



Next generation toolbox for greener pharmaceuticals design
and manufacturing towards reduced environmental impact

D7.2 – Fact-based report to regulatory authorities

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Executive Summary

Pharmaceuticals provide essential health benefits, while their production, use, and end-of-life management may contribute to environmental pressures across multiple stages of the pharmaceutical lifecycle. Addressing pharmaceutical-related environmental challenges therefore requires holistic, lifecycle-oriented approaches that explore opportunities for sustainability from early drug development and manufacturing through to use, disposal, wastewater treatment, and environmental exposure, with the aim of reducing the overall environmental footprint of pharmaceuticals while maintaining therapeutic effectiveness and innovation.

This deliverable, D7.2 – Fact-based report to regulatory authorities, presents a project-wide synthesis of the main scientific and technological outcomes of the ENVIROMED project, interpreted through a lifecycle-oriented perspective. The deliverable aims to demonstrate how diverse technological developments collectively contribute to shared environmental objectives. Project results are evaluated across disciplines and translated into fact-based, policy-relevant considerations for regulatory authorities.

Upstream in the lifecycle, the project investigated in-silico tools for green drug development, illustrating how predictive models can support early environmental screening and safer-by-design strategies. In the manufacturing phase, ENVIROMED explored sustainable production approaches, including continuous biomanufacturing, digitalisation, and advanced process monitoring, demonstrating their potential to reduce resource use and environmental footprint.

Downstream, coordinated environmental monitoring campaigns addressed emissions associated with pharmaceutical use and disposal across clinical facilities, wastewater treatment plants, and receiving environments. These campaigns confirmed the continuous presence of selected pharmaceutical compounds and highlighted the limitations of conventional treatment processes. Complementary ecotoxicity assessments showed that pharmaceutical residues may induce biologically relevant effects even at low concentrations under chronic and mixed exposure scenarios.

In parallel, in-silico ecotoxicity and bioaccumulation models were applied to support screening and prioritisation of pharmaceuticals and their metabolites detected in the environment, demonstrating how predictive approaches can complement monitoring and biological studies within integrated assessment strategies.

Across all lifecycle stages, the results underline the importance of integrated, risk-based, and prevention-oriented approaches to managing pharmaceutical-related environmental pressures. By synthesising evidence across disciplines and lifecycle stages, this deliverable aims to inform regulatory dialogue and support the development of coherent and proportionate EU and national policies aligned with the European Green Deal, the Zero Pollution Action Plan, and the Pharmaceutical Strategy for Europe.

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List of Acronyms

Table 1: Acronyms and abbreviations

Term	Definition
API	Active Pharmaceutical Ingredient
ATEX	ATmosphères EXplosibles
CE	Conformité Européenne
CFD	Computational Fluid Dynamics
DG ENV	Directorate-General for Environment
ECHA	European Chemicals Agency
EEA	European Environment Agency
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
GMP	Good Manufacturing Practice
GUI	Graphical User Interface
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	Infrared
IRRAS	Infrared Reflection-Absorption Spectroscopy
LCA	Life Cycle Assessment
LMA	Liquid Monitoring Analyser
LOD	Limit of Detection
MIR	Mid-infrared
MSF	Multi-Stage Filtration
MSFD	Marine Strategy Framework Directive
NSAID	Non-Steroidal Anti-Inflammatory drug
OECD	Organisation for Economic Co-operation and Development
PAT	Process Analytical Technology
PLS	Partial Least Squares
PM-IRRAS	Polarization-Modulation Infrared Reflection-Absorption Spectroscopy
PTD	Photothermal Deflection
PTI	Photothermal Interferometry
PTL	Photothermal Lens
PTM	Photothermal Mirror

Term	Definition
QbD	Quality by Design
REACH	Registration, Evaluation, Authorisation, and Restriction of CHemicals
SIA	Surface Inspection Analyser
SPE	Solid Phase Extraction
UWWTD	Urban Wastewater Treatment Directive
WFD	Water Framework Directive
WSA	Wastewater Spectroscopic Analyser
WWTP	Wastewater Treatment Plant

1 Introduction

Pharmaceuticals deliver significant societal benefits by improving human and animal health. At the same time, their design, manufacturing, use, and disposal can lead to environmental pressures, including emissions of active pharmaceutical ingredients, metabolites, and associated substances across multiple environmental compartments. These pressures may affect ecosystems, contribute to long-term environmental exposure, and challenge existing regulatory and management frameworks. Addressing the environmental footprint of pharmaceuticals therefore requires a holistic, lifecycle-oriented approach, spanning drug design, manufacturing processes, use and disposal patterns, and environmental exposure and effects.

This deliverable presents an integrated synthesis of the main scientific and technological results of the ENVIROMED project, interpreted through a lifecycle and policy-oriented perspective. While the deliverable builds on evidence generated in WP7 related to environmental monitoring and impact assessment, its scope has been expanded to encompass key project outcomes across all lifecycle stages, including green drug design, sustainable manufacturing, digitalisation technologies, environmental monitoring, and ecotoxicity assessment.

The expanded scope of this deliverable aims to demonstrate how the different technological outcomes collectively contribute to the project's environmental objectives. D7.2 therefore uses the available project results to evaluate findings across disciplines and to translate them into concrete, fact-based considerations and recommendations relevant to regulatory and policy authorities.

The objectives of this deliverable are to:

- ✦ synthesise key results from across the project that address the environmental footprint of pharmaceuticals at different lifecycle stages;
- ✦ demonstrate how upstream and downstream technological solutions contribute to shared environmental objectives;
- ✦ provide a coherent, lifecycle-oriented interpretation of pharmaceutical-related environmental pressures and mitigation opportunities;
- ✦ highlight the relevance of project findings for EU and national environmental, pharmaceutical, and water policies;
- ✦ formulate fact-based observations and recommendations to support regulatory dialogue and evidence-based decision-making.

Throughout the deliverable, project results are interpreted in relation to relevant EU and national policy frameworks. Policy-relevant considerations are presented at the end of each thematic chapter, reflecting the cross-cutting nature of regulatory implications across the pharmaceutical lifecycle. In addition, a concise policy brief (<https://doi.org/10.5281/zenodo.19721292>), synthesising the project's key findings and recommendations, has been prepared to contribute to dialogue with regulatory and policy authorities and is included as an Annex to this deliverable.

The technologies and approaches developed within the project are presented as illustrative examples, demonstrating broader principles and pathways for reducing environmental impact, without implying regulatory endorsement of specific solutions.

The structure of the deliverable is as follows:

- **Chapter 2** introduces the lifecycle-oriented framework underpinning the ENVIROMED approach and the project’s central scientific rationale;
- **Chapter 3** addresses in-silico tools for green drug development and their role in early environmental screening and safer-by-design strategies;
- **Chapter 4** focuses on sustainable pharmaceutical manufacturing, including continuous biomanufacturing and digitalisation approaches aimed at reducing resource use and emissions;
- **Chapter 5** presents advanced analytical and sensing technologies supporting environmentally sustainable manufacturing practices;
- **Chapter 6** reports on environmental field monitoring campaigns addressing emissions associated with pharmaceutical use and disposal;
- **Chapter 7** addresses the environmental effects of pharmaceutical residues following use and disposal, integrating literature-based evidence, ecotoxicity studies, and predictive assessment tools;
- **Chapter 8** concludes the deliverable by synthesising cross-cutting insights across the pharmaceutical lifecycle and highlighting the added value of the ENVIROMED approach.

By integrating results across disciplines and lifecycle stages, this deliverable aims to support ongoing EU and national efforts to reduce the environmental footprint of pharmaceuticals while fostering innovation, sustainability, and regulatory coherence.

2 From Design to End-of-Life: A Lifecycle Approach to Sustainable Pharmaceuticals

This chapter presents the rationale underpinning the ENVIROMED project and its *holistic, lifecycle-oriented approach* to addressing the environmental impacts of pharmaceuticals. It outlines how the project integrates multiple disciplines, technologies, and assessment methods to improve understanding of pharmaceutical pollution and to support the transition toward more sustainable pharmaceutical development, manufacturing, use, and end-of-life management.

By framing pharmaceutical sustainability as a cross-cutting challenge spanning the entire lifecycle of medicinal products, this chapter provides the conceptual foundation for the technology-specific results and policy-relevant evidence presented in the subsequent chapters of this deliverable.

2.1 Project Rationale

Pharmaceuticals deliver substantial societal benefits by improving health outcomes and quality of life. At the same time, their increasing use, combined with complex manufacturing processes and incomplete removal in wastewater treatment systems, has led to the widespread detection of pharmaceutical residues and metabolites in aquatic environments across Europe. These residues may enter the environment through multiple pathways, including manufacturing emissions, clinical and domestic use, disposal practices, and wastewater discharges, resulting in continuous, low-level exposure of ecosystems.

Current regulatory frameworks primarily address environmental risks at specific lifecycle stages, most notably through Environmental Risk Assessment (ERA) of medicinal products and water protection policies. However, growing evidence indicates that isolated, stage-specific measures are insufficient to fully address pharmaceutical pollution. Instead, a lifecycle-oriented perspective is required, enabling upstream prevention, improved process efficiency, and better-informed environmental management decisions.

ENVIROMED was envisioned to respond to this need by adopting an integrated approach that spans:

- **drug design**, through early screening of environmental hazards,
- **manufacturing**, through digitalisation, process intensification, and reduced resource consumption,
- **use and disposal**, through improved understanding of emissions from clinical and urban sources,
- **environmental exposure and effects**, through coordinated monitoring and ecotoxicity assessment.

This integrated rationale reflects EU policy priorities under the European Green Deal, the Zero Pollution Action Plan, the Pharmaceutical Strategy for Europe, and related water and chemicals legislation.

2.2 A Lifecycle Framework for Reducing Pharmaceutical Environmental Footprint

The ENVIROMED project operationalises a lifecycle approach by addressing both upstream prevention and downstream mitigation of pharmaceutical pollution.

Upstream, the project focuses on:

- identifying environmental risks at the drug design stage, enabling safer-by-design choices,
- reducing the environmental footprint of manufacturing processes, particularly through continuous biomanufacturing, digital twins, and advanced monitoring tools that enable more efficient use of energy, water, solvents, and cleaning resources.

Downstream, the project addresses:

- emissions from clinical facilities and wastewater treatment systems, recognising their role as key nodes in the pharmaceutical pollution pathway,
- the presence and persistence of pharmaceuticals in receiving aquatic environments, including marine ecosystems,
- the potential biological effects associated with long-term, low-level exposure.

By linking these stages, ENVIROMED moves beyond a purely reactive approach to pollution control and instead supports preventive and system-level solutions that align environmental protection with innovation and competitiveness.

2.3 Multidisciplinary Integration of Technologies and Evidence

A key feature of ENVIROMED is the integration of digital, analytical, and biological tools across lifecycle stages. Rather than developing isolated solutions, the project combines:

- **in-silico tools** that support early environmental screening and prioritisation of pharmaceutical compounds,
- **continuous biomanufacturing and digital twin technologies** that improve process robustness while reducing environmental burdens,
- **advanced inline, online, and surface monitoring technologies** that enable resource-efficient manufacturing and more informed compliance practices,
- **field monitoring campaigns** that generate high-resolution data on pharmaceutical emissions and environmental exposure,
- **in-vitro, in-vivo, and computational ecotoxicity assessments** that provide complementary evidence on potential ecological effects.

This multidisciplinary evidence base enables ENVIROMED to generate fact-based insights that are directly relevant to regulatory authorities, water managers, and policymakers.

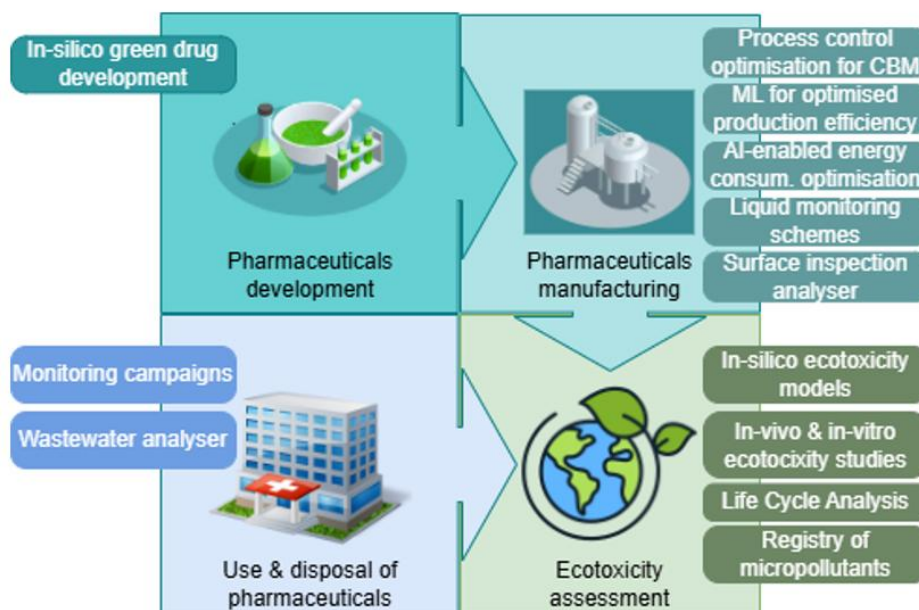


Figure 1: ENVIROMED high-level concept

2.4 Relevance for Policy and Regulatory Dialogue

By addressing pharmaceutical pollution across the lifecycle, ENVIROMED supports a shift toward integrated, proportionate, and prevention-oriented policy approaches. **The project does not seek to replace existing regulatory frameworks, but rather to inform their evolution by demonstrating how innovation, monitoring, and assessment tools can strengthen environmental protection while maintaining high standards of quality, safety, and efficacy.**

The chapters that follow present the project’s technologies, findings, and evidence-based considerations in detail, structured to facilitate dialogue with European and national authorities responsible for pharmaceuticals, chemicals, water management, and environmental protection.

3 In-Silico Tools for Green Drug Development

3.1 Overview of the in-silico tools

The G.A.I.A Toolbox (www.gaiatox.eu), developed within the ENVIROMED project, is an in-silico decision-support platform designed to support the early identification of potential environmental concerns associated with active pharmaceutical ingredients (APIs) and their metabolites. The toolbox integrates validated machine-learning models to predict aquatic ecotoxicity and bioaccumulation potential, endpoints that are directly relevant to the Environmental Risk Assessment (ERA) of medicinal products as required under EU regulatory frameworks.

G.A.I.A has been developed to function as a screening and prioritisation tool, providing predictive outputs that can inform decision-making prior to, or in support of, experimental testing. In addition to quantitative predictions, the toolbox identifies structural alerts, functional groups, and chemical fragments associated with ecotoxicity or bioaccumulation, supporting transparency and interpretability of model outputs.

The platform architecture allows for model updating and retraining, enabling adaptation to evolving regulatory expectations, including updates to toxicity thresholds or endpoint definitions.

The platform allows updating and retraining of models, enabling adaptation to evolving regulatory requirements, including changes to toxicity thresholds or assessment criteria. The G.A.I.A Toolbox is presented in detail in D6.1.

3.2 Main Findings

Application of the in-silico tools within the project demonstrated that the implemented models provide consistent and robust predictions for aquatic ecotoxicity and bioaccumulation endpoints within their validated applicability domain. The inclusion of metabolite-level predictions supports a more comprehensive environmental consideration, addressing a recognised challenge in Environmental Risk Assessment (ERA) where information regarding metabolites' ecotoxicity is often limited.

The platform also provides structural alert and descriptor-based insights, supporting mechanistic interpretation of predicted outcomes and facilitating scientific justification. Its design allows alignment with current and future ERA requirements, including the integration of revised cut-off values or assessment criteria through model updating.

The predictive performance of the acute aquatic ecotoxicity classification model has been evaluated and documented in detail in D6.1. Experimental validation was conducted using standardised assays in accordance with OECD Guideline 236 (*Danio rerio* embryo toxicity test), enabling direct comparison between predicted and experimentally observed toxicity classes. Across the experimental validation set, the model correctly classified 16 out of 19 compounds, corresponding to an accuracy of 84.21%, consistent with external validation results obtained using a substantially larger independent dataset, where an accuracy of approximately 90% was achieved.

Model outputs are accompanied by confidence indicators and interpretability features, enabling identification of borderline cases and supporting transparent, proportionate use of predictions. Overall, these findings indicate that the tool provides robust screening-level performance within its defined applicability domain, suitable for use as a supporting tool within a tiered

ERA approach, particularly at early development stages or when refining the scope of experimental testing.

3.3 Policy Relevance and Recommendations

The project results demonstrate how predictive in-silico tools for ecotoxicity and bioaccumulation assessment can support upstream pollution prevention and lifecycle-oriented pharmaceutical sustainability. By enabling early identification of substances with elevated environmental concern within a “green-by-design” framework, such tools reduce the likelihood that persistent, bioaccumulative, or toxic compounds progress to later stages of pharmaceutical development, where mitigation options are more limited and environmental impacts are harder to address.

When scientifically validated and applied within clearly defined applicability domains, predictive tools can provide early, screening-level information that complements experimental testing and supports tiered, proportionate regulatory approaches. In a regulatory and policy context, such tools can support:

- early environmental screening of active pharmaceutical ingredients and their metabolites,
- prioritisation of substances for further assessment or monitoring,
- identification of specific functional groups and chemical fragments within compounds that are associated with elevated environmental risk potential.

These functions are particularly relevant in contexts where large numbers of substances require screening, experimental data on metabolites or transformation products are limited, and early identification of environmental concern can reduce downstream regulatory, monitoring, and mitigation burdens.

The use of predictive tools in this manner is relevant across multiple EU policy domains, including Environmental Risk Assessment (ERA) of medicinal products under EMA guidance, chemical safety assessment under REACH coordinated by ECHA, water protection policy under the Water Framework Directive, and the objectives of the EU Zero Pollution Action Plan.

Policy Recommendations

#1.1 Support early environmental screening using predictive tools

EU and national authorities may encourage the use of validated in-silico models as supporting tools for early identification of potential environmental concern during substance development and assessment, where experimental data are not yet available.

#1.2 Clarify the role of predictive models within tiered assessment frameworks

Regulatory guidance could further clarify how predictive ecotoxicity and bioaccumulation tools may be used as screening or prioritisation inputs, consistent with tiered ERA approaches under EMA and chemical safety assessment frameworks under ECHA, without replacing mandatory testing requirements.

#1.3 Promote coherence across regulatory domains

Enhanced coordination between EMA, ECHA, DG ENV, and the European Environment Agency (EEA) could support consistent and complementary use of predictive tools across medicinal and chemical regulatory contexts, reducing duplication and strengthening environmental protection outcomes.

#1.4 Encourage data sharing and validation under EU governance frameworks

Access to high-quality experimental data, under appropriate governance and confidentiality arrangements, would further strengthen the robustness, transparency, and regulatory acceptance of predictive tools. EU-level initiatives could support curated datasets relevant to pharmaceuticals and chemicals.

#1.5 Address metabolites and transformation products more systematically

Predictive tools can provide valuable screening information for metabolites and transformation products, which are increasingly recognised as relevant for environmental exposure but often lack experimental data. Regulatory frameworks may benefit from clearer guidance on how such information can inform prioritisation and monitoring strategies.

#1.6 Support innovation aligned with pollution-prevention objectives

The use of predictive ecotoxicity tools supports upstream pollution prevention, enabling early identification of substances with lower anticipated environmental impact. This aligns with the objectives of the Water Framework Directive, the Zero Pollution Action Plan, and the Pharmaceutical Strategy for Europe.

4 Continuous Biomanufacturing Line

4.1 Overview of the Implemented Technologies

Continuous biomanufacturing or fermentation offers several advantages over conventional batch and fed-batch systems by maintaining cells in their most productive physiological state and enabling steady, uninterrupted product formation. Because fresh medium is continuously supplied and product is constantly removed, productivity per unit reactor volume and time is typically higher, and downtime for cleaning, sterilization, and setup is minimised. This steady-state operation also improves process consistency, simplifies downstream integration, and can reduce substrate inhibition or by-product accumulation that commonly limits batch and fed-batch processes. Overall, continuous fermentation provides enhanced efficiency, stability, and scalability – especially valuable for large-volume or commodity bioprocesses.

Within the ENVIROMED project, the concept of continuous aerobic fermentation for the production of a therapeutic API was developed and implemented, supported by digitalisation tools and a digital twin. The digital twin uses sensor data to control and predict biomass growth and API expression, enabling a resilient and process-intensified biomanufacturing operation. Further, concepts were developed for the transition of batch and fed-batch processes focusing on process design and optimization of energy demand. In addition, an experimentally validated computational toolset was developed during the project to investigate flow fields in bioreactors via multiphase computational fluid dynamics (CFD) allowing to predict key operating characteristics for process scale-up.

4.2 Main Findings

4.2.1 Establishing Continuous Biomanufacturing supported by a Digital Twin

A digital twin controlled continuous fermentation was developed within ENVIROMED and successfully implemented for a showcase proteinic API with the potential to extrapolate the findings and apply the toolsets to other APIs. The strategy derived from the successful implementation involves following stages:

- Operation of a classical batch or fed-batch cultivation mode as a benchmark
- Process characterization in terms of strain physiological parameters, feeding strategies, and product formation kinetics from the fed / fed-batch operation
- Consideration of intensified upstream bioprocessing strategies including an API dependent concept of repetitive fed-batch process, chemostat operation (with the identification of strain-dependent triggers, growth limiters, dilution rates and aeration) and/or process cascading to separate cell growth and API expression.
- Training of a digital twin based on the fermentation operating parameters and suitable continuously operating sensor data including cell density, extracellular API (if

applicable) oxygen take-up, off-gas analytics, pH, conductivity and soft-sensor concepts

- Implementation and validation of the trained digital twin to monitor and predict the performance of the continuous process.

Within ENVIROMED, this concept was successfully applied to the proteinic showcase API. Due to savings of bioreactor downtimes, repeated sterilisation requirements, savings of cleaning water (water for injection), an increase of productivity could be achieved at optimal conditions predicted by the digital twin further leading to significantly higher yields and volumetric productivities.

Furthermore, computational fluid dynamics supported scale-up concepts – where inputs to stirrer design, aeration, mixing behaviour, maximum shear rates, heat transfer, energy demand and improved geometric design recommendations could be provided for optimised operation scale-up.

4.2.2 Comparative Life Cycle Assessment of reactor operation modes

A Life Cycle Assessment (LCA) was performed based on primary data for the lab-scale production of the E. coli-based antibody fragment. The analysis examined the various reactor operation modes, media formulations, and feeding regimes, integrating real time electricity consumption data to capture process-specific energy demands. The assessment focused on two key environmental impact indicators: global warming potential and water usage. Additionally, several sensitivity scenarios were evaluated, including alternative electricity mixes (e.g. country specific grids, the European average, and renewable sources), different sterilisation methods applied between batches, and variations in API productivity, providing crucial insight into the environmental burdens associated with resource use and upstream inputs in biopharmaceuticals production.

Energy demand associated with sterilisation processes emerged as the primary hotspot across all operational modes, followed by bioreactor electricity use and glucose inputs, highlighting the combined influence of energy consumption and carbon-based feedstock usage. Continuous operation showed the lowest specific impact, primarily because a single sterilisation cycle was distributed over longer fermentation time and higher volumetric productivity, thereby reducing the relative influence of start up energy on the overall footprint. The cascade mode demonstrated a mid range performance, characterised by moderate electricity consumption and reduced specific media requirements. Contributions from consumables and cleaning agents were minimal, underscoring that improvements in process energy efficiency hold the greatest potential for emission reduction.

Overall, the results show that continuous operation can achieve a substantial reduction in upstream greenhouse gas emissions (on the order of 40%) compared with repetitive fed-batch operation, underscoring its potential as a more environmentally efficient production strategy. The analysis also indicates that the use of renewable electricity sources or waste-heat-based sterilisation approaches could further reduce environmental impacts across all operation modes.

Regarding the water footprint, the overall pattern across the examined configurations closely mirrored the trends observed for the carbon footprint. The continuous mode exhibited the lowest specific water demand, followed by fed-batch and cascade operation, while repetitive fed-batch showed the highest specific water demand. This pattern reflects the fact that major water-intensive activities, such as sterilisation, aeration, and cleaning, are largely fixed per production run and therefore contribute proportionally less when the process operates for longer periods and achieves higher product output, as is the case in continuous operation. In addition to direct water use during biomanufacturing, upstream contributions were found to be significant, particularly those associated with electricity generation and glucose production.

Finally, sensitivity analyses showed that the two examined factors, electricity source and glucose-to-product yield, strongly influence the upstream environmental footprint across all operation modes. While changes in electricity mix and process efficiency substantially affect absolute impacts, the relative ranking of operation modes remained consistent, with continuous processing emerging as the most environmentally efficient, followed by cascade, with fed-batch and repetitive fed-batch showing the highest impacts.

4.3 Policy Relevance and Recommendations

The ENVIROMED results demonstrate that continuous biomanufacturing supported by digital twins and process digitalisation can contribute meaningfully to EU objectives on sustainable industrial production, digital transformation, and pollution prevention. By enabling real-time process monitoring, soft-sensing, and predictive control, the demonstrated approach supports the implementation of Quality by Design (QbD) and Process Analytical Technology (PAT) principles within existing EMA and ICH frameworks.

From an environmental perspective, the combined evidence from process demonstration and LCA shows that operational optimisation of bioreactor systems represents a particularly effective pathway for reducing the environmental footprint of pharmaceutical manufacturing. Unlike changes to formulations or critical raw materials, adjustments to operation mode, control strategy, and process intensity can often be implemented without altering critical quality attributes, thereby remaining compatible with GMP and existing marketing authorisations.

The findings are directly relevant to EU policy initiatives including the European Green Deal, the EU Industrial Strategy, the Pharmaceutical Strategy for Europe, and emerging biotechnology and biomanufacturing initiatives, all of which emphasise resource efficiency, digitalisation, and lifecycle-oriented sustainability.

Recommendations for policymakers and regulators

#2.1 Facilitate regulatory clarity for digitalised and continuous bioprocesses

Regulatory guidance could further clarify pathways for the validation and acceptance of digital twins, soft sensors, and model-based control approaches within existing EMA, PAT, and QbD frameworks, supporting innovation while maintaining product quality and patient safety.

#2.2 Support operational optimisation as a sustainability lever

Policies may recognise continuous processing and advanced control strategies as viable approaches for reducing energy, water, and resource consumption in pharmaceutical manufacturing, provided that product quality remains unchanged.

#2.3 Encourage systematic use of life cycle assessment in process development

Promoting LCA during early-stage bioprocess design can help identify environmental hotspots, such as sterilisation energy demand and feedstock use, and inform evidence-based optimisation strategies.

#2.4 Develop best-practice guidance for energy and water efficiency in biomanufacturing

EU-level benchmarks and guidance for sterilisation, aeration, mixing, and bioreactor energy use could support harmonised improvements across the sector, including consideration of waste-heat-based sterilisation and renewable electricity integration.

#2.5 Invest in digital capabilities and skills for biomanufacturing

Targeted support under EU digital and industrial programmes could strengthen infrastructure, interoperability, and workforce skills needed for wider deployment of digital twins and advanced process control in biopharmaceutical production.

5 Liquid Monitoring & Surface Inspection Technologies

5.1 Overview of the Implemented Technologies

5.1.1 Inline/Online Liquid Monitoring Analyser

Within the scope of the project, four different measurement techniques based on photothermal spectroscopy have been investigated for their applicability in the use cases described in D2.3:

- Photothermal Interferometry (PTI)
- Photothermal Lens (PTL)
- Photothermal Mirror (PTM)
- Photothermal Deflection (PTD)

The most promising technology was the PTD configuration, which was then implemented in an analyser for the quantification of solutes in liquids with a focus on determining trace water concentrations in organic solvents. Focus was given to this use case both because of its relevance for the quality control in the pharmaceutical industry as well as for its advantageous analytical characteristics for mid-IR laser based photothermal sensing.

Various organic solvents containing traces of water were investigated by all four techniques to investigate their applicability as an online monitoring tool for the pharmaceutical industry.

5.1.2 Surface Inspection Analyser

The Surface Inspection Analyzer (SIA) is a handheld, fiber-coupled mid-infrared (mid-IR) spectroscopic sensor developed for non-destructive detection and analysis of pharmaceutical residues (APIs) on industrial surfaces, including flat, curved, and confined geometries such as vessels and pipes. The system is designed to support reduced environmental impact of pharmaceutical manufacturing by enabling rapid surface cleanliness verification and improved process control. The sensing principle is based on reflection-absorption infrared spectroscopy (IRRAS), implemented in a compact single-bounce SP-IRRAS geometry, with an optional polarization-modulated IRRAS (PM-IRRAS) mode.

The SIA architecture is modular and comprises interchangeable measurement heads optimized for different use cases, coupled via optical fibers. A vessel-adapted head (approx. 15 × 8 × 6 cm) is used for flat and curved surfaces, while a miniaturized pipe head (approx. 80 mm length, 46 mm diameter) is spring-loaded for stable operation in pipes with diameters of 45–47 mm. The fully optical coupling separates the mid-IR laser source from the measurement head, which facilitates on-site operation and is advantageous in ATEX-restricted or hard-to-access environments. Detection is performed using a fiber-coupled mercury cadmium telluride (MCT) detector.

The spectroscopic subsystem operates with broadband mid-IR laser sources (primarily QCL) enabling label-free identification and detection of active pharmaceutical ingredients (APIs) via their characteristic mid-IR absorption features. Measurement time per spot, including acquisition and data processing, is approximately 1 second, allowing near-real-time surface assessment. It should be noted that a patent application for the developed spectroscopic sub-

system for instantaneously broadband emitters (wavefront division Fourier transform spectrometers) has been submitted.

5.2 Main Findings

5.2.1 Inline/Online Liquid Monitoring Analyser

While all investigated technologies showed promising results for their application in the analysis of water traces in organic solvents, only the photothermal mirror (PTM) and PTD techniques could be readily implemented in an inline/online analyser. This is because in these measurement modalities all required optics can be placed on one side of the window-sample interface whereas the other two modalities would require a flow cell for successful implementation and detecting the probe beam after passing the flow cell. In the end, focus was given on the PTD technique, since its sensitivity was tuneable, while it was fixed for the PTM configuration.

The developed analyser featured a user-friendly software that allowed the determination of water traces in different organic solvent. The results were validated by Horiba and Fraunhofer for measurements of water in ethanol and chloroform. Further organic solvents typically used in industrial settings (THF, methanol) were also investigated. Different data evaluation strategies were assessed and compared to move towards automated data analysis necessary for monitoring technologies. TUW performed numerical simulations to understand the complex signal generation process involved in photothermal spectroscopy and related these to the results of the experimental work. As a result different data evaluation strategies can be recommended for evaluating the photothermal sample response. In case of weakly absorbing solvents such as organic solvents it is recommended to employ lock-in detection for the quantification of the induced changes in the signal magnitudes. In doing so LODs in the ppm range can be achieved. However, in case solutes need to be measured in a spectral region with strong background absorption by the solvent a steepness of the slope of the photothermal signal needs to be taken to obtain a linear calibration curve.

The retrieved results showed that the obtained limit-of-detection were also dependent on the thermal properties of the solvent under investigation paving the way for further scientific investigations that could potentially lead to better understanding the underlying principle and, consequently, achieving better performances.

5.2.2 Surface Inspection Analyser

Performance verification and pre-validation were conducted under laboratory and simulated industrial conditions using quantified API samples on stainless steel substrates. A limit of detection (LOD) of below 2 $\mu\text{g}/\text{cm}^2$ (worst case API) was experimentally validated with a 1-second acquisition time. Based on signal-to-noise analysis, extrapolated LODs of 0.4 $\mu\text{g}/\text{cm}^2$ (50 Hz scan rate) and 0.09 $\mu\text{g}/\text{cm}^2$ (20 s integration time) can be achieved by increasing the laser scanning speed. The effective sampling spot size is approximately 1.9 mm for the vessel head and 0.9 mm for the pipe head, enabling localized measurements while supporting spatial averaging strategies where required.

The SIA software framework provides real-time operation via a graphical user interface (GUI) and includes automated spectral reconstruction, chemometric evaluation, and decision support.

Quantification is based on partial least squares (PLS) models, and measurement outputs are presented as binary, color-coded results with associated confidence scores. Developer and calibration modes allow model training and adaptation to different APIs, substrates, and regulatory thresholds, supporting traceability and reproducibility.

Known limitations relevant for regulatory interpretation include the influence of non-uniform residue distributions (e.g. coffee-stain effects) on absolute quantification. These effects have been experimentally analyzed, and mitigation strategies such as increased probe beam size, spatial averaging, and standardized sample preparation are identified. It should be noted, however, that the SIA system is from other side is highly sensitive for spatially localized contaminations, while state-of-the-art systems average the local spikes out and cannot detect them. Consequently, the SIA is primarily positioned as a rapid screening and verification tool that generates actionable evidence to support compliance decisions, targeted follow-up sampling, and process optimization.

Overall, the SIA technology demonstrates technical feasibility, sensitivity, portability, and modularity suitable for integration into pharmaceutical manufacturing quality assurance and environmental compliance frameworks. By enabling near-real-time, on-site surface residue detection, the system supports a shift from sporadic, laboratory-based analysis toward more efficient, data-driven monitoring practices, contributing to greener manufacturing processes and improved regulatory oversight.

Experimentally validated detection limits are found in the low $\mu\text{g}/\text{cm}^2$ range (comparable and lower than that of the state-of-the art), however with higher spatial resolution, shorter measurement times and maximum flexibility due to fiber coupling. The results confirm the technical feasibility of deploying modular, on-site surface inspection sensors to support rapid cleaning verification and improved process control, while also identifying quantification challenges related to non-uniform residue distribution that can be mitigated through measurement and processing strategies. The further advancement of the technology requires optimization of the laser sources, which includes: higher scan/sweep rate (enabling lower limits of detections and acquisition rate) with automated tuning, stability (higher signal-to-noise ratio), and miniaturization, eventually completed by CE certification.

5.3 Policy Relevance and Recommendations

The results achieved within ENVIROMED demonstrate the potential policy relevance of advanced fluid monitoring and surface inspection technologies as tools for reducing the environmental footprint of pharmaceutical manufacturing, particularly regarding cleaning processes, solvent and water consumption, and process control.

Cleaning and cleaning verification in the pharmaceutical industry are areas where strict regulatory requirements go hand in hand with significant resource consumption. While current practices are effective in ensuring patient safety, they can lead to conservative cleaning approaches, increased water and cleaning agent consumption, and longer equipment downtime. These factors are directly related to the environmental performance of pharmaceutical production and are therefore important for EU policy in the areas of pollution prevention, resource efficiency, and sustainable production. The demonstrated capability to perform rapid, on-site, non-destructive detection of trace pharmaceutical residues enables a shift from conventional Fourier spectrometer based analysis toward mid-IR laser based near-real-time evidence generation. This supports more timely regulatory decision-making, improved

compliance monitoring, and enhanced transparency in cleaning and contamination control practices.

From a policy perspective, the LMA and SIA technology provides a scalable monitoring capability that can complement existing regulatory frameworks for cleaning validation, environmental risk reduction, and good manufacturing practice (GMP) inspections. By enabling fast screening and verification across multiple APIs, the technology can support risk-based inspection strategies, targeted follow-up sampling, and more efficient enforcement without prescribing specific process changes or chemical restrictions.

Policy-relevant observations

The project findings support the following observations of direct relevance to regulatory and policy actors:

- Cleaning verification represents a key leverage point for reducing water, solvent and energy use in pharmaceutical manufacturing without compromising product quality or patient safety.
- Chemical-specific and near-real-time measurements have the potential to reduce reliance on conservative, worst-case cleaning assumptions when used as supporting information.
- Current regulatory frameworks allow for scientifically justified optimisation of manufacturing practices, provided that safety and data-integrity requirements are fully met.
- Advanced monitoring tools are particularly relevant in process optimisation and development phases, where their use does not interfere with validated GMP routines but can inform improved future practices.

These observations align with the objectives of the EU Pharmaceutical Strategy, the Zero Pollution Action Plan, and the broader EU Chemicals Strategy for Sustainability, which all emphasise pollution prevention, efficiency and lifecycle-oriented approaches.

Recommendations for policymakers and regulators

#3.1 Support the use of advanced monitoring technologies as optimisation tools

Regulatory authorities may recognise the role of advanced liquid monitoring and surface inspection technologies as *complementary* tools for optimising cleaning processes and resource use within pharmaceutical manufacturing. When used alongside established methods, such tools can support pollution prevention objectives without altering existing compliance requirements.

#3.2 Encourage risk-based process optimisation within existing frameworks

Guidance at EU or national level could further clarify how data from chemical-specific, near-real-time monitoring tools may support risk-based optimisation of cleaning procedures, particularly in early development stages or during process improvement activities, while maintaining full compliance with GMP and patient safety requirements.

#3.3 Link manufacturing optimisation to environmental policy objectives

Policies addressing pharmaceutical pollution and resource consumption could explicitly acknowledge manufacturing-stage optimisation as a complementary measure to downstream control strategies, such as wastewater treatment. This would strengthen lifecycle-oriented approaches under the Water Framework Directive and related policies.

#3.4 Promote interoperability, data integrity, and standardisation readiness

Policy frameworks may encourage the alignment of advanced monitoring technologies with established data integrity, traceability, and validation principles. Compatibility with existing process analytical technology (PAT) concepts and data-management ecosystems can support scalable and compliant deployment, facilitate integration into current manufacturing environments, and enable the use of monitoring data to inform guideline development, standardisation activities, and regulatory oversight, without prescribing specific technologies or process changes.

#3.5 Foster further validation and benchmarking in collaboration with industry and regulators

Support for collaborative validation, intercomparison, and benchmarking activities involving technology developers, pharmaceutical manufacturers, and regulatory bodies could help define appropriate use contexts, performance expectations, and uncertainty ranges, facilitating responsible uptake without creating new regulatory obligations.

Contribution to EU environmental objectives

The ENVIROMED findings illustrate how innovation at the manufacturing stage can contribute to upstream pollution prevention, complementing measures that focus on emissions and environmental exposure. By enabling more efficient and informed cleaning processes, advanced monitoring technologies can support measurable reductions in water consumption, chemical use and operational inefficiencies, in line with EU sustainability and zero-pollution objectives.

6 Environmental Field Monitoring Campaigns

6.1 Overview of the Field Studies

The environmental field monitoring campaigns conducted under the project were designed to assess pharmaceutical contamination across key stages of the pharmaceutical lifecycle, from upstream point sources associated with use and disposal to downstream receiving environments. The campaigns were structured around three complementary monitoring pillars, covering clinical facility wastewater, wastewater treatment plant (WWTP) influent and effluent, and receiving marine waters.

Together, the three monitoring pillars provide an integrated evidence base to:

- characterise the occurrence and temporal variability of selected pharmaceutical compounds and an industrial additive,
- assess removal performance across wastewater treatment stages,
- evaluate the transfer of pharmaceutical residues from anthropogenic sources to the aquatic environment,
- support lifecycle-oriented assessment of contamination pathways relevant to EU water and pollution-prevention policies.

6.1.1 Monitoring Pillar A – Clinical Facility Wastewater

Monitoring Pillar A focused on wastewater generated by MITERA Hospital, a large clinical facility in Athens, representing a significant point source of pharmaceutical residues associated with medical use. The monitoring campaign aimed to characterise pharmaceutical concentrations in clinical wastewater streams, assess temporal variability, and support understanding of the contribution of healthcare facilities to downstream municipal wastewater systems.

The use of high-frequency sampling provided enhanced temporal resolution. Across all monitored components, the dominant feature of the time series was high temporal variability driven by sporadic concentration peaks. While seasonal patterns could be identified for selected substances, the overall concentration profiles were largely governed by event-driven episodes, which strongly influenced summary statistics and average values.

In one sampling campaign, an increase in concentrations toward the end of the study period was observed, potentially reflecting changes in in-hospital usage patterns, disposal practices, or upstream operational inputs. In another case, a dual seasonal pattern was identified, consistent with a combination of chronic pharmaceutical use and cyclic hospital treatment activities.

The magnitude of several peaks substantially exceeds values commonly reported in the literature for municipal and hospital wastewater, indicating that hospital sewer systems can act as high-intensity point sources of pharmaceutical residues, even when their overall volumetric contribution to the wastewater network is relatively small. These findings underline the relevance of source-oriented monitoring approaches and highlight the potential value of targeted management measures at clinical facilities to reduce downstream pharmaceutical loads.

6.1.2 Monitoring Pillar B – WWTP Inputs & Outputs

Monitoring Pillar B consisted of an annual monitoring campaign at a major wastewater treatment plant, namely EYDAP's WWTP at Psyttalia, focusing on influent and effluent streams. High-frequency sampling was conducted to capture both short-term variability and seasonal trends in the concentrations of selected pharmaceutical compounds and an industrial additive.

The campaign demonstrated the continuous presence of all targeted compounds in both influent and effluent samples throughout the monitoring period. While seasonal variations were observed for selected substances, overall concentration levels remained relatively stable over the year, as confirmed by repeated sampling.

The concentrations measured were largely consistent with values reported for comparable European wastewater treatment plants. Importantly, the results indicate that conventional wastewater treatment processes provided limited removal for several pharmaceutical compounds, including substances included in the Urban Wastewater Treatment Directive (UWWTD) watch list, resulting in their persistent detection in treated effluents.

These findings highlight the importance of systematic and high-frequency monitoring to accurately characterise pharmaceutical emissions from WWTPs and provide robust evidence to inform treatment performance evaluation and regulatory decision-making. In conclusion, the observed limited removal of several pharmaceutical compounds indicates that upgrading wastewater treatment plants with advanced or tertiary treatment technologies would be necessary to improve the removal of pharmaceuticals and reduce their release into receiving aquatic environments.

6.1.3 Monitoring Pillar C – Marine / Receiving Waters

Monitoring Pillar C addressed receiving marine waters downstream of wastewater discharges, aiming to assess environmental exposure and downstream transport of pharmaceutical residues. Sampling was conducted at multiple locations and depths to capture spatial variability, and across seasons to account for temporal dynamics.

Marine monitoring results revealed spatial and seasonal variability in organic compound concentrations, providing preliminary insights into the processes governing their distribution in the receiving environment. Elevated concentrations at stations located closer to the Psyttalia WWTP discharge points, particularly at southern stations, suggest an influence of treated effluent, acting in combination with dilution, dispersion, and local hydrodynamic conditions. Comparable concentration levels between surface and near-bottom water layers indicate enhanced vertical mixing in the studied area.

Seasonal variations observed for selected compounds may be related to changes in consumption patterns, hydrodynamic conditions, and compound-specific physicochemical properties, including persistence, solubility, and degradation potential under varying environmental conditions. The limited variability observed for several compounds across seasons and stations may therefore reflect a combination of relatively steady inputs via WWTP effluent and inherent substance properties.

Although detected concentrations of micropollutants in marine waters were generally low, their widespread occurrence confirms their persistence in the marine environment. Interannual

differences observed between the October 2024 and October 2025 campaigns indicate potential variability over time; however, extended and continued monitoring would be required to robustly assess longer-term trends.

Overall, the findings provide valuable baseline information for coastal environments influenced by wastewater discharges and support the need for continuous, spatially resolved monitoring to better understand the fate, transport, and persistence of pharmaceutical residues and other organic micropollutants in marine ecosystems.

The results demonstrate the presence of pharmaceutical compounds in marine waters receiving treated wastewater, confirming the connectivity between upstream emission sources, wastewater treatment systems, and sensitive aquatic environments. The detection patterns support the relevance of integrating marine monitoring into lifecycle-oriented assessments of pharmaceutical pollution.

6.2 Wastewater Spectroscopic Analyser

Alongside the field monitoring campaigns, the project developed a laser-based Wastewater Spectroscopic Analyser (WSA) to support near-real-time monitoring of selected pharmaceutical compounds in wastewater streams. The system is intended for on-site use and allows faster analytical turnaround compared to conventional laboratory workflows, which typically involve sample collection, transport, and off-site processing.

The WSA incorporates an integrated sample preparation and measurement sequence, combining membrane-based filtration (MSF), solid-phase extraction (SPE), and a mid-infrared (MIR) spectroscopic measurement unit. MSF is applied to remove larger particles and suspended solids from the wastewater, ensuring stable operation of downstream components, while SPE is used to increase the concentration of target pharmaceutical compounds prior to analysis. The treated sample is then analysed using MIR spectroscopy to determine pharmaceutical concentrations.

In contrast to laboratory-centred analytical approaches, the WSA can be deployed at relevant locations within the wastewater system, including influent, effluent, and upstream discharge points, allowing more frequent measurements and improved temporal coverage. This supports the identification of short-term concentration variations that may not be captured through periodic sampling. The combined sample preparation and spectroscopic configuration improves measurement reliability when compared to direct analysis of untreated wastewater, while maintaining analysis times compatible with operational, on-site monitoring needs.

The WSA is intended to complement established laboratory methods by providing timely, screening-level data that can support targeted sampling, trend evaluation, and operational assessments.

Overall, the WSA illustrates the potential of automated, field-deployable sensing technologies to enhance monitoring of pharmaceutical emissions to wastewater systems. When used alongside conventional analytical methods and structured monitoring programmes, such tools can contribute to improved understanding of emission dynamics and risk-based assessment of pharmaceutical emissions in wastewater systems, in line with evolving EU water and environmental policy objectives.

6.3 Main Findings

The integrated analysis of results across the three monitoring pillars highlights several consistent patterns relevant to understanding pharmaceutical pollution across the water cycle:

1. Continuity of contamination pathways across the water cycle.

Pharmaceutical compounds are detected across all monitored stages, from clinical facility wastewater to WWTP effluents and further to receiving marine waters, confirming the continuity of contamination pathways.

2. Clinical facilities as episodic high-intensity point sources.

Wastewater from clinical facilities exhibits strong temporal variability, with overall concentration patterns largely driven by short-lived, event-related peaks rather than by consistent seasonal trends. Peak levels often exceed those reported for municipal wastewater, indicating that clinical facilities can act as high-intensity point sources of contaminants despite their relatively small contribution to total wastewater volumes.

3. Limited removal of selected pharmaceuticals during conventional wastewater treatment.

Conventional wastewater treatment processes may provide limited removal for selected pharmaceuticals, leading to persistent detection in treated effluents at concentrations comparable to those reported for other European wastewater treatment plants.

4. Confirmed downstream environmental exposure.

The presence of pharmaceuticals in receiving waters confirms downstream environmental exposure and the continuity of contamination pathways.

5. Spatial and vertical patterns in marine waters.

Spatial patterns in marine waters, including elevated concentrations at stations closer to WWTP discharge points and comparable levels between surface and near-bottom layers, indicate the combined influence of treated effluent inputs, hydrodynamic dispersion, and enhanced vertical mixing.

6. Value of high-frequency monitoring for capturing variability.

High-frequency monitoring reveals temporal variability and seasonal patterns that may not be captured through sporadic sampling.

7. Persistence of pharmaceutical residues at low environmental concentrations.

Although detected concentrations in marine waters were generally low, their widespread occurrence across stations and seasons underscores the persistence of pharmaceutical residues in the marine environment.

Overall, the findings indicate that pharmaceutical pollution in aquatic environments is systemic and lifecycle-driven rather than site-specific, and that its assessment requires integrated analysis across multiple stages of emission, treatment, and environmental reception.

6.4 Policy Relevance and Recommendations

The results of the environmental monitoring campaigns are directly relevant to EU and national policies addressing pharmaceutical pollution in aquatic environments. The combined evidence from clinical facilities, wastewater treatment plants, and receiving waters confirms that pharmaceuticals can enter and persist in the aquatic environment through multiple interconnected pathways.

The findings underscore the importance of a lifecycle-oriented approach to pharmaceutical pollution management, consistent with the objectives of the Urban Wastewater Treatment Directive (UWWTD), the Water Framework Directive (WFD), the Marine Strategy Framework Directive (MSFD), and the EU Zero Pollution Action Plan.

Policy-Relevant Observations

- Clinical facilities, although contributing a relatively small fraction of urban wastewater volumes, can function as locally significant point sources of pharmaceutical pollution due to episodic high-concentration discharges.
- The strongly episodic nature of discharges highlights the importance of targeted, high-resolution monitoring and source-oriented risk management measures, including improved disposal practices and mitigation at the facility level.
- Wastewater treatment plants represent a critical control point, yet conventional processes may not fully remove certain pharmaceuticals of regulatory concern.
- Detection of pharmaceuticals in receiving waters demonstrates the transfer of residues beyond treatment systems into the wider environment.
- Long-term, high-frequency monitoring provides more reliable evidence of persistence and variability than sporadic sampling.
- Comparable concentration levels across sites indicate a widespread and systemic challenge across water systems.

Advanced on-site and automated monitoring approaches, such as the Wastewater Spectroscopic Analyser (WSA) that was developed and demonstrated in the project, can support the implementation of water and environmental policies by enabling more frequent and spatially resolved monitoring of pharmaceutical residues across the urban water cycle. When used alongside conventional laboratory-based analyses, WSA-type systems provide complementary evidence on temporal variability, persistence, and treatment performance that may not be captured through sporadic sampling.

Such data can strengthen evidence-based prioritisation of substances of concern, support evaluation of wastewater treatment effectiveness, and inform targeted, proportionate mitigation measures. The use of harmonised on-site analytical tools across multiple locations can also enhance data comparability and trend analysis, supporting national and EU-level assessment and decision-making.

Recommendations for Policymakers and Water Authorities

#4.1 Strengthen integrated monitoring across the water cycle

Authorities should support monitoring strategies that encompass upstream sources, WWTP influent and effluent, and receiving waters to enable a coherent lifecycle-oriented assessment of pharmaceutical pollution.

Within this context, large hospitals should be explicitly considered within monitoring and assessment frameworks, reflecting their potential to generate episodic high-concentration emissions despite relatively small wastewater volumes.

#4.2 Enhance routine monitoring of pharmaceuticals of regulatory interest

Monitoring data should continue to support the prioritisation of pharmaceuticals within existing WFD and UWWTD frameworks, including Watch Lists and related assessment mechanisms with attention to substances associated with clinical use.

Where appropriate, clinical facilities may be included in targeted EU surveillance and watch-list programmes with monitoring approaches adapted to capture episodic discharges and avoid underestimation of pollutant loads.

#4.3 Use monitoring evidence to inform treatment performance evaluation

Evidence of limited removal for certain pharmaceuticals supports systematic assessment of wastewater treatment performance. Where justified, this may inform the proportionate and site-specific consideration of supplementary or advanced treatment options, both at centralised wastewater treatment plants and, where relevant, at upstream sources.

#4.4 Support risk-based prioritisation and regulatory decision-making

Systematic and comparable monitoring data can inform prioritisation of substances for further regulatory attention, risk assessment, and targeted mitigation measures at national and EU levels, supporting proportionate and evidence-based decision-making.

#4.5 Promote harmonisation and data comparability across Member States

Harmonised monitoring protocols and EU-level data sharing would enhance comparability across Member States, support trend analysis, and strengthen the evidence base for policy development and regulatory evaluation.

#4.6 Link monitoring results to upstream pollution prevention measures

Integrated interpretation of monitoring results should support source-oriented pollution prevention, including improved management practices in clinical and urban settings, contributing to reduced emissions at source in line with EU pollution prevention objectives.

7 Ecotoxicity Assessment

7.1 Overview of Approaches

The assessment of environmental effects associated with pharmaceuticals following their use and disposal was conducted using a complementary set of approaches, reflecting the complexity of pharmaceutical pollution in aquatic environments. These approaches combine empirical evidence, predictive tools, and existing knowledge to support a comprehensive and proportionate evaluation of environmental relevance.

Specifically, the project integrated:

- **literature-based assessment**, to contextualise project findings within existing scientific knowledge and identify substances of concern;
- **effect-based ecotoxicity studies**, to evaluate biological responses under environmentally relevant exposure scenarios;
- **in-silico ecotoxicity models**, to support screening, prioritisation, and interpretation of ecotoxicity data.

Together, these approaches provide a coherent assessment framework that complements the environmental monitoring activities presented in Chapter 6 and supports lifecycle-oriented interpretation of pharmaceutical pollution. Rather than focusing on detailed experimental outcomes, this chapter highlights key patterns, insights, and implications relevant to environmental risk assessment and policy dialogue.

The literature-based assessment, environmental monitoring activities, biological effect-based studies, and in-silico modelling presented in this chapter were conducted as complementary and largely parallel activities within the project. While these approaches address different aspects of pharmaceutical pollution and environmental effects, none of the individual activities was designed to guide or constrain the others.

The purpose of their combined presentation in this chapter is to enable an integrated interpretation of evidence, whereby findings from literature, monitoring, biological assessment, and modelling can be jointly considered to identify consistent patterns, confirm observed trends, and highlight remaining uncertainties relevant to environmental risk assessment. References to complementarity between approaches should therefore be understood as *ex post* synthesis, rather than a sequential or hierarchical dependency among methods.

7.1.1 Literature-based assessment of pharmaceutical ecotoxicity potential

A literature-based assessment was conducted to support the interpretation of environmental monitoring and ecotoxicity findings and to place project results within a broader European policy and scientific context, using Greece as a representative case study. The objective of this assessment was to identify pharmaceutical substances and therapeutic classes of potential environmental relevance, and to inform risk-based prioritisation approaches.

The literature review considered published data on the occurrence, persistence, and ecotoxicity of pharmaceuticals, as well as existing risk assessment indicators and monitoring evidence. This synthesis enabled identification of substances that are frequently detected in aquatic

environments, including cases where monitoring coverage may not fully reflect usage patterns or potential ecological relevance.

Rather than generating new risk thresholds, the literature-based assessment provided contextual evidence to support:

- interpretation of monitoring and ecotoxicity results generated within the project,
- identification of pharmaceuticals and metabolites warranting closer attention,
- alignment with ongoing EU efforts to strengthen risk-based prioritisation in water and marine policies.

Detailed methodologies and compound-level analyses are reported in D6.1. In the context of this deliverable, the literature-based assessment serves to frame and reinforce the subsequent findings presented in Sections 7.1.2–7.3, ensuring that project-specific evidence is interpreted within a wider scientific and regulatory landscape.

7.1.2 In-Vitro/In-Vivo Ecotoxicity Studies

The *in vitro* and *in vivo* ecotoxicity studies conducted under the project examined the biological effects of pharmaceutical residues detected in marine environments, with a particular focus on sublethal stress responses in ecologically relevant marine organisms. The objective was not to identify acute toxicity, but to assess whether long-term, low-level exposure to pharmaceuticals, alone or as mixtures, can interfere with key biological functions.

Marine invertebrates commonly found in European coastal waters were selected as representative organisms, due to their ecological importance and their sensitivity to environmental stress. These organisms were exposed either to individual pharmaceuticals commonly detected in the aquatic environment or to seawater samples collected in the vicinity of wastewater treatment plant discharges.

The studies focused on early-warning biological indicators, such as cellular stress, immune system function, and genetic damage, which are known to respond to chronic environmental pressure before visible ecological damage occurs. Across the different test conditions, the results showed that several pharmaceuticals were able to trigger measurable biological responses, even at concentrations considered environmentally relevant.

Observed effects varied between substances and test conditions, but included:

- increased cellular stress responses,
- alterations in immune-related functions,
- indications of genetic damage in immune cells.

Importantly, organisms exposed to seawater samples collected near wastewater discharges exhibited stronger stress responses than those exposed to local reference seawater, despite measured pharmaceutical concentrations remaining below levels traditionally considered acutely toxic. This indicates that combined exposure to multiple compounds and site-specific environmental factors can contribute to biological effects that are not readily predicted by chemical analysis alone.

Overall, these findings highlight that pharmaceutical residues present in the marine environment may exert biologically relevant effects at low concentrations under conditions of chronic and mixed exposure. The results support the value of integrating effect-based

biological tools alongside chemical monitoring (as described in Chapter 6) to improve understanding of environmental risks associated with pharmaceutical pollution.

7.1.3 In-Silico Ecotoxicity Models

In-silico ecotoxicity models provide an important complementary tool for the environmental assessment of pharmaceuticals already present in the aquatic environment, supporting the interpretation of monitoring results and the prioritisation of substances for further assessment. Within a lifecycle perspective, their role extends beyond drug design and includes the evaluation of existing active substances, metabolites, and transformation products detected following use and disposal.

In the context of ecotoxicity assessment, in-silico models enable rapid screening of potential environmental hazards based on chemical structure, supporting the identification of substances with elevated concern for acute toxicity, persistence and bioaccumulation of chemical compounds and their biotransformation products. This capability is particularly relevant where experimental ecotoxicity data are limited or unavailable, as is often the case for metabolites and transformation products identified through environmental monitoring.

The in-silico platform developed within the project illustrates how such models can support post-market environmental assessment by providing indicative predictions of ecotoxicity and bioaccumulation for pharmaceuticals detected in wastewater and receiving waters. In addition to overall hazard screening, the identification of structural features associated with increased environmental risk can support grouping approaches, read-across, and prioritisation within regulatory assessment frameworks.

By complementing chemical monitoring and effect-based biological studies, in-silico models contribute to an integrated assessment approach for environmental risk assessment. They can help guide decisions on where more detailed experimental testing or targeted monitoring is warranted, thereby supporting efficient use of resources and reducing unnecessary animal testing.

Overall, the use of in-silico ecotoxicity models at this later stage of the pharmaceutical lifecycle enhances the predictive capacity and coherence of environmental assessment, supporting more informed, proportionate, and sustainable management of pharmaceutical pollution in line with EU environmental and pharmaceutical policy objectives.

7.2 Main Findings

The literature-based assessment, conducted using Greece as a representative case study, confirms that pharmaceutical residues are widely present across aquatic environments, including wastewater, surface waters, and coastal ecosystems. The reviewed evidence indicates that detection patterns do not match consumption patterns in Greece. They likely reflect broader trends associated with not only pharmaceutical use, but also disposal practices, historical prominence, analytical convenience, and/or wastewater treatment performance. The analysis revealed major mismatches between pharmaceutical consumption, monitoring frequency, and ecological risk, with many widely used substances under monitored and several metabolites posing higher risks than their parent compounds.

Repeated detection of certain APIs and API mixtures confirms that environmental exposure to pharmaceuticals likely occurs on a continuous basis, raising questions about long-term and mixture-related effects that may not be fully addressed through substance-by-substance assessments alone. These findings provide important context for the project's monitoring and ecotoxicity results and support the need for *risk-based prioritisation and integrated assessment approaches* in environmental policy and regulation.

In addition to the literature-based assessment, the combined analysis of chemical monitoring data and biological effect-based studies provides important insights into the environmental relevance of pharmaceutical residues detected in marine environments.

Overall, the results indicate that pharmaceutical concentrations measured in surface seawater at the monitored sites were generally below levels associated with acute toxic effects. However, the biological studies demonstrated that sublethal stress responses and immunological modulation can occur under conditions of exposure, highlighting the importance of considering biological responses alongside chemical concentration data.

Differences in baseline sensitivity were observed between organisms collected from different geographical locations, indicating that site-specific factors and population-level variability can influence biological responses to environmental stressors. These findings suggest that environmental vulnerability is not uniform and may depend on local conditions, background exposure, and organismal status.

Exposure of marine organisms to seawater samples collected near wastewater discharges resulted in measurable stress responses, which could not be directly attributed to individual pharmaceutical compounds based on chemical analyses alone. This observation underscores the relevance of mixture effects and combined environmental pressures, which may not be fully captured through substance-by-substance chemical monitoring.

Taken together, the findings indicate that the absence of exceedances of known toxicity thresholds does not necessarily preclude biologically relevant effects, particularly under chronic, low-level, and mixed exposure scenarios. The results support the integration of effect-based biological tools with chemical monitoring to improve environmental risk interpretation and to better inform prioritisation, monitoring strategies, and regulatory decision-making.

7.3 Policy Relevance and Recommendations

The combined evidence from literature-based assessments, environmental monitoring, biological effect-based studies, and in-silico modelling provides a comprehensive perspective on the environmental relevance of pharmaceuticals following their use and disposal. Together, these findings support a lifecycle-oriented and proportionate approach to managing pharmaceutical pollution in marine and aquatic environments.

Policy-Relevant Insights

The assessment confirms that certain widely used pharmaceuticals, including non-prescription medicines such as non-steroidal anti-inflammatory drugs (NSAIDs), are frequently detected in wastewater effluents and receiving waters, despite not necessarily being among the highest in terms of reported per-capita consumption. Their prevalence reflects a combination of usage

patterns, incomplete removal in conventional wastewater treatment systems, and disposal practices.

While measured environmental concentrations were generally below levels associated with acute toxicity, the ecotoxicity studies demonstrated that sublethal biological responses may occur under chronic and mixed exposure conditions, and that site-specific sensitivity and population-level variability can influence biological outcomes. These findings underline the limitations of relying solely on concentration-based chemical monitoring and support the integration of complementary assessment tools.

The results also highlight that improper disposal of unused or expired pharmaceuticals can contribute to environmental emissions, even in contexts where collection schemes are well established. This indicates that infrastructure alone is insufficient, and that sustained public engagement and awareness remain critical components of pollution prevention.

Recommendations for Policymakers and Regulatory Authorities

#5.1 Strengthen integrated assessment of pharmaceutical pollution

Authorities should promote assessment approaches that combine chemical monitoring, effect-based biological tools, and predictive in-silico models to improve interpretation of environmental risks associated with pharmaceuticals, particularly under chronic and mixed exposure scenarios.

#5.2 Support risk-based prioritisation of pharmaceuticals in water and marine policies

Regulatory frameworks under the Water Framework Directive (WFD), the Urban Wastewater Treatment Directive (UWWTD), and the Marine Strategy Framework Directive (MSFD) should continue to prioritise substances based on environmental occurrence, persistence, and hazard potential, rather than detection frequency alone. Widely used pharmaceuticals with demonstrated environmental relevance may warrant closer attention.

#5.3 Enhance the role of effect-based tools in monitoring programmes

Biological effect-based assays targeting sublethal responses can provide valuable complementary information to chemical monitoring and should be considered as part of integrated monitoring strategies, while recognising their supportive role within broader assessment frameworks.

#5.4 Promote the use of predictive tools for post-market environmental assessment

In-silico ecotoxicity and bioaccumulation models can support screening and prioritisation of pharmaceuticals, metabolites, and transformation products detected in the environment, particularly where experimental data are limited. Their use can help focus monitoring efforts and guide decisions on the need for further testing.

#5.5 Support harmonisation and comparability across Member States

Greater harmonisation of monitoring approaches, assessment criteria, and data reporting would enhance comparability of results across regions and strengthen the EU-wide evidence base for managing pharmaceutical pollution.

#5.6 Reinforce upstream pollution prevention through public engagement

Continued efforts are needed to strengthen public awareness and participation in pharmaceutical take-back and disposal schemes across Member States. Lessons learned from national experiences indicate that sustained communication and accessibility are essential to reduce environmental releases.

#5.7 Encourage further assessment of long-term and mixture effects

To reduce remaining uncertainties, regulatory and research initiatives should continue to support studies addressing long-term exposure, mixture effects, and site-specific vulnerability, thereby improving the robustness of environmental risk assessments.

8 Conclusions

This deliverable has presented a lifecycle-oriented synthesis of the main scientific and technological outcomes of the ENVIROMED project, responding to the need for integrated approaches to address the environmental footprint of pharmaceuticals. By examining pharmaceutical-related environmental pressures from early drug development and manufacturing through to use, disposal, environmental exposure, and effects, the project demonstrates the value of addressing sustainability challenges across the full lifecycle rather than at isolated stages.

A central conclusion of the project is that no single intervention is sufficient to reduce pharmaceutical-related environmental impacts. Meaningful progress requires the combined application of upstream and downstream measures, including green-by-design principles, sustainable manufacturing practices, advanced monitoring technologies, environmental surveillance, and effect-based assessment tools. When considered together, these approaches provide a more comprehensive understanding of contamination pathways, environmental exposure, and potential biological effects.

The results further highlight the importance of integrated and risk-based assessment frameworks. Environmental monitoring alone, while essential, may not fully capture long-term, sublethal, or mixture-related effects, while predictive and biological tools are most effective when interpreted alongside robust monitoring data. The ENVIROMED findings illustrate how combining chemical measurements, biological responses, and predictive modelling can support more informed prioritisation, interpretation, and decision-making.

From a policy and regulatory perspective, the project outcomes reinforce ongoing EU efforts to promote pollution prevention, lifecycle thinking, and proportional regulation. The fact-based observations and considerations presented throughout this deliverable are relevant to multiple policy domains, including pharmaceutical regulation, chemical safety, water and marine protection, and broader sustainability strategies. While the technologies demonstrated in the project are presented as illustrative examples, the underlying principles are transferable and can inform future regulatory dialogue and policy development.

Overall, the ENVIROMED project demonstrates how interdisciplinary collaboration and lifecycle-oriented innovation can support the transition towards more environmentally sustainable pharmaceutical systems. By synthesising evidence across disciplines and lifecycle stages, this deliverable aims to inform regulatory dialogue and support the development of coherent and proportionate EU and national policies aligned with the European Green Deal, the Zero Pollution Action Plan, and the Pharmaceutical Strategy for Europe.

Annex



Policy Brief
April 2026



Reducing the Environmental Footprint of Pharmaceuticals Across the Lifecycle

**Evidence and policy-relevant recommendations
from the ENVIROMED project**

Why This Matters

Pharmaceuticals deliver essential health benefits. At the same time, their environmental footprint is shaped by decisions and processes occurring across multiple lifecycle stages: from molecular design and manufacturing to use, wastewater treatment, and environmental exposure.

Reducing the environmental impact of pharmaceuticals requires a co-ordinated lifecycle strategy combining

upstream prevention, sustainable production, integrated monitoring, and proportionate regulatory action.

ENVIROMED demonstrates how innovation and environmental assessment across these stages can support EU sustainability objectives and contribute to the effective implementation and continuous strengthening of existing regulatory frameworks.



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A Lifecycle Strategy for Environmental Sustainability

ENVIROMED generated integrated evidence across four key intervention stages:

1. Designing Safer Pharmaceuticals

- In-silico tools enable early screening of active pharmaceutical ingredients (APIs) and relevant metabolites for ecotoxicity and bioaccumulation potential.
- Predictive models support tiered Environmental Risk Assessment (ERA) approaches.
- Structural alert identification contributes to safer-by-design strategies before large-scale development.

Policy relevance:
Supports EMA ERA guidance, REACH chemical assessment frameworks, and upstream pollution-prevention objectives of the EU Zero Pollution Action Plan.

2. Sustainable and Digitalised Manufacturing

- Continuous biomanufacturing demonstrated lower energy demand and water consumption compared to repetitive fed-batch systems.
- Digital twins and advanced control strategies support process optimisation and resource efficiency.
- Liquid monitoring and surface inspection technologies enable chemical-specific, near-real-time optimisation of cleaning processes.
- Life Cycle Assessment identified sterilisation energy demand as the main environmental hotspot in biomanufacturing.

Policy relevance:
Relevant to the EU Pharmaceutical Strategy for Europe, the Chemicals Strategy for Sustainability, circular economy objectives, and EU decarbonisation targets.

3. Environmental Monitoring Across the Water Cycle

- Clinical facilities can act as episodic high-intensity emission sources, where short-lived concentration peaks may significantly influence pollutant loads but remain undetected in low-frequency monitoring schemes.
- Monitoring confirmed continuity of contamination pathways from hospital effluents through wastewater treatment plants to receiving marine waters.
- Conventional wastewater treatment shows variable removal efficiency for selected pharmaceuticals, leading to their continued presence in treated effluents and receiving waters.
- High-frequency and on-site monitoring improves detection of discharge events, reducing the risk of underestimating pollutant loads.

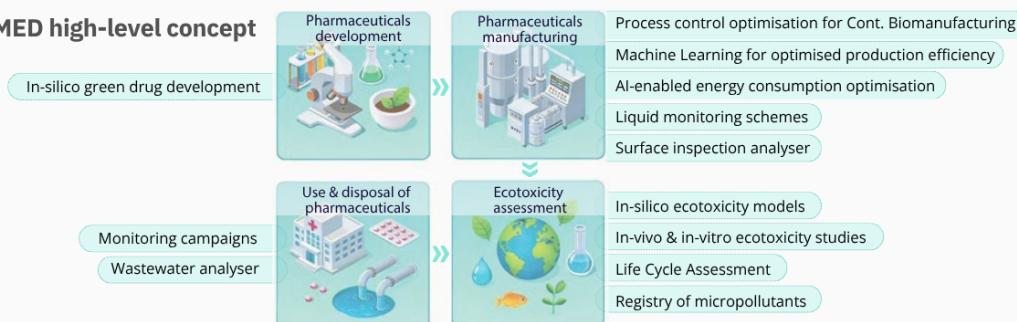
Policy relevance:
Directly relevant to the implementation of the Urban Wastewater Treatment Directive (UWWTD), the Water Framework Directive (WFD), and EU risk-based prioritisation mechanisms.

4. Ecotoxicity and Environmental Effects Assessment

- Effect-based ecotoxicity assays indicated that pharmaceutical residues may induce sublethal biological responses even when concentrations remain below acute toxicity thresholds.
- Differences in organism sensitivity highlight the importance of environmental context and site-specific vulnerability.
- Predictive models complement monitoring by supporting qualitative understanding of combined exposure patterns across substances and environmental pathways.

Policy relevance:
Supports environmental risk interpretation under EMA ERA frameworks and complements monitoring and prioritisation processes under the WFD.

ENVIROMED high-level concept



Key Insights

- Pharmaceutical pollution is lifecycle-driven and systemic.
- Upstream prevention reduces downstream mitigation burdens.
- Manufacturing configuration and process optimisation are important sustainability levers.
- Integrating chemical, biological, and predictive evidence enhances environmental assessment.
- Innovation can support the effective implementation and progressive evolution of existing regulatory structures, without necessarily requiring new obligations.

Policy Recommendations

The following recommendations aim to reinforce lifecycle-oriented environmental sustainability by strengthening implementation and coherence within existing EU regulatory frameworks.

A. Strengthen Upstream Environmental Prevention

1. Integrate early environmental screening within existing frameworks

- Encourage structured use of validated in-silico tools for screening APIs and relevant metabolites.
- Support tiered approaches combining predictive models and experimental data.
- Facilitate data-sharing initiatives to improve model validation and applicability.

These measures can enhance the implementation and practical effectiveness of EMA ERA guidance and REACH assessment processes, without replacing mandatory testing requirements.

B. Recognise Sustainable Manufacturing as a Pollution-Prevention Lever

2. Support operational optimisation as a sustainability strategy

Policies may recognise continuous processing, advanced control strategies, and digital twin-based optimisation as viable approaches for reducing energy, water, and raw material use in pharmaceutical manufacturing, provided product quality and safety remain unchanged.

Life Cycle Assessment evidence indicates that process configuration significantly influences greenhouse gas emissions and water demand. Integrating sustainability considerations during development can reduce downstream environmental pressures, supporting objectives under the Pharmaceutical Strategy for Europe and broader EU industrial and sustainability policy objectives.

3. Encourage advanced monitoring technologies as optimisation tools

Chemical-specific and near-real-time monitoring technologies, including liquid monitoring and surface inspection systems, can complement established GMP-compliant methods by:

- Supporting risk-based optimisation of cleaning cycles
- Reducing water and solvent use
- Strengthening process evidence generation

Their use supports pollution-prevention objectives without altering compliance requirements under existing GMP frameworks, and contributes to EU pollution prevention and resource efficiency objectives, including under the Zero Pollution Action Plan.

4. Promote alignment with GMP and PAT principles

Broader uptake of advanced monitoring and digital tools can be facilitated through compatibility with established Good Manufacturing Practice (GMP), Process Analytical Technology (PAT), data integrity, and traceability standards, ensuring sustainability-driven optimisation remains aligned with quality and safety requirements, within the EU pharmaceutical regulatory framework.

C. Enhance Integrated Monitoring Across the Water Cycle

5. Strengthen lifecycle-oriented monitoring strategies

Monitoring approaches may integrate:

- Upstream sources, including large clinical facilities
- Wastewater treatment plant influent and effluent
- Receiving environments

High-frequency and on-site analytical tools can complement laboratory methods by improving temporal resolution and identifying episodic emissions.

Such approaches can strengthen proportionate and evidence-based implementation of the UWWTD and WFD, supporting EU water policy objectives.

D. Support Evidence-Based Risk Prioritisation

6. Combine chemical, biological, and predictive assessment tools

Integrated interpretation of chemical monitoring data, effect-based biological assays, and predictive models can improve understanding of combined exposure patterns relevant to regulatory prioritisation.

Such approaches support proportionate, risk-based decision-making under the WFD, UWWTD, EMA ERA guidance, and REACH frameworks.

Added Value for EU Policymakers

ENVIROMED shows that prevention, optimisation, monitoring, and environmental assessment must operate together across the pharmaceutical lifecycle.

By integrating upstream innovation with downstream environmental evaluation, the project contributes to EU ambitions under the European Green Deal, the Zero Pollution Action Plan, the Pharmaceutical Strategy for Europe, and EU water and chemicals legislation, while reinforcing regulatory coherence, proportionality, and evidence based decision making.

About ENVIROMED

ENVIROMED is a Horizon Europe project developing and validating technological and assessment solutions to reduce the environmental footprint of pharmaceuticals across their lifecycle.

Further resources

Information on the project's results and policy-relevant findings is available via the [ENVIROMED project website](#), including public deliverables and publications. The ENVIROMED deliverable *D7.2 – Fact-based report to regulatory authorities* provides a more detailed presentation of these findings and an extended set of policy-relevant recommendations underpinning this brief.

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