



ETERNAL's overall purpose is to contribute to sustainable development of pharmaceutical manufacture, use and disposal, by using and promoting full life cycle approaches covering design, manufacture, use, and disposal. The ETERNAL consortium unites a world class consortium of sixteen organisations from seven countries across Europe.

This includes assessing the environmental risks of active pharmaceutical ingredients, residues, metabolites, and other chemicals and by-products of the production process.



Dr. Pablo Ferrer Pérez
Project Coordinator, AIMPLAS



1. Describe your project through key words/key phrases that identify it.

While emerging green manufacturing processes bode well for the environment, their impacts on industry need to be considered and addressed. The EU-funded project ETERNAL intends to contribute to the sustainable development of manufacturing, use and disposal of pharmaceuticals. It will promote a full life-cycle approach to support this sustainability, as well as assess the environmental risks of the production process. Project research involves a wide scope of case studies. Targeted application of ETERNAL's risk and life-cycle assessment approaches to these studies aims to facilitate the work of industry and policymakers as green manufacturing starts to take centre stage.

2. In terms of impact, what will be the most tangible your project will achieve?

We have proposed a roadmap focused on the use of production methods that are less aggressive to the environment. We also focus on one-step treatment methods of the waste generated, where the drugs are completely metabolized in the body or broken down immediately and harmlessly in the environment. In the same way, we are making progress in achieving a better understanding, modelling and control of the processes involved in several of the ETERNAL case studies. This implies a detailed analysis of all the processes involved in the different cases, both from a qualitative and quantitative point of view. This complex study allows the creation of exact digital twins of each of these procedures. By monitoring virtual systems and process performance and

analyzing the data that emerges from the virtual environment, problems in the real environment can be avoided before they occur and thus optimize the life cycle of the products involved.

Water pollution is one of the main risks, as pharmaceutical waste and APIs often end up in seas and rivers through effluents from wastewater treatment plants, direct discharges or agricultural runoff. This can cause aquatic toxicity, affecting aquatic flora and fauna, and may include hormonal effects, where some APIs act as endocrine disruptors, interfering with the hormonal systems of aquatic organisms.

Another major risk is the persistence and bioaccumulation of many APIs in the environment, which means that they do not degrade easily and can remain in the environment for long periods. These can accumulate in the tissues of living organisms, moving up the food chain and affecting higher predators, including humans. In addition, the misuse and elimination of antibiotics can promote the emergence of antimicrobial resistance, selecting resistant bacteria that can transfer their resistance genes to other bacteria, creating multidrug-resistant strains, and affecting the efficacy of medical treatments.

It has been estimated that up to 80% of the waste derived from the manufacture of APIs is related to the use of solvents, so addressing their selection, use, recovery and disposal can drastically contribute to alleviating this problem. However, as these have a great influence on the quality of the final products, it can be difficult to find suitable substitutes. By applying the twelve principles of Green Chemistry, it is possible to devise more sustainable processes, opening the way, for example, to the use of recognized and environmentally friendly solvents.

One of these options is dry mechanochemical synthesis, which involves joining finely distributed chemicals without the need to use solvents to mix them. This means that no solvent-associated waste is generated and, in addition, the entire process can take place tens of times faster than a conventional reaction. Hot Melt Extrusion (HME) has emerged in recent years as a pioneering manufacturing technology for the pharmaceutical industry, and its use is growing due to its cost-effective, continuous, and solvent-free nature as a unit operation. This, for example, is one of the methods that AIMPLAS applies in the ETERNAL project and that allows us to shorten the production times of final formulations of medicines, while reducing the consumption of resources, both human and energy and material.

In addition to the incorporation of mechanochemistry as a continuous production method, within the ETERNAL project we are working on other methods to reduce the consumption of resources and the production of waste. Optimized processes of distillation, membrane filtration, use of degradative enzymes and photocatalysis to purify and reuse solvents are being developed. These techniques make it possible to reduce the number of solvents needed and minimize chemical waste, thus reducing the carbon footprint and energy consumption.

But we are not only staying in the purely experimental, but we are also working to incorporate digitization and artificial intelligence tools into these processes. The implementation of process analysis tools (PAT) and digital twins allows real-time monitoring and control of manufacturing processes. This facilitates the early detection of problems, the optimization of processes and the reduction of waste and consumption of resources.

We are also conducting specific studies to assess the toxicity of pharmaceuticals and their by-products to ecosystems. Using mathematical models to predict their transport in and around the environment, we will collect monitoring data and produce a roadmap for integrating new scientific knowledge into regulatory risk assessment.

3. Please describe your project's overall impact, if applicable, at the European level.

The European Commission has adopted a strategic approach to pharmaceuticals in the environment that covers all phases of their life cycle, from design and production to use and disposal. Thus, the life cycle of a pharmaceutical product includes several stages: synthesis of active ingredients, formulation, production, distribution, consumption and disposal. Each of these stages has different processes and materials involved, which makes it difficult to carry

out a comprehensive environmental impact assessment.

Another great challenge is the evaluation of the final destination of these products, as they can affect different components of the environment, such as water, soil and air. For example, drug residues can enter marine ecosystems through wastewater treatment plants, affecting aquatic life. Assessing impacts on these various media requires an interdisciplinary understanding and methods specific to each.

The study of the complete life cycle of pharmaceutical products is the basis of the ETERNAL project, as we make a great effort to assess the environmental impact of manufacturing processes to make them more environmentally friendly. Considering current approaches and placing them in the context of the new EU pharmaceutical regulations, we are thus placing more emphasis on environmental risk assessment throughout the entire life cycle of products. We believe that this holistic approach is crucial to providing meaningful environmental protection.

4. As an applicant, what advice would you have wanted in the Horizon project design process? What support did you receive from National Contact point (NCP) and your organisation, and what improvement of support would you benefit from?

In the ETERNAL project we must work closely with the JRC (Joint Research Center), during the preparation we always obtained support from the National Contact Point (NCP) to build a close relationship that has been able to help and lay the foundations for a close collaboration.

From the ETERNAL project we are working closely with companies and organizations in the pharmaceutical sector, which act as advisors so that we guide and align our research with their interests and the regulations they must follow. We are also carrying out awareness-raising activities among the general public so that they know the benefits of medicines produced by more environmentally friendly methods, with the aim of making them prefer these over medicines produced in a more polluting way.

However, all these efforts will end up being in vain if there is not a drastic change from regulatory bodies and governments towards sustainable production. For example, economic benefits, such as grants, credits or tax deductions, can be offered to companies that implement these practices. These incentives can help offset the upfront costs of

adopting green technologies and encourage investment in sustainability.

It is imperative, in turn, to implement stricter environmental regulations that force pharmaceutical companies to comply with sustainability standards. Developing certification programs and eco-labels that recognize and reward companies that meet high sustainability standards can improve the reputation of companies and increase demand for their products by environmentally conscious consumers. It is important to have a support network to be able to work with society and with policy-makers, in this sense the European Commission provides and gives support to carry out the necessary dissemination actions and to be able to reach the largest number of stakeholders.

5. Please highlight aspects of your Horizon project's strengths that you consider important and that may constitute good practice for other applicants.

Like any research and development project, we strongly believe that the selected technological approaches and the underlying science are fundamentally sound and applicable to the challenges they address. We also rely on ETERNAL's co-creative process with companies and bodies in the sector to define industry specifications and requirements, as well as business, environmental and regulatory impact indicators that guide our case studies.

Thanks to the participation of large companies in the international pharmaceutical sector, such as AstraZeneca, Reig Jofré or Angelini Pharma, we are one step closer to making the transition to a more sustainable and environmentally friendly production a reality.

