involves a combination of international agreements, national laws, and local regulations, depending on the country. Below is a structured overview of this framework:

The Basel Convention regulates hazardous waste movement across borders, including pharmaceutical industry waste.[32] The Stockholm Convention addresses Persistent Organic Pollutants (POPs), some of which can be pharmaceutical by-products. The WHO provides guidelines on managing pharmaceutical waste and mitigating contamination.[33]

The relevant SDGs include Goal 6 for Clean Water and Sanitation and Goal 12: Responsible Production and Consumption.[23]

4.2.1. Core EU Water Regulations

The European Union has established a regulatory framework for pharmaceutical wastewater management, bringing together various policies, directives, and strategies to minimize water pollution, ensure water quality, and promote sustainability. These frameworks aim to improve wastewater treatment standards, promote circular economy principles, and ensure

compliance with Predicted No-Effect Concentrations (PNECs) for pharmaceutical contaminants.

The LIFE PHARMA-DETOX project, using advanced detoxification technologies, catalytic hydrogenation, and renewable energy sources, is closely related to these regulations, including the Water Framework Directive, the Industrial Emissions Directive, and the revised Urban Wastewater Treatment Directive. The project offers an innovative solution for pharmaceutical wastewater treatment, reducing the risk of antimicrobial resistance (AMR), supporting the reuse of treated water, and reducing dependence on freshwater resources.

The Water Framework Directive (2000/60/EC)[34] establishes strategies to reduce water pollution, including pharmaceutical contaminants and sets Environmental Quality Standards (EQS) for pollutants in water bodies.

Water FD sets a series of environmental objectives (Article 4) for water bodies, targeting at least 'good status'. Moreover, the Water FD has as an aim to achieve the elimination of priority hazardous substances (such as pharmaceutical compounds) and contributes to achieving concentrations in the marine environment near background values for naturally occurring substances. This is the main objective of this project that when completed, the wastewater from 3 manufacturing plants out of 9 Medochemie Ltd. will be treated effectively and the clean water thus produced will be used either in the manufacturing plants or for irrigation purposes. The discharge of wastewater into the central sewage system may lead to a series of unwanted effects to the biological wastewater treatment process of WWTPs, while the final release of pharmaceutical compounds/residues (within treated wastewater) to surface or ground waters poses significant hazards to the ecosystem itself.

The EU Regulation 2020/741 on Minimum Requirements for Water Reuse[35] promotes the reuse of treated wastewater to address water scarcity while setting strict quality standards to ensure safe application, particularly in agriculture and industrial processes. The LIFE PHARMA-DETOX project directly supports these goals by removing pharmaceutical pollutants from wastewater through advanced catalytic hydrogenation and reverse osmosis, ensuring compliance with PNEC limits to prevent AMR and environmental contamination. Additionally, the project contributes to resource efficiency by enabling safe water reuse in irrigation and industrial cleaning, reducing dependency on freshwater sources.

EU Marine Strategy Framework Directive (MSFD)[36] recognizes chemical pollution, including hazardous substances like pharmaceuticals, as a major threat to marine biodiversity and ecosystem health. The MSFD highlights microbial pollution as a pressure on marine ecosystems, and pharmaceuticals, especially antibiotics, contribute to AMR development in marine bacteria. The MSFD aims to achieve Good Environmental Status of the EU's marine waters. To implement this directive, each Member State is required to develop a marine strategy for its waters, minimizing hazardous substances in marine waters to protect aquatic species and habitats. LIFE PHARMA-DETOX directly reduces API concentrations, minimizing AMR risks in wastewater discharges and preventing the spread of resistant bacteria into marine environments.

4.2.2. Regulations Specific to Pharmaceutical Pollution and AMR Prevention

According to the Environmental Quality Standards Directive (EQSD)[37] 2008/105/EC as amended by Directive 2013/39/EU a mechanism was needed to provide high-quality monitoring information on the concentrations of potentially polluting substances in the aquatic environment to support future prioritization exercises in line with Article 16(2) of Directive 2000/60/EC (Water Framework Directive), and improve the protection of the aquatic environment and human health via the environment.

Directive 2013/39/EU[38], adopted on 12 August 2013, amends Directives 2000/60/EC and 2008/105/EC concerning priority substances in water policy. This amendment includes the addition of 12 new substances or groups of substances to the list of priority substances, six of which are classified as priority hazardous substances, bringing the total to 45 regulated substances or groups. The directive also introduces a "watch list" mechanism to monitor emerging pollutants that may pose a risk to or via the aquatic environment but lack sufficient monitoring data. [39]

The mechanism aimed at emerging pollutants and other substances for which the available monitoring data are either insufficient or of insufficient quality for the purpose of identifying the risk posed across the EU. It involves creating a Watch List (WL) with a limited number of such substances and monitoring them EU-wide for up to 4 years. The 1st WL for substances in surface waters was established by Commission Implementing Decision (EU) 2015/495 in March 2015. [38]The list was first updated in June 2018 by the Commission Implementing Decision (EU) 2018/840 and in August 2020 by Commission Implementing Decision (EU)

2020/1161[40]. The last update was in July 2022 by Commission Implementing Decision (EU) 2022/1307[41].

The main criteria for inclusion in the first list of candidate substances[39] were that i) the substance is suspected of posing a significant risk to, or via, the aquatic environment, meaning there is reliable evidence of hazard and of possible exposure to aquatic organisms and mammals, but ii) there is not enough information to assess the EU-wide exposure for the substance, i.e. insufficient monitoring data or data of insufficient quality, nor sufficient modeled exposure data to decide whether to prioritize the substance.

One of the first compounds which was in the 1st WL was diclofenac, to collect sufficient monitoring data for the determination of risk reduction measures. Diclofenac is a non-steroidal anti-inflammatory drug. The PNEC value in 2015 was 0.1 µg/l and the updated PNEC value was 0.05 µg/l.[38]

The 1st list was updated in June 2018 by the Commission Implementing Decision 2018/840. During the WL update, the Commission concluded that the substance diclofenac should be removed from the WL since the monitoring data quality was good enough to perform the risk assessment. One of the new substances which were included was antibiotic amoxicillin. Amoxicillin was kept during the second update of the WL in 2020 (2020/1161). The 4th WL was established in 2022 by Commission Implementing Decision 2022/1307[41]. The period of continuous monitoring for any WL substance should not exceed four years (Article 8b of the EQSD), for this reason in 2022 amoxicillin removed from the WL. The 4th WL includes some pharmaceutical substances that belong to the same groups as some of the substances of interest in the LIFE PHARMA-DETOX project. Specifically, Midazolam, which was added to the list, belongs to the Benzodiazepine group, like Diazepam and Lorazepam. Additionally, Clindamycin, included in the watch list, is part of the Lincosamide class, like Lincomycin HCl, which is of interest in the project

The purpose of WHO Guidance on Wastewater and Solid Waste Management for Manufacturing[24] is to provide an independent scientific basis for the determination and inclusion of targets in the binding instruments of different target audiences to prevent the emergence and spread of antibiotic resistance. While this guidance is not binding, it provides a foundation for coherence in any applicable policy or market instrument, binding or non-binding, to improve transparency and prevent fragmented or insufficient approaches. This guidance is directly related to the LIFE PHARMA-DETOX project, as both focus on reducing pharmaceutical pollution, managing antibiotic residues, and preventing AMR in the

environment. The WHO guidance establishes PNECs for antibiotic residues in wastewater, ensuring that pharmaceutical manufacturing effluents do not contribute to AMR or ecological harm.

One of the major concerns addressed in the WHO document is the role of antibiotic pollution in promoting AMR, particularly when untreated residues enter natural water bodies and municipal wastewater treatment plants. LIFE PHARMA-DETOX mitigates this risk by treating pharmaceutical wastewater at the source, preventing the spread of antibiotic-resistant bacteria. Additionally, the WHO guidance establishes science-based discharge limits and mandates monitoring programs for pharmaceutical facilities, which aligns with the project’s approach of ensuring treated wastewater meets EU regulatory standards and WHO-recommended PNECs.

To achieve effective antibiotic removal, the WHO document recommends tertiary treatment technologies, such as ozonation, activated carbon filtration, and membrane technologies. The WHO framework aligns with EU water policies, including the EU Zero Pollution Action Plan, the Water Framework Directive, and the Industrial Emissions Directive, which also guide the LIFE PHARMA-DETOX project’s objectives.

The table in WHO guidance presents PNEC values for selected pharmaceutical substances, categorized into PNEC for resistance selection (PNECres) and PNEC for ecological effects (PNECeco). PNECres values indicate antibiotic concentrations that do not promote AMR, minimizing risks to public health. PNECeco values represent thresholds that prevent disruptions to aquatic ecosystems, ensuring microbial communities remain unaffected. Based on EMA guidelines, these targets use cyanobacteria growth inhibition as a surrogate endpoint for assessing environmental risks.

Table 2 includes only the pharmaceuticals expected in wastewater from the 1st and 2nd line Ampoules Injectable Facility, Oral Penicillin Facility, and Injectable Facility.

Table 4-1 List of PNECres and PNECeco. [24]

Active Pharmaceutical Ingredient	Facility	PNECres (µg/L)	PNECeco (µg/L)
Amikacin	2 nd line Ampoules injectable	16	-
Amoxicillin	Oral Penicillin	0.25	0.57
Ampicillin	Oral Penicillin	0.25	0.6
Cloxacillin	Oral Penicillin	0.13	20
Flucloxacillin	Injectable Penicillin	-	26.8

Gentamicin	2 nd line Ampoules injectable	1	0.15
Lincomycin	2 nd line Ampoules injectable	2	0.81
Penicillin G Procaine	Oral Penicillin	-	16
Phenoxymethylpenicillin	Oral Penicillin	0.06	-

Source WHO Guidance on Wastewater and Solid Waste Management for Manufacturing

The Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use [42] mandates an Environmental Risk Assessment as part of the approval process for medicinal products, requiring evaluations of potential impacts on surface water, groundwater, soil, and sewage treatment plants (STPs). It highlights the need for risk mitigation measures and adherence to PNEC to ensure that pharmaceutical residues do not pose a threat to ecosystems or contribute to AMR. The guideline also identifies hotspots of pharmaceutical pollution, such as hospitals and pharmaceutical manufacturing sites. By treating wastewater at the source, the project prevents pharmaceutical residues from reaching municipal wastewater treatment plants, ensuring compliance with PNEC limits and EU discharge regulations.

4.2.3. Industrial Emissions and Wastewater Treatment Regulations

The Directive on Industrial Emissions (IED) - Directive 2010/75/EU [43] establishes regulations to control pollution from industrial activities, including pharmaceutical manufacturing, with the aim of minimizing emissions to air, water, and soil. Under this directive, pharmaceutical plants are required to obtain permits that outline specific wastewater treatment standards and mandate the use of BAT to reduce environmental impact. Additionally, BAT Reference Documents (BREFs) provide detailed guidelines for the pharmaceutical industry, ensuring compliance with wastewater treatment regulations and emission reduction technologies.

The BREF for the Production of Large Volume Organic Chemicals (LVOC) [44] provides a framework for minimizing environmental impact and emissions in chemical production processes. The principles and techniques outlined in the BREF are closely aligned with the goals and technologies employed in the LIFE PHARMA-DETOX project.

The use of catalytic hydrogenation is a core process in both the BREF and the LIFE PHARMA-DETOX project. In the BREF, catalytic hydrogenation is highlighted as a highly effective method for reducing hazardous organic compounds by breaking them down into non-toxic forms.

Similarly, in the PHARMA-DETOX system, the catalytic hydrogenation reactor plays a central role in detoxifying APIs from pharmaceutical wastewater. This process transforms harmful pharmaceutical compounds into harmless organic matter, effectively reducing ecotoxicity and mitigating risks associated with AMR. The BREF also emphasizes the importance of minimizing emissions to water by using advanced treatment processes, which aligns with the LIFE PHARMA-DETOX system's use of reverse osmosis and advanced catalytic detoxification. These technologies work in synergy to ensure that APIs and other hazardous substances are removed from wastewater, producing clean water that can be reused in non-critical applications such as irrigation and industrial cleaning. By achieving high levels of water purification, the PHARMA-DETOX system directly addresses one of the core objectives of the BREF: reducing emissions of hazardous substances to water.

The BAT guidelines promote the recovery and reuse of resources, including energy and water, as well as the integration of sustainable energy sources. The focus on wastewater containing toxic organic compounds in BREF aligns with the specific challenge addressed by LIFE PHARMA-DETOX. The catalytic hydrogenation process used in the project serves as a practical implementation of BAT techniques, providing a scalable and transferable solution for other chemical and pharmaceutical industries.

Revised Urban Wastewater Treatment Directive (2024/3019)[45]: Approved by the European Parliament in 2024, this directive introduces stricter requirements for wastewater treatment, particularly concerning micropollutants such as pharmaceuticals. It emphasizes the "polluter pays" principle, holding producers of pharmaceuticals and cosmetic products financially responsible for the costs associated with removing these substances from wastewater. This directive is expected to impose significant additional costs on pharmaceutical companies operating within the EU. This legislation will have to be passed by the national parliaments by 2027. It will come into force from 01/01/2029 with a phased implementation and should be completed by 2045. It concerns manufacturers of medicinal products and cosmetics. Water from wastewater of patients, pharmaceutical and cosmetic manufacturers will have to be treated to a quaternary level, bringing zero pollutants from drugs/cosmetics into the environment. There is not this kind of technology available at this time; the purification of the water must reach the highest level. Pharmaceutical and cosmetic producers must cover at least 80% of quaternary treatment costs, and 100% coverage of data collection costs. Full coverage of administrative costs for EPR implementation. The revised Directive will bring financial benefits of approximately €6.6 billion per year by 2040.

4.2.4. Climate and Energy Framework Regulations

The EU 2030 Climate Target Plan[46] aims to a 40% reduction in greenhouse gas (GHG) emissions, a 32% share of renewable energy (RES) in total energy consumption, and a 32.5% improvement in energy efficiency by 2030.

The project is fully in line with the 'European Green Deal' Roadmap (EGD), the Energy Efficiency Directive 2012/27/EU (EED) and the Renewable Energy Directive 2018/2001/EU (RED). The EED requires the use of highly efficient technologies, while the EGD 'sets the roadmap for a sustainable EU economy, based on the full exploitation of renewable sources through innovative technologies'. The project aims to demonstrate novel technology for the treatment of pharmaceutical wastewater, which will operate with renewable energy (solar), as we have already mentioned.

The Roadmap to a Resource Efficient Europe (COM (2011) 571 final). [47] According to the roadmap, water is a vital resource for human health and essential input for agriculture, tourism, industry, transport and energy. The wastewater treatment plant that will be constructed and operated in Medo B manufacturing site of Medochemie Ltd. will be able to process up to 2,5 m³/day, converting it to reusable, clean water that can be returned for use to the manufacturing plant or used for irrigation purposes. This also means that a lot of drinking water is saved and used elsewhere.

4.3. Current Legal Framework for Pharmaceutical Industries Wastewater Treatment in Partners' Countries

4.3.1. Cyprus

In Cyprus, pharmaceutical wastewater can be generated by various sources, particularly in the healthcare and pharmaceutical sectors. The Cyprus Government to eliminate the dependency of the domestic water supply on annual rainfall, decided to:

- Construction of sea water desalination plants
- Replace fresh water used in agriculture by treated effluents of the WWTPs
 - Irrigation purposes
 - Enrichment of aquifers
- Sludge produced during the treatment of wastewater: recycled and used as a soil conditioner for plantations (not for soft fruit and vegetables)

Eliminating APIs from WWTP effluents is crucial for reusing them in agriculture and industry.

The current legal framework for industrial wastewater in Cyprus is described in the below legislation:

- The Law on Industrial Emissions (Integrated Prevention and Pollution Control) of 2013 (N.184(I)/2013)[48]
- The Law on the Protection and Management of Water of 2003 – 2023 (N.13(I)/2004)[49]
- The Sewerage Regulations of Limassol-Amathus[50]
- The Sewerage Systems Law of 1971 – 2020 (N.1/1971)[51]
- The Law on the Control of Water Pollution of 2002 – 2013 (N.106(I)/2002)[52]
- The EU Urban Wastewater Treatment Directive (91/271/EEC)

Once local pharmaceutical manufacturing facilities have ensured that all treated wastewater consistently meets regulatory limits for key pollutants such as nitrogen, phosphorus and other chemical or biological contaminants, the wastewater from the facilities is discharged to the central sewer system of the city and then directly to the local WWTP. In general, WWTPs are not able to completely remove all active pharmaceutical ingredients from the wastewater stream.

Medochemie is an international company that has manufacturing plants in 3 countries (Cyprus, the Netherlands and Vietnam), core offices in 21 countries and operates in 107 countries. The project includes a replication in one pharmaceutical company in the Netherlands. Pharmaceutical wastewater treatment in the Netherlands follows strict regulatory frameworks due to the potential environmental and public health impacts of pharmaceutical residues. The Netherlands has implemented various strategies to address the issue, including compliance with European Union (EU) directives and national regulations:

- Legislative framework
 - National laws, such as the Dutch Environmental Management Act, regulate wastewater discharge.
- Advanced treatment technologies
 - Advanced treatment technologies include ozonation, activated carbon filtration, and membrane bioreactors (MBRs).
- Monitoring and research
 - Regular monitoring of pharmaceutical residues in water is conducted through research partnerships.

- Source control
 - Source control focuses on minimizing pharmaceutical waste through green chemistry and closed-loop systems

4.3.2. Denmark

In Denmark, the management of pharmaceutical wastewater is governed by a comprehensive legal framework designed to protect the environment and public health. The key components of this framework include:[53], [54]

Environmental Protection Act

Denmark's Environmental Protection Act serves as the cornerstone for environmental regulation, encompassing provisions for wastewater management. It mandates that all wastewater discharges, including those containing pharmaceutical residues, comply with environmental quality standards to prevent pollution.

Statutory Order on Wastewater Discharges[55]

The Statutory Order No. 501 of 21 June 1999 outlines specific rules for licensing wastewater discharges. It requires that any discharge into water bodies or soil must obtain prior authorization, ensuring that wastewater treatment meets established environmental standards.

BAT Requirement

Danish law mandates that facilities, including hospitals, adhere to the BAT for wastewater treatment. This ensures the implementation of the most effective and advanced methods to minimize environmental impact.

Focus on Micropollutant Removal[53]

Denmark places significant emphasis on the removal of micropollutants, particularly pharmaceutical residues, from wastewater. Advanced treatment technologies are being implemented to address these contaminants, reflecting the country's commitment to surpassing regulatory requirements and protecting its aquatic environment.

Municipal Initiatives[55]

Municipalities in Denmark are proactive in enhancing wastewater treatment facilities to effectively remove pharmaceutical residues. For instance, the Hillerød Centralrenseanlæg (HCR Syd) wastewater treatment plant has incorporated advanced treatment steps to eliminate micropollutants, demonstrating local commitment to environmental protection.

Hospital Wastewater Treatment Standards[56], [57]

Hospitals in Denmark are required to comply with stringent wastewater treatment standards to ensure the removal of pharmaceutical residues. Facilities like the Herlev Hospital have implemented advanced treatment plants, setting new benchmarks for municipal regulation of hospital wastewater.

In summary, Denmark's regulatory framework for pharmaceutical wastewater treatment is characterized by stringent environmental laws, the application of best available techniques, and proactive municipal and institutional initiatives. This comprehensive approach ensures effective management of pharmaceutical residues in wastewater, safeguarding both environmental and public health.

4.3.3. Greece

In Greece, the management of pharmaceutical wastewater is governed by a combination of national legislation and European Union directives aimed at protecting public health and the environment. The discharge of wastewater into the sewerage system is governed by the Joint Ministerial Decision 5673/400/1997, which incorporates Directive 91/271/EEC[58] and lays down the measures and conditions for the treatment of urban wastewater. According to this directive, companies are required to treat their wastewater before discharging it into the sewerage system to meet the prescribed pollutant limits. In addition, the discharge must comply with the operating regulations of the relevant sewerage network operator, such as EYDAP or the local Municipal and Sewerage Utilities (Municipal Water and Sewerage Utilities). EYDAP has adopted a specific regulation for the discharge of liquid industrial waste, which sets out the conditions and limits of acceptable parameters for discharge into its network. Joint Ministerial Decision 26857/553/1988 establishes measures and restrictions for the protection of groundwater from the discharge of hazardous substances, prohibiting the disposal of waste that may pollute the aquifer. In addition, Law 3199/2003[59], which transposes Directive 2000/60/EC, set the framework for integrated water protection and management, imposing strict conditions for the protection of water resources from polluting activities.

Water Framework Directive (2000/60/EC) Implementation: Greece has transposed the EU Water Framework Directive into national law, aiming to achieve good qualitative and quantitative status of all water bodies. This includes monitoring and controlling pollutants, such as those from pharmaceutical sources, to prevent water contamination.

Studies have indicated that conventional wastewater treatment plants in Greece may not fully remove pharmaceutical compounds, leading to environmental risks. For instance, research

has detected various pharmaceuticals in wastewater treatment plants, with some compounds showing limited removal efficiency.

To address these challenges, Greece is encouraged to adopt advanced treatment technologies and stricter monitoring to enhance the removal of pharmaceutical pollutants from wastewater, aligning with both national and EU environmental protection goals.

Joint Ministerial Decision 145116/2011 establishes measures, limits, and procedures for the reuse of treated wastewater in Greece. It sets quality criteria for treated water, including parameters such as E. coli concentrations, to ensure safe reuse in applications like irrigation and industrial processes.

4.3.4. Sicily

In Sicily, wastewater treatment faces significant challenges, including limited infrastructure and environmental concerns.[60]

Sicily faces recurring droughts, exacerbating the need for effective wastewater treatment and reuse strategies to alleviate pressure on freshwater resources. Approximately 75 municipalities in Sicily lack adequate wastewater treatment facilities, leading to untreated urban wastewater being discharged into the environment.[60] This situation has resulted in environmental degradation and legal actions against Italy for non-compliance with EU directives. Many coastal cities in Sicily either lack wastewater treatment facilities or have inadequate systems, contributing to marine pollution in the Mediterranean.[60] Recent Initiatives and Projects include the Marsala Wastewater Treatment Plant implemented by the municipality of Marsala aimed at reducing pressure on local groundwater resources by treating and reusing wastewater for agricultural purposes.[61] In Grammichele, treated wastewater is stored and distributed for agricultural irrigation, promoting sustainable water resource management in the region.[61] In the Catania Treatment Facility, a sewage treatment plant treats oily emulsions and bilge water from the nearby port area, addressing industrial wastewater challenges. [62]

While steps are being taken to improve wastewater treatment in Sicily, the region continues to face significant challenges in effectively managing pharmaceutical contaminants. Ongoing efforts to upgrade infrastructure and comply with EU regulations are essential to mitigate environmental and public health risks associated with pharmaceutical wastewater.

In Sicily, the treatment of pharmaceutical wastewater is a critical environmental concern, particularly considering recent European Union (EU) regulatory developments.

The implementation of the revised Urban Wastewater Treatment Directive is anticipated to have a substantial impact on the pharmaceutical industry.[63] The directive's emphasis on extended producer responsibility will require pharmaceutical companies to contribute financially to the costs of upgrading wastewater treatment facilities to effectively remove micropollutants. This aligns with the EU's broader environmental objectives but also presents economic and operational challenges for industry.

In a nutshell, the regulatory framework for pharmaceutical wastewater management is shaped by comprehensive national legislation and evolving EU directives. The industry faces ongoing challenges in effectively removing pharmaceutical residues from wastewater, necessitating continued advancements in treatment technologies and adherence to stringent regulatory standards to protect environmental and public health.

Studies have evaluated the potential for reusing treated wastewater in Sicily for irrigation. However, the restrictive nature of Italian regulations, such as Ministerial Decree 185/03, poses challenges to widespread implementation. [63], [64]

4.4. Coordinating beneficiary - MEDOCHEMIE Case Study

Medochemie, is deeply committed to environmental sustainability and strictly adheres to the local legal framework for wastewater treatment, including compliance with the Laws mentioned in section 4.3 “Current Legal Framework for Pharmaceutical wastewater treatment – wastewater generation-wastewater streams”.

Every week, a detailed water sampling and analysis is conducted to ensure that all treated wastewater consistently meets the regulatory limits for key pollutants, such as nitrogen, phosphorus, and other chemical or biological contaminants. These regular assessments assist to the verification that discharges are within the permissible thresholds, protecting local water bodies and supporting biodiversity in the region.

Moreover, by embracing the preventive practices during the production stage, it is MEDOCHEMIE aim to minimize the environmental footprint while continuing to deliver safe and efficient production processes. This proactive, systematic approach underscores Medochemie's dedication to both regulatory compliance and the broader goal of long-term environmental stewardship.

5. Business Plan Development Process

5.1. Background

The identification of exploitable results – PHARMA-DETOX process – is the primary step. The identification of the PRODUCT (data, result, product, process, report or any material that could be exploitable) in any task is generated, and stored, the partners involved in its development and the “Product Description Datasheet” as well as the level of protection are critical parameters to be determined between LIFE PHARMA-DETOX beneficiaries.

The second step, based on product and process description, is to perform a preliminary “Free to Operate” analysis to ensure that no third-party patents prevent the LIFE PHARMA-DETOX consortium from further exploitation.

The third step includes the drafting of a “Value Map” to help the project “product” meeting consumer expectations.

The fourth step will consist of a Business model Canvas used to define the main aspects of the business plan. Then a road map for implementation of the solution in MEDOCHEMIE plant will be depicted. Finally, a road map for examining the implementation of the solution in other pharmaceutical industries European countries will be drafted.

5.2. Freedom to Operate analysis

Freedom to Operate (FTO) analysis is a crucial step for businesses planning to develop and launch new products or technologies. Its purpose is to determine whether commercialization of a given product or process might infringe on existing IP rights held by others. Here are the key steps involved in conducting an FTO analysis:

1. Patent Literature Search:

- Begin by searching patent databases for issued or pending patents related to the technology or product in question.
- Obtain a legal opinion on whether the product, process, or service could potentially infringe any existing patents owned by others.

2. Understanding Patent Limitations:

- Recognize that patent protection is territorial. While technology may be protected in certain markets, it might be in the public domain elsewhere.

- Consider the limited duration of patents (usually 20 years). After expiration, a patent becomes part of the public domain and can be freely used by anyone.

3. Risk Mitigation Strategies:

- Explore licensing agreements or cross-license arrangements with patent holders to secure "freedom to operate."
- Evaluate whether the product can be modified to avoid infringing patents.
- Seek legal advice to assess the risks and explore opportunities for minimizing infringement risks¹.

Absolute freedom to operate is challenging to guarantee, but a well-executed FTO analysis can significantly reduce risks and enhance a company's ability to bring innovative products to market.

5.2.1. Value Map

A Value Map is a visual tool used in business strategy and product management to plan how a product or service addresses the problems or desires of customers, allowing to find a match between the product and the expectations customers.

It is composed of its three main components:

- **The Product & Service:** A list of all the products and services your value proposition is built around. It helps you answer questions like: What products and services do you offer that help your customer get either a functional, social, or emotional job done, or help them satisfy basic needs? What ancillary products and services help your customer perform their roles? Are your products and services tangible, digital/virtual, intangible, or financial?
- **The Pain Reliever:** This describes how your products and services alleviate customer pains. It helps you answer questions like: Do your products and services produce savings? Do they make your customers feel better? Do they put an end to the difficulties and challenges your customers encounter? Do they eliminate risks your customers fear? Do they limit or eradicate common mistakes customers make? Do they get rid of barriers that are keeping your customer from adopting solutions?
- **The Gain Creator:** This describes how your products and services create customer gains. It helps you answer questions like: Do your products and services produce outcomes your customer expects, or do they go beyond their expectations? Do they

outperform current solutions that delight your customers? Do they make your customer's job or life easier? Do they produce positive outcomes matching your customers' success and failure criteria?

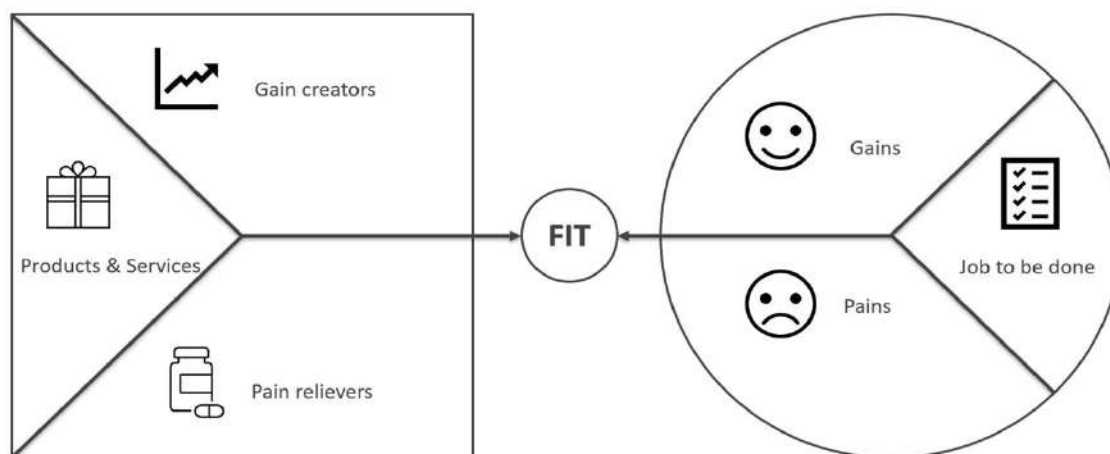
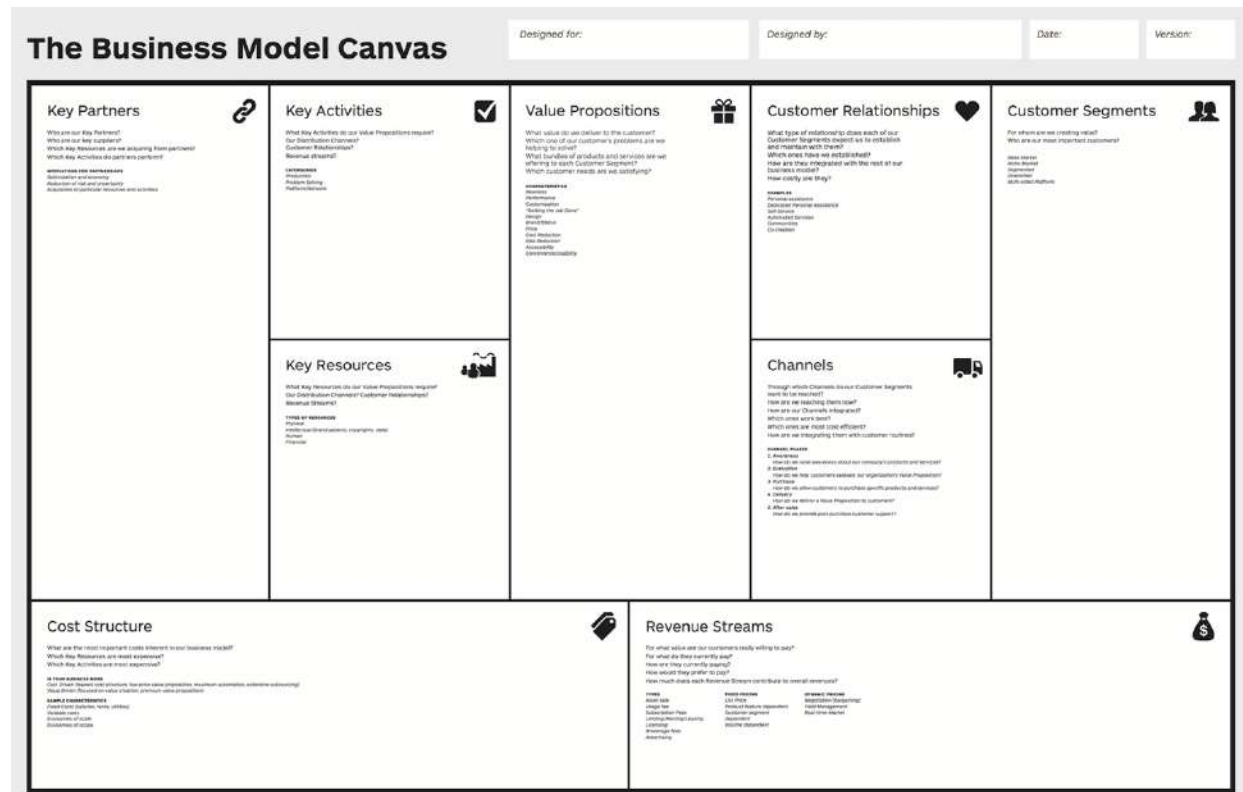


Figure 5-1: Value Map template.

To depict the business model, the “Business Model Canvas” (BMC) will be defined, being a strategic management tool used to outline the goals and objectives of a business¹. It's a single-page template that allows stakeholders to quickly understand the key needs and goals of any business. The BMC consists of nine building blocks:

1. Key partners: Stakeholders, joint ventures, and strategic alliances that will help the business carry out its objectives.
2. Key activities: Tasks and responsibilities that need to be done to make the business model work.
3. Key resources: Primary assets needed to complete key activities.
4. Value proposition: The unique offering or solution that a business offers its customers.
5. Customer relationships: Defines the customer's relationship with the business and examines the customer experience.
6. Customer segments: Defines the customer base, or the types of people (or businesses) the company will target.
7. Channels: How businesses communicate with and market to their customers.

This model helps to have a global overview of the business model.



5.2.2. Road map

Drafting a roadmap for implementing a business model involves several key steps.

Based on the proposed business model the definition of a road map needs to:

1. Set Clear Objectives: Define specific, measurable, achievable, relevant, and time-bound (SMART) goals.
2. Create a Timeline: outlining key milestones and deadlines in short-term and long-term goals.
3. Identify Critical Activities: List of the essential tasks required for successful implementation.
4. Allocate Resources: Determine the necessary resources: financial, human, technological, etc.
5. Risk Assessment and Mitigation: Identify potential risks and challenges, and mitigation strategies.
6. Define KPI to monitor progress.

The objective of the roadmap is to ensure alignment, accountability, and successful implementation of the business model.

The road map can be completed with an “Operational Plan” that details the day-to-day operations required to implement the business model.

- Include supply chain management, production, logistics, etc.
- Be prepared to adapt based on feedback, market changes, and unforeseen circumstances.

6. MEDOCHEMIE Demonstration Case – LIFE PHARMA-DETOX Business Model

6.1. Introduction

In the developing field of pharmaceutical wastewater management, innovative solutions are reshaping traditional approaches to wastewater treatment.

This section focuses to the complex value chain and business model of an innovative wastewater treatment system that combines catalytic hydrogenation, solar-powered electrolysis, and reverse osmosis technologies.

The system's value chain includes many stakeholders, from the pharmaceutical facilities that generate wastewater to the end users who benefit from the treated water. The Business Model Canvas is used to illustrate how this system creates, delivers and captures value across different sectors. The model demonstrates the integration of sustainable practices with business viability, showcasing how environmental solutions can generate multiple revenue streams while serving diverse customer segments.

This innovative approach not only addresses the critical challenge of pharmaceutical wastewater management but also creates new opportunities for reclaimed water reuse.

6.2. Existing competitive to LIFE PHARMADETOX technologies

In the pharmaceutical wastewater treatment sector, companies like Arvia, Evedal, and Veolia offer innovative technologies. Arvia's Nyex™ systems[69], such as Nyex Rosalox[70], use a combination of adsorption and electrochemical oxidation to remove organic pollutants such as APIs and Chemical Oxygen Demand (COD) from wastewater. [71]The system regenerates in situ, eliminating the need for media replacement or chemical dosing. This approach is energy-efficient, eliminates toxic sludge, and reduces costs compared to incineration. It is particularly effective for APIs, biocides, pesticides, and other micropollutants in

pharmaceutical wastewater. Arvia's solutions also support water reuse and compliance with stringent discharge regulations.[70]

Evaled, a Veolia subsidiary, offers evaporation-based systems designed for pharmaceutical wastewater treatment. These systems focus on water recovery, Zero Liquid Discharge (ZLD), and significant reduction in waste volume. They can handle complex effluents containing APIs, antibiotics, glycols, and other contaminants. Evaled evaporators produce high-quality distillate that can be reused for applications like cleaning, boiler feeding, and cooling. They also reduce operational costs by minimizing waste disposal needs and enabling water reuse. The systems are modular, automated, and adaptable to varying treatment needs. [72], [73], [74]

Veolia[74] provides a range of technologies tailored to pharmaceutical wastewater treatment. These include Membrane Biological Treatment (MBR), RO, multi-effect evaporators, forced evaporation systems, advanced oxidation processes, and ZLD technologies which are adaptable to various industrial settings. A patented MBBR technology specifically designed for pharmaceutical wastewaters, incorporating carbon and other treatment stages to ensure comprehensive pollutant removal. [75]

While these systems offer significant advantages in terms of efficiency and environmental sustainability, potential drawbacks include high initial investment costs for some technologies and the need for specialized maintenance and operation expertise. Implementation areas span pharmaceutical manufacturing facilities, specialty chemical plants, and other industries dealing with complex organic pollutants. Overall, these technologies help companies comply with stringent environmental regulations while optimizing resource use.

These technologies provide an innovative and sustainable alternative to conventional wastewater treatment systems, particularly for industries dealing with persistent organic pollutants. Its combination of efficiency, low environmental impact, and operational flexibility makes it a standout choice in tertiary water treatment.

Company	Key Technology	Features & Benefits
Arvia	Nyex™ Adsorption + Oxidation	Energy-efficient, no chemical dosing, in-situ regeneration[71]
Evaled	Evaporation Systems	ZLD capability, water reuse, modular design[72], [73]

Veolia	Integrated Solutions	Combines MBR, RO, evaporation; advanced sludge treatment[76].
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6.3. LIFE PHARMADETOX Value Proposition – Comparative advantages

PHARMA-DETOX project offers a special approach to wastewater treatment, combining RO unit with catalytic hydrogenation. Comparing other conventional wastewater treatment systems like conventional Active Oxidation Processes (AOPs) and Ozonation & Sand filtration, PHARMA-DETOX technology eliminates the need for chemical dosing or frequent media replacement. [65]. The process consumes less energy compared to traditional AOPs, making it cost-effective for long-term operations.[66], [67]. Unlike many conventional systems like Granular Activated Carbon (GAC), PHARMA-DETOX system, does not produce toxic sludge or secondary waste streams, reducing disposal challenges and environmental impact.[66], [68].

Table 6-1 Comparison of PHARMA-DETOX with other conventional wastewater treatment technologies

Feature	PHARMA-DETOX technology	Conventional AOPs	GAC	Ozonation + Sand Filtration
Energy Consumption	Low	High	Moderate	Moderate
Chemical Dosing Required	No	Yes	No	Yes
Sludge Generation	None	Possible	Yes	No
Removal Efficiency	High	High	High	High
Maintenance Requirements	Minimal	Moderate	High (media replacement)	Moderate
Environmental Impact	Low	Moderate to high	Moderate	Moderate

The LIFE PHARMA-DETOX project has developed an innovative process and value chain that benefits multiple sectors while addressing environmental and sustainability challenges. The system provides eco-friendly pharmaceutical wastewater treatment by utilizing advanced technologies to detoxify wastewater, removing harmful substances such as APIs, and protecting natural ecosystems and water bodies. The key outcome of the system is the production of clean water that can be reused in many non-critical applications, such as irrigation, cleaning, and heat exchange systems. This promotes circular economy model by ensuring that water resources are reused rather than wasted. Additionally, the system is a promising and reliable solution for industries to meet regulatory requirements, helping them comply with stringent environmental standards.

6.4. Technological solution validation

The validation of the technological solution for the LIFE PHARMA-DETOX system involves several key steps and processes that confirm its effectiveness, efficiency, and suitability for the targeted application. The system's core technologies, including the catalytic reactor process, reverse osmosis unit and hydrogen production system, have been extensively tested at the bench scale. Parameters such as the catalyst composition, catalyst lifetime, duration of reaction efficiency, effect of detergent use on final toxicity of the treated water, and H₂/O₂ ratios were optimized during these tests. Results demonstrated successful detoxification of pharmaceutical compounds, with low toxicity in the treated water.

Treated water is validated through High-performance Liquid Chromatography, toxicity test to microorganisms (such as *Daphnia magna*) and phytotoxicity test in three different plants (*Sorghum saccharatum*, *Lepidium sativum*, *Sinapis alba*) for reuse in non-critical applications (e.g., irrigation, cleaning), meeting safety and toxicity thresholds set by regulatory bodies. The system meets stringent environmental regulations and standards by detoxifying active pharmaceutical ingredients and other hazardous substances in wastewater.

The pilot-scale prototype system was tailored to Medochemie's specific needs, with adjustments made to increase the system's capacity to ensure it meets production requirements while remaining efficient under operating conditions. Validation involved adjustments of the Process Flow Diagram, based on realistic data such as wastewater volume (2.5 m³/day) and operational limitations (e.g., 8-hour daylight operations).

Safety measures for the ATEX Zone II area, including the catalytic reactor and hydrogen-handling systems, will be validated to prevent risks associated with explosive atmospheres. Use of ATEX-rated components, along with gas detection systems, alarms, and proper

ventilation, ensures operational safety and compliance with pharmaceutical industries safety standards. The system’s photovoltaic panels and water electrolysis unit will be validated for energy efficiency and renewable energy usage.

Successful installation and demonstration at the facilities of Medochemie will serve as a critical validation step for its performance and adaptability in real-world conditions. The prototype system has been designed and engineered to treat wastewater from multiple pharmaceutical manufacturing processes (e.g., injectable penicillin, oral penicillin, and ampoule plants). The containerized design ensures that the proposed system is easily transferable to other pharmaceutical facilities across Europe and beyond.

Process Validation	Quality Validation	System Integration Validation
<ul style="list-style-type: none"> - Effectiveness of the catalytic reactor in detoxifying APIs using the H₂/O₂ mixture - Detoxification process ability to produce water with low toxicity levels. - RO system effectiveness for initial treatment. - RO unit performance achieving 80-90% wastewater volume reduction. - H₂ production efficiency through solar-powered electrolysis unit - Sustainability and cost-efficiency of solar energy integration 	<ul style="list-style-type: none"> - Verification of low toxicity levels in produced water - Test the treated water to ensure it meets quality standards for specific applications: - Irrigation - Heat exchange systems - Cleaning purposes 	<ul style="list-style-type: none"> - Confirm that all components (RO unit, catalytic reactor, and electrolysis) work efficiently together. - Assess energy efficiency across the system. - Overall system efficiency in handling multiple waste streams from: <ul style="list-style-type: none"> o Ampoules Injectable Facility o Oral Penicillin Facility o Injectable Penicillin Facility o Laboratory and laundry detergents washing
<p>Environmental Compliance Validate that the system meets regulatory standards for wastewater treatment and environmental protection.</p>		

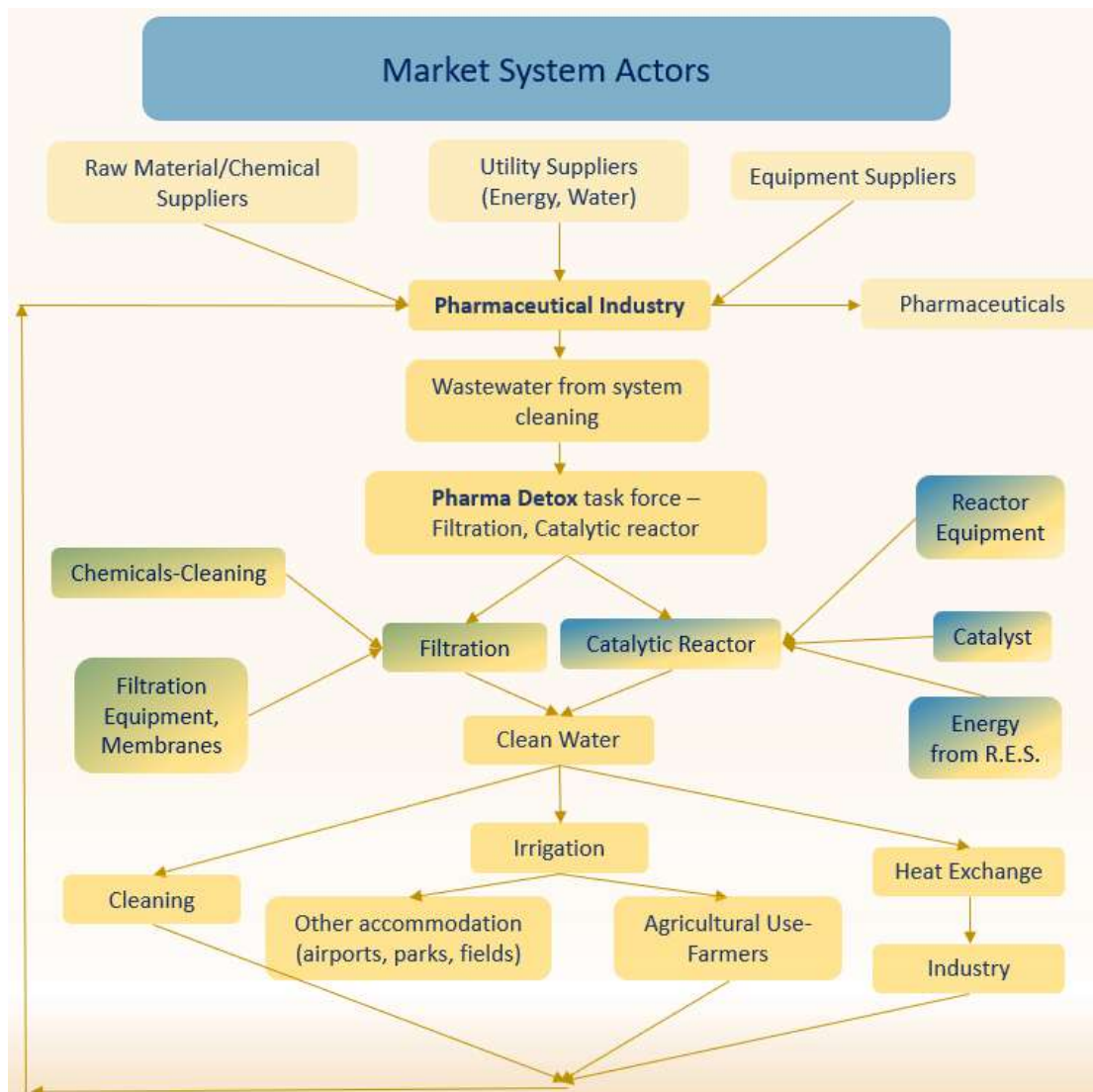


6.5. Draft Business Canvas

Key Partners	Key activities	Value Proposition	Customer Relationships	Customer segments
<ul style="list-style-type: none"> - Consortium Partners - Technology / service providers including Solar power equipment suppliers, RO and membrane technology providers - Pharmaceutical Industries - Water treatment specialists - Regulatory Bodies (Environmental and Safety Compliance Agencies) - Logistics and Maintenance service providers - Investors - Media & Networks - Research stakeholders 	<ul style="list-style-type: none"> - Wastewater collection and treatment system design & construction - System maintenance - Solar-powered hydrogen production system design & construction - Catalytic hydrogenation process system design & construction - Reverse osmosis treatment system design & construction - System validation - Systems operation, Quality monitoring, control and testing - Patent Maintenance & Protection - Communication & Marketing 	<ul style="list-style-type: none"> - Cost-effective Eco-friendly pharmaceutical wastewater treatment process with integrated sustainable power supp 	<ul style="list-style-type: none"> - Design & customization - Integration into existing systems - Technical support & maintenance services - Compliance reporting - Performance monitoring - Training and consultation 	<ul style="list-style-type: none"> - Pharmaceutical manufacturing facilities - Laboratory facilities - Industrial cleaning operations - Chemicals manufacturing industries - Wastewater treatment plants in hospitals and nursing homes - Wastewater treatment plants - Agricultural Use-Farmers, requiring irrigation water - Industrial Users (Heat exchange system operators, cleaning service providers)
	<p>Key resources</p> <ul style="list-style-type: none"> - Treatment facility infrastructure 		<p>Key channels</p> <ul style="list-style-type: none"> - Awareness (demo, marketing) 	

	<ul style="list-style-type: none"> - Solar power generation system - Catalytic reactor technology - RO systems - Technical expertise and personnel - Water electrolysis unit - Financial assets (industrialization) - Intellectual Assets (eg IPR) 		<ul style="list-style-type: none"> - Direct sales & delivery to pharmaceutical facilities - Industry partnerships - Technical demonstrations - Environmental consulting firms - Industry conferences - Agricultural cooperatives - Associations and networks - Online channels - Media 	
<p>Cost structure</p> <p>CAPEX: Infrastructure & Equipment OPEX: Operation and maintenance, technical personnel, Energy costs, Quality control processes, Patent Licencing Fees</p>		<p>Revenue Streams</p> <p>Wastewater treatment service fees, clean water supply contracts, Consultation services Maintenance contracts, Technology licensing, Training programs, Agricultural water supply contracts, Heat exchange system installations, Industrial cleaning service agreements</p>		
<p>Social & Environmental Cost</p> <p>End of life products</p>		<p>Social & Environmental Benefit</p> <p>Human Health Protection</p> <p>Wastewater treatment process with low environmental footprint</p> <p>Improvement of water quality & supply</p>		

6.6. Value Creation & Delivery



The image illustrates the market system actors and processes involved in the LIFE PHARMA-DETOX system, highlighting its value chain and interconnections. At the center is the pharmaceutical industry, which generates wastewater as a byproduct of equipment cleaning from facilities such as the Ampoules Injectable Facility, Oral Penicillin Facility, and Injectable Penicillin Facility. This wastewater may also contain contaminants like laboratory and laundry detergents. A combination of filtration-RO unit and catalytic reactor processes, treat this wastewater. The RO unit requires chemicals for cleaning and membranes as consumables. The catalytic reactor that detoxifies pharmaceutical compounds requires reactor equipment, uses a specific catalyst and hydrogen produced by renewable solar energy. The product of the system is clean, low-toxicity water, which has various applications:

- Irrigation: Providing a sustainable water source for agricultural use by farmers.

- Cleaning: Used in industrial processes to reduce reliance on freshwater.
- Other accommodations: Such as parks, fields, and airports.
- Energy Recovery: Clean water can also be used in heat exchange systems, further supporting energy recovery in industrial applications.

The entire process is supported by actors such as raw material and chemical suppliers, utility suppliers (energy and water), and equipment suppliers. These stakeholders provide the essential resources and tools required for system operation. Additionally, renewable energy plays a crucial role, powering catalytic detoxification, ensuring the system aligns with sustainability goals and reduces dependency on fossil fuels. The image demonstrates a circular economic approach, where wastewater is transformed into reusable clean water and energy, contributing to environmental sustainability, resource efficiency, and economic value. This integrated framework highlights the collaboration of market actors and the technological innovation of the LIFE PHARMA-DETOX system.

7. Value Capture

7.1. Economic Assumptions

The business model is designed for a pilot with a treatment capacity of 2.5 m³ of wastewater per day, i.e. all the wastewater produced by the three production units of the Medochemie B building. The pilot will be fully containerised, in a 20-foot container that will be located near the main building of the Medochemie facilities.

7.2. CAPEX & OPEX

The cost breakdown for the LIFE PHARMA-DETOX covers all necessary components to ensure the construction and operation of the described pilot's efficient and sustainable wastewater treatment operation.

Major costs include:

- the containerized system, housing critical technologies such as the catalytic reactor, reverse osmosis unit, and water electrolysis unit, alongside the photovoltaic (PV) system to power operations
- safety features, plumbing system modifications, and advanced materials to ensure durability and compliance with ATEX standards.

Designed for economic viability, the budget balances initial capital investment with minimized operational costs through renewable energy reliance and low-maintenance components,

supporting long-term sustainability goals. The pricing of all system components was applicable for the year 2024.

Component	Cost
Photovoltaic System	33,000 €
Electrolyzer	28,850 €
Catalytic Reactor	90,800 €
Reverse Osmosis Unit* & Container	52,350€
Gas Detector H₂ and O₂ & Gas Cylinders	4,970€
Total cost	209,970€

* This cost includes membranes, filters, pumps and sensors and the central electricity board

The revised CAPEX for the PHARMA-DETOX prototype system is now estimated at €210,000, compared to the initial estimation of €440,000 in the Grant Agreement. This reduction is due to a couple of factors. Firstly, the system does not include an H₂ fuel cell. Due to regulatory restrictions and Medochemie's strict safety policies, the system will only operate for 8 hours per day under the supervision of trained technical personnel. As a result, the system will only operate during daylight hours, eliminating the need for a fuel cell. Another important factor is the recalculation of wastewater production from Medochemie's three production facilities. The initial volume of wastewater was estimated at 10m³/day, but updated calculations indicate a lower volume of 2m³/day. This reduced capacity demand resulted in a smaller reactor and overall system.

The key Operating Costs (OC) include

- the Salaries (S) for permanent employees of the WF during the operational phase (from installation completion to the end of the lifetime of the system (should be defined in the contract)
- Maintenance Costs (M): The costs associated with extending the service contract with system manufacturers.
- Insurance of the system (Ins): Typically, a standard percentage based on the initial investment cost.
- Other Equipment Costs (Eq): Maintenance and replacement costs for electrical, electronic, and mechanical equipment.

- Land Lease: Costs for leasing the land on which the system will be set up – it is assumed here that the land belongs to Medochemie.
- Administration Costs: Administrative overheads.
- Unexpected or Additional Costs (V): Contingency of unforeseen expenses.

The Operating Expenditure (OPEX) for the LIFE PHARMA-DETOX system is based on projected estimates. These estimates are derived from the system's design, technology specifications, and expected operational parameters.

- Electricity costs: The system relies entirely on solar power generated by its photovoltaic system eliminating traditional energy expenses. This cost includes the daily operation of the catalytic reactor, RO unit and electrolysis unit for 8 hours. The system requires 14.5 Kwh/day and the cost of 1 Kwh in Cyprus is €0.26. The energy cost of the system for 1 year, based on 50 working weeks, is €1,000.
- Maintenance and repair costs: The RO system has a lifecycle of 3 to 5 years, the absence of oxidants in the system will help keep the membranes clean, extending their operational life. The annual maintenance cost will be around 300€-400€ and the repair cost for 3-5 years will be around 600€. The electrolysis after 3-5 years operation is possibly needed around 2,000 – 5,000 € repair cost. The photovoltaic (PV) system has a lifespan of 10 years, while the electrolysis unit has a lifetime of 3 to 5 years, requiring periodic maintenance and part replacements to ensure optimal performance.
- The personnel costs cover the salary of a qualified technician responsible for the operation and maintenance of the system during the 8-hour daily shifts. One technician will be required to operate the pilot system, with annual salary will be €25,000.
- Chemical Cost: Consumables for the system, including gases for the operation of the electrolysis unit and catalytic reactor, catalyst and reagents for the catalyst activation process, and chemicals for the cleaning of the system, are expected to contribute quietly to the running costs. The total cost for gases (N₂, H₂, O₂ and He) is 400€ monthly and 2,920€ yearly. The reverse osmosis (RO) system requires 2 litres of NaOH (50%) per week. The photovoltaic (PV) requires cleaning of the panels, which is done with distilled water produced by the RO unit, without any additional cost. The electrolysis unit requires periodic cleaning of its cells with potassium hydroxide (KOH) and distilled water. As the system provides its own distilled water, the only cost is for KOH, the unit requires 2 liters per week. The catalytic reactor also requires regular cleaning, but as this is done using distilled water from the RO system, there are no extra costs associated with its

maintenance. The use of chemicals for cleaning the RO unit and electrolysis unit have an annual cost close to €100. In addition, the cost of the catalyst and reagents required for the catalyst synthesis process is estimated at €2,000. The catalyst can be regenerated many times, which eliminates the need to synthesize more than 2 or 3 batches of catalyst. As a result, the annual cost for catalysts is estimated to be €6,000.

Table 7-1 Estimated annual cost of operating the LIFE PHARMA-DETOX System (OPEX)

Component	Description	Calculation Method	Cost €
Electricity Cost	Cost for the electricity required for the operation of the system	Based on operational data from pilot	1,000
Chemical & Gases Cost	Cost for the chemicals required for the operation of the system	Based on operational data from pilot	9,000
Maintenance	Cost for the maintenance of the technologies	300€-400€ of RO unit	400
Operating Labor	Cost for the employees working in the facility	1 employee annual	25,000
Total cost			35,400 €

Regulatory compliance and monitoring will include periodic testing of the treated effluent to ensure it meets environmental standards and verifies system efficiency. These tests will be conducted in Medochemie's analytical lab, with no extra operational costs.

Overall, OPEX is projected to remain low due to the system's reliance on renewable energy and its modular, low-maintenance design. These preliminary estimates will be refined further once the system begins operation and actual data becomes available, ensuring financial planning aligns with real-world performance.

Other costs include IPR costs. According to the Grant Agreement, this expense is estimated at approximately €50,000. We will review this cost with Medochemie to determine the countries in which they would like to apply for the IPR.

7.3. Results-Revenues/Foregone Costs

The operation of the system has both financial and environmental benefits by optimizing water savings, reuse, and wastewater treatment efficiency.

- Foregone costs from Water treated
- Foregone costs for tariffs on wastewater disposed

The system is designed to treat 2.5 m³ of wastewater per day and reuse the treated water, effectively saving 2.5 m³ of water daily, or 650 m³ per year.

The cost of water supply as of end 2024 is on average €1.70 per m³. Thus, the reuse of treated water is estimated to generate €1,100 in foregone cost. Additionally, the treatment of wastewater on-site through the operation of LIFE PHARMA-DETOX system results in zero disposal charges for Medochemie, which currently stand at €13,800 per year (monthly cost amounts to €1,150). In total, the system is estimated to bring €14,900 in annual revenue, demonstrating its economic benefits and contribution to sustainable water management.

The PV system installed will power the PHARMA-DETOX system, requiring approximately 15 kW of power. Utilizing solar energy, the system will power the electrolyzer to produce pure hydrogen (H₂) during daylight hours and the operation of catalytic reactor. It is estimated that during 8 hours of operation, the PV system can generate 15 kWh, which covers nearly all the system's energy needs (15 kWh). This will result in additional savings on electricity costs, amounting to approximately €1,000 annually.

Proposed Financial Plan

The financial structure of the project in many cases is typically divided into three parts: Equity, Bank loan, and Subsidy (in many cases this is dependent on the company size and location of the system). The Operating Cash Flow is based on a typical private equity and loan structure. The Unamortized Value, the Depreciation and Loan Repayment (installments) should be calculated based on a specific repayment period (typically 10 years or half of the duration of the system's lifetime - where interest is considered). In this format, these figures are updated yearly, based on the remaining loan balance. Pre-tax earnings (Pp-tax) are calculated based on the tax rate of large companies and such investments. Afterwards, the post-tax profits (Pa-tax) are calculated, which results in the Net Income (NI), which is also the Net Cash Flow and the Net Repayment Amounts.

Typically, to evaluate the financial viability of the project, we calculate the Cumulative Cash Flow over the 20-year period (or the lifetime of the system – maybe 25 years) by summing the Final Net Income for each year. This allows for the calculation of the Net Present Value, which

is the discounted value of all cash flows over the project's lifetime. The Internal Rate of Return is determined by identifying the discount rate that makes the NPV equal to zero.

8. Replicability Potential

The LIFE PHARMA-DETOX structured replication plan starts in Cyprus and extends to other EU pharmaceutical industries, particularly in the Netherlands, Greece and Italy. As part of the second demonstration phase, the PHARMA-DETOX system will be transferred and operated for nine months at Farmaceutisch Analytisch Laboratorium Duiven B.V. in the Netherlands to validate its performance in a different industrial environment. In addition, two pharmaceutical companies - one in Greece and one in Italy - will be selected under sub-Action B.4.3. Their wastewater characteristics will be analysed at the Greek Brine Excellence Centre, providing valuable design parameters, technical feasibility assessments and cost estimates for the implementation of similar wastewater treatment systems in the pharmaceutical sector.

Deliverable B.4.1. on "Replicability and Transferability potential and road map" will set strategy for the system's replication and transfer to pharmaceutical manufacturing sites and other sectors across Europe.

9. Candidate Sectors for Transferability

The LIFE PHARMA-DETOX consortium has identified several industries and sectors as candidates for transferability. These industries may generate wastewater containing toxic compounds which must be detoxified before being released into the environment. As the EU is likely to expand its environmental guidelines to include other chemical compounds beyond pharmaceutical wastewater, the developed technology can be applied across a broader range of sectors.

The end-users of the proposed technology can be chemical industries producing paints, cosmetics, chemicals for industry and laboratory use, petrochemicals, polymers, plastics and specialty chemicals. With Cyprus and Europe having a significant presence in chemical manufacturing, these regions are priorities for technology transfer.

Urban wastewater treatment plants are another potential sector for implementation. The detoxification process can be applied as a tertiary treatment to remove pharmaceutical and other chemical compounds from wastewater. In Cyprus, there are 39 operational public wastewater treatment plants, with six additional facilities under development. The Water

Development Department of the Cyprus Ministry of Agriculture, Rural Development, and Environment has expressed interest in applying the technology to these treatment plants. On-site wastewater treatment plants at hospitals and nursing homes also represent significant opportunities for transferability. These facilities are hotspots for the release of pharmaceutical compounds into wastewater. Cyprus alone has five major district hospitals, one pediatric/gynaecological hospital, three rural hospitals, 38 health centers, and, according to a 2010 study, 121 nursing homes, all of which could benefit from this technology.

Detailed analysis will be provided by Deliverable B.4.1. on “Replicability and Transferability potential and road map”.

10. Conclusions

The pharmaceutical industry sector is a robust and dynamically growing sector in Europe and worldwide. The innovative LIFE PHARMADETOX system provides a process for wastewater treatment which:

- enables the conformity of the pharmaceutical industrial sector to the requirements set forth by the Revised Urban Wastewater Treatment Directive (2024/3019): approved by the European Parliament in 2024. This directive introduces stricter requirements for wastewater treatment and is expected to impose significant additional costs on pharmaceutical companies operating within the EU following the polluter pay principle.
- promotes circular economy principles by ensuring that water resources are reused rather than wasted
- contributes to water saving
- is powered by RES thus lowers power consumption costs and minimizes the use of electricity

The preliminary business plan shows that the viability of the business model is largely dependent on relevant policy measures and directly affected by the price of water and possible subsidies or other incentives for investment.

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