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Mechanochemistry

Making greener pharmaceuticals

Funded by the European Union

Impactive

Annual Report

Table of contents

Editorial

BY EVELINA COLACINO, IMPACTIVE COORDINATOR

Evelina Colacino

IMPACTIVE Coordinator

Dear readers, it's hard to believe, but we are already approaching the final year of IMPACTIVE. And what a journey it has been. Our strategy has focused first and foremost on protecting the results of our work, which explains why you will find more patents than papers at this stage. We want to make sure our innovations are secure before sharing them widely because we know their potential value for the future of pharmaceutical manufacturing.

At the same time, much of our energy has been devoted to scaling up our discoveries, moving beyond proof-of-concept and towards processes that can truly make an impact at industrial level. This has been a challenging yet rewarding effort, bringing us closer to one of our central goals: demonstrating that mechanochemistry can be greener, safer, and more efficient than conventional methods.

As the project enters its final stretch, the pressure is on. The next months will demand dedication and focus from all of us, but they also promise to deliver some of the most exciting results yet. We cannot wait to share them with you in the coming year.

All yours,

Evelina Colacino

Effective management for better results

A project like IMPACTIVE needs a solid managing and coordination team to steer it towards fulfilling its objectives. This means guaranteeing an effective communication flow between partners and addressing any issues that might arise during the project's lifespan. For a huge consortium such as ours, with 17 partners spread across 11 countries, this is no small thing! Work Package 1 (WP1) has a lot to juggle across the administrative, scientific and financial domains. Thanks to the work of the management team, we are glad to say that **we managed to fulfil all our deliverables and achieve the promising results you'll see scattered across this annual report.**

The WP1 team ensured that the consortium stayed aligned with its goals and objectives and liaised with the European Commission. Their duties also included research data and outputs management, in line with IMPACTIVE's Open Science Strategy.

Ethical and risk management considerations are also central, given the sensitive nature of pharmaceuticals. Clear ethics guidelines were followed without exception. However, our coordinator was not alone in this task. Periodic risk monitoring was conducted by the WP leaders, who provided vital support in identifying and managing potential challenges.

Management, however, is not just about strategy. It is also about fostering communication and collaboration. **Our consortium met virtually at the end of September to review progress and decide on the next strategic steps.** Beyond the annual meeting, each work package held monthly online meetings to ensure that everything remains on track.

Last but not least, management duties included taking care of the financial resources. We know that talking about money is hard, but in a project such as ours, we need to use it wisely so that all partners can implement their work effectively. **WP1 has carefully balanced the budget to meet all partners' needs.**

> “We managed to fulfil all our deliverables and achieve the promising results you’ll see scattered across this annual report”

IMPACTIVE Zenodo community

To ensure open access dissemination, **IMPACTIVE uses Zenodo as its repository for publications and other materials.** Zenodo is a free, non-profit platform launched by CERN in 2013 and supported by the European Commission through OpenAIRE. **It provides long-term preservation, assigns DOIs for easy citation,** and even integrates with platforms like GitHub. This guarantees that IMPACTIVE’s outputs will remain accessible beyond the project’s funding period.

Batch and continuous synthesis at lab-scale

One of IMPACTIVE's main goals is to replace solvent-based steps in the synthesis of active pharmaceutical ingredients (APIs) with mechanochemical alternatives. Over the past year, our colleagues in WP2 have continued to make progress in this direction.

Last year, we successfully completed the total synthesis of some targeted APIs and transversally explored across the other scientific WPs. Building on this achievement, we explored different mechanochemical methods for obtaining the same molecules. This has not only strengthened the robustness of our processes but also ensured flexibility by providing multiple options to select the most effective route.

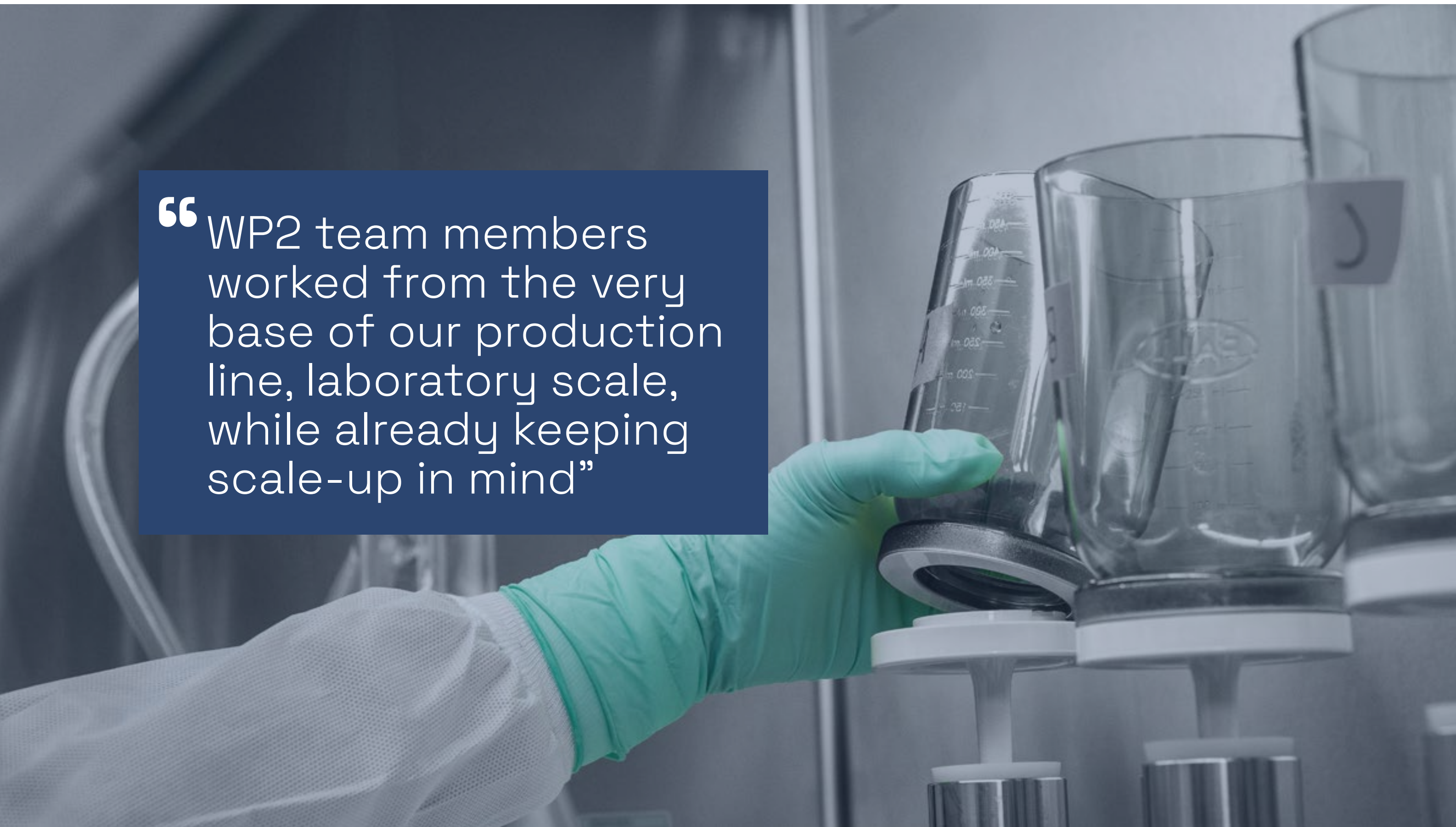
Importantly, WP2 team members worked from the very base of our production line, laboratory scale, while already keeping scale-up in mind. In practice, this means deliberately choosing synthetic pathways that are not only efficient at the laboratory bench but also scalable in future industrial applications.

Our researchers at WP2 have employed a variety of methods to pursue these goals, including ball milling, extrusion and resonant acoustic mixing. One example is highlighted in our recent publication in which we used resonant acoustic mixing to explore different reactions at the multi-gram scale. You can read more about it in our blogpost.

Of course, research is not without its hurdles. Alongside successful results, we have also encountered obstacles, from lower-than-expected yields to new synthesis strategies that did not perform as well as anticipated. These lessons are just as valuable, helping us refine and improve our reactions.

Beyond synthesis itself, understanding the properties of the target compounds is crucial and it could not be tackled without a close interaction with WP3 team members for solid-state characterisations. At the same time, our researchers have been focusing on obtaining enantiomerically pure drugs via solid-state deracemization approaches. This work involves adapting traditional solution-based techniques to a mechanochemical setting.

These results represent important progress, but they are not yet ready for full disclosure: protecting intellectual property is a necessary first step. Several of our findings are currently being protected through patent demands, with WP7 leading this effort.



> “WP2 team members worked from the very base of our production line, laboratory scale, while already keeping scale-up in mind”

Enantiopure **co-crystals**

Straddling WP2 and WP3 lies the achievement of **producing enantiomerically pure drugs.** Some chemical compounds are like our hands: they have the same shape and structure, but they cannot be superimposed. In chemistry, this property is called chirality. Obtaining only one of these ‘chemical hands’, or enantiomers, through synthesis can be achieved by a chemical process known as deracemisation. This involves **converting one enantiomer into the other, so we don’t waste any.** Why is this important? Both enantiomers can behave very differently, and usually only one is the desired target. It is well known how to achieve this with current solution-based deracemisation techniques. The tricky part is doing it in a mechanochemical setting and this is precisely what our experts have focused on over the past year.

Improving APIs properties
through multicomponent systems

Multicomponent pharmaceutical materials are solid forms in which at least one component is an API. The development of new multicomponent crystal forms offers an opportunity to create medicines with enhanced properties such as solubility, stability, and bioavailability, bringing clear public health benefits. Within IMPACTIVE, this area is a central focus, addressed by a dedicated WP, this one.

The rational design of multicomponent forms of APIs began at the project's launch and was completed last year. Through extensive data mining of scientific databases and literature searches, WP3 has identified promising combinations and has developed several new crystal forms for different target APIs. Many of these multicomponent systems involve compounds that are either naturally occurring or considered safe for use.

Once identified, the focus shifted to the actual mechanochemical synthesis. These reactions were implemented and optimised to deliver the desired products. Here, IMPACTIVE researchers have explored a wide range of reaction parameters, including milling time, ball size and material, milling frequency, catalytic solvents, and jar composition. For comparison, they have also conducted synthesis in solution and slurry conditions.

> "WP3 has identified promising combinations and has developed several new crystal forms for different target APIs"

Characterisation of APIs and multicomponent systems has been essential, supporting both WP2 and WP3. As mentioned before, structural evaluation has relied primarily on X-ray diffraction techniques. The resulting data has been vital in determining which systems progress to WP4, WP5, and WP6 for further ex situ and in-situ characterisation, kinetic studies, scale-up, impurity checks, and life cycle assessments.

WP3 also investigates multicomponent systems in the context of formulation, gathering the information needed to select the best systems and conditions for launch. Recent work has focused on incorporating excipients by spray drying from ball milling protocols, with particular emphasis on a specific system that remains confidential for now. You'll might need to wait for the next annual report to discover it.

Kinetics and reaction mechanisms

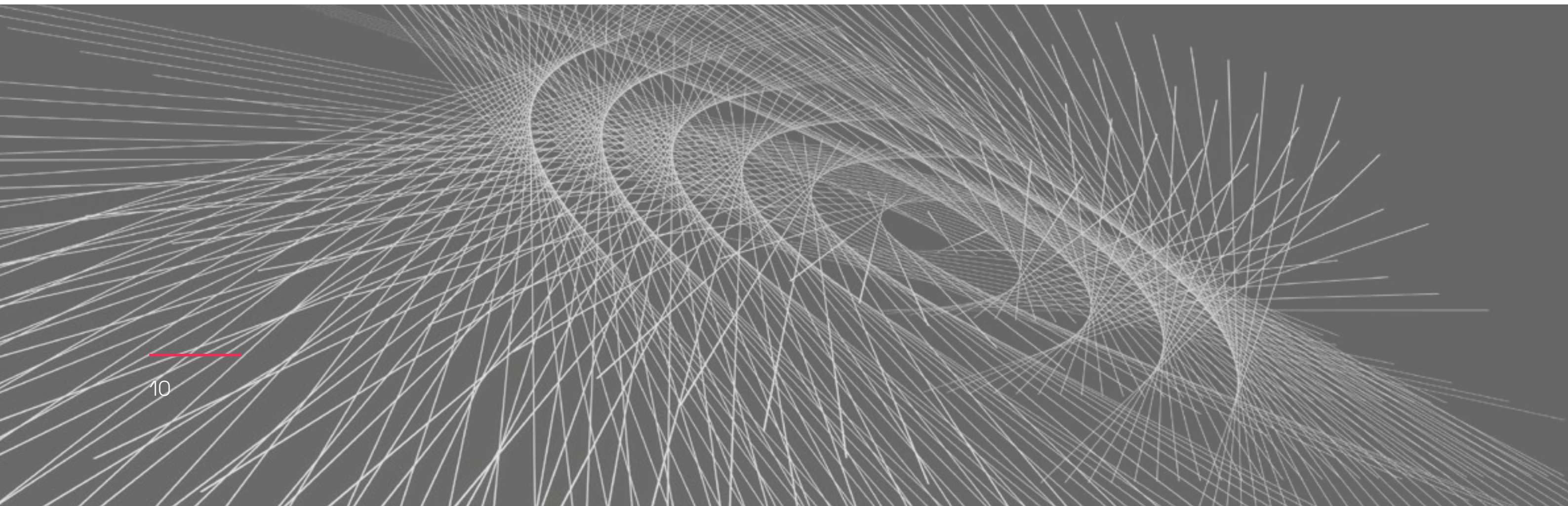
What happens between molecules when they are smashing with each other? WP4 team looks at reactions really, really closely. The aim is to understand how atoms and molecules behave upon mechanical stress, to analyse reaction rates and optimise reactions.

Over the past year, this work has evolved applying the numerical simulation codes previously developed to describe the milling dynamics in ball mills. We were able to accurately reproduce these dynamics, even generating short videos that map ball movements inside the reactor. This is of great help to simulate different configurations, varying impact velocity, angle and frequency, and then choose those that deliver the best performance in our experiments. While ball mill is our best characterised technique, other equipment such as resonant acoustic mixers and extruders are also under assessment.

In parallel, the team has generated high-quality kinetic datasets to validate theoretical models and provide detailed descriptions of mechanochemical processes. This required ex situ and in-situ monitoring of the reactions. Reaction characterisation has involved also optimising experimental protocols to ensure reproducibility and robustness in data acquisition. This was essential as the second part of this task involved modelling reaction kinetics.

WP4 extended the kinetic modelling framework to scenarios where reactions are driven simultaneously by mechanical and thermal contributions. This was thanks to different kinetic models to extract local kinetics transformation factors from the thermal contribution based on global kinetic data.

But the main achievement here has been modelling versatility: the ability to compare kinetic data obtained under different milling conditions and with different types of equipment, regardless of the specific mechanochemical setup. As a result, WP4 has provided a robust basis for extrapolating lab-scale results to larger-scale processes, thereby supporting the scale-up activities foreseen in WP5 and WP6.



From gram to multigram

and hopefully to kilogram

At the laboratory level, only a few grams of a drug can be obtained. However, to move from promising research to practical application, we need to scale up to commercial production levels. This is where WP5 plays a pivotal role. WP5 team works to achieve kilograms of APIs, which usually means refining some aspects of the reactions to ensure efficiency.

Last year, we made significant progress within this WP. Even though we cannot disclose publicly the outputs for the moment, WP5 provided valuable insights into operational parameters, scale-dependent challenges, and the capabilities of different milling devices. Building on these findings, the focus has now shifted towards the mechanochemical synthesis of target APIs and their key intermediates.

We cannot disclose (yet) the specific molecules we are working with. However, we can say that the scaling up of the previously optimised reactions is ongoing, ensuring that each stage of development is carefully validated to establish a strong foundation for a possible industrial-scale implementation. Both batch and continuous processing approaches are under evaluation, broadening the range of potential industrial applications. WP5 is working also on adjusting and optimising every step, alongside the development.

A central objective of this work is to identify sustainable upscaling strategies. All processes are being designed to comply with the 12 Principles of Green Chemistry and the 12 Principles of Green Engineering. Preliminary strategies for the recovery and recirculation of both material and energy streams have already been defined, with the aim of improving overall efficiency while reducing environmental impact.

Together, these advances are expected to deliver robust, reproducible, and scalable processes for API production. The ultimate goal is ambitious: production capacities of many kilograms per day in an industrial plant. An initial schedule for industrial-scale implementation has also been drafted, paving the way for future large-scale production. Supported by data from other work packages, WP5 is laying the foundation for sustainable and scalable manufacturing of APIs, bridging the gap between laboratory innovation and real-world impact.

> “WP5 is laying the foundation for sustainable and scalable manufacturing of APIs, bridging the gap between laboratory innovation and real-world impact”

More data are needed

“More data are needed” is a mantra repeated over and over in research articles everywhere. However, to innovate is to tread where no human has gone before. And in WP5’s case, it’s been a real struggle. To scale-up the reactions, **WP5 partners need to look deeply into the physicochemical information about the reactions under study.** And sadly, there’s no unified source of information to go to. So, the researchers in WP5 have delved deep into the literature, to obtain the parameters they need in their calculations from trusted sources. When data are not publicly available, the partners responsible for experimental characterisation jump to the rescue—when they can—to determine those properties in the lab.

Even greener mechanochemistry

Mechanochemistry has already been established as a sustainable way to do chemistry, yet within IMPACTIVE we want to push these boundaries further. WP6 is leading this effort by applying life cycle assessment (LCA), techno-economic analysis (TEA), and green chemistry tools to evaluate the environmental footprint of the new mechanochemical processes under development in IMPACTIVE. The objective is to replace traditional steps in the manufacturing of APIs with greener, safer, and more efficient methods.

To do this, the WP6 team has measured material and energy flows across the full life cycle of targeted APIs. By tracking green chemistry metrics, WP6 researchers can assess the economic, environmental, and human health implications of new processes. At the same time, eco-design principles can be applied to minimise waste, reduce pollution, and mitigate risks linked to production. An important element of this work has been the identification of hazardous impurities and eco-toxic pollutants and implement ad hoc mitigation measurements, together with solutions for waste management and material recycling.

Our experts developed a workflow that includes routine analysis of impurities and evaluation of green chemistry metrics, supporting several work packages. This approach was validated in the mechanochemical synthesis of the model compound Imatinib and could eventually be applied to our target APIs.

To understand the broader impact, WP6 has analysed the mechanochemical processes developed across the other WPs using different mechanochemical technologies such as ball milling, resonant acoustic mixing, and twin-screw extrusion, from the point of view of environmental and economic data. These studies revealed the challenge of impurities formation in some cases, leading our partners to adjust the mechanochemical synthesis, processes and nature of raw materials to move towards pollutant-free products. This highlighted the critical importance of robust protocols. Another significant outcome was the establishment of a baseline and the identification of data gaps that will guide future improvements. Performance comparison between different mechanochemical approaches were also compiled and they could design mitigation measures based on identified hotspots.

IMPACTIVE consortium has still some work to do: implementing solutions that meet both the Twelve Principles of Green Chemistry and pharmaceutical standards. We are fully committed to achieving this goal, thereby paving the way for a cleaner future in pharmaceutical manufacturing.

> “The WP6 team has measured material and energy flows across the full life cycle of targeted APIs”

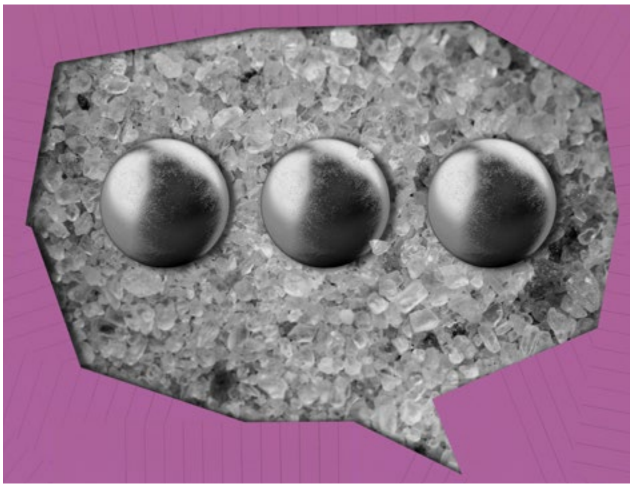
Life-cycle assessment (LCA) to achieve more sustainable products

Life-cycle assessment (LCA) is **a comprehensive approach for evaluating the effects that a product, process, or service has on the environment.** In the pharmaceutical industry, this means looking well beyond the laboratory or factory floor. LCA considers every stage, from the extraction of raw materials and the synthesis of APIs to formulation, packaging, distribution, use, and end-of-life disposal or recycling. This powerful tool does more than quantify environmental impacts. It also helps identify opportunities to minimise them, such as reducing resource consumption, lowering emissions, or improving waste management.

Increasing the project's visibility

We not only do science, but we also explain it to make IMPACTIVE understandable to everyone while increasing the project's visibility. Communicating and disseminating about the project and its results involve many different actions. Through our social media channels (X and LinkedIn) and our website, we have been sharing our latest developments, from publications to events, as well as writing more in-depth articles, such as this feature on solvents and the risks associated to their use. This is one of the driving forces in using mechanochemistry as a solvent-free approach to chemistry, as we do at IMPACTIVE.

But without doubt, one of the main novelties in our communication efforts during the last year was the launch of the IMPACTIVE webinar series, focusing on mechanochemistry — of course! The first three sessions featured the coordinator, Evelina Colacino, and two of the sister projects, ETERNAL and TransPharm. They are available on the IMPACTIVE YouTube channel, but more is to come...



Another important milestone was the design and development of the Educational Platform, a meeting point for teveryone interested in the field, which was released in September 2025.

This WP has also showcased the project at various events, including the joint participation of the communication and exploitation partners at The Pharma Days and The Pharma Sustainability Days in Geneva (Switzerland), where they delivered an oral presentation on the project and hosted a booth. Our exploitation partner also took part in CPHI in Milan (Italy), where numerous valuable contacts were made regarding the potential exploitation of the project's outcomes.

Following the European Commission's motto "as open as possible, as closed as necessary", the consortium has decided to prioritise patents, currently at various stages of the patenting process, and two additional ones now in preparation.

> “One of the main novelties in our communication efforts during the last year was the launch of the IMPACTIVE webinar series”

IMPACTIVE Educational Platform

Mechanochemistry is on trend, with more and more people showing interest in this promising branch of chemistry. However, resources remain limited, and the actors involved do not always know each other. **We want to change this by launching our educational platform.**

The two key pillars that build this knowledge hub are a rich repository of resources and a network to connect with other initiatives. Our final goal is to bring together individuals and institutions to actively participate in the platform, which will be the core of a vibrant community ‘thinking chemistry differently’.

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