

ANNUAL REPORT



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IMPACTIVE

Building a greener
chemistry

MECHANOCHEMISTRY



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ANNUAL REPORT

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Foreword

by **Evelina Colacino**, **IMPACTIVE Coordinator**

IMPACTIVE is a very ambitious project, with a clear industrial perspective. We want to **get rid of the solvents** in the current pharmaceutical processes **and substitute them with mechanochemistry**, a greener, more sustainable approach. The first year of IMPACTIVE is now over, and it has been a rush.

During these initial 12 months we have explored new synthesis routes towards different pharmaceutical compounds. Currently, **we're exploring many different routes to produce Active Pharmaceutical Ingredients (APIs) of three main families**: anticancer, antidiabetics and antihypertensives. To do this, we harness a myriad of techniques: ball milling, extrusion, resonant acoustic mixing, spray drying... the list goes on and on. We are leaving no stone unturned in our quest to develop mechanochemical replacements for the pharmaceutical industry.

And because we want to produce actual alternatives, we have also started to analyse which of these new pathways are more easily scalable. This involves a ton of factors: from evaluating environmental impacts, that guarantee that the processes we design are indeed greener, to socioeconomic analysis, so we develop solutions that are more attractive to the industry. We want to transition from grams to kilograms, so we have to make sure that our discoveries are able to go big.

After one year of hard work, one of my takeaways as IMPACTIVE coordinator is that **mechanochemistry forces you to reimagine everything, all the time**. We have to come up with new chemical reactions that don't use solvents, we need to design scalable processes, and adapt laboratory techniques to work without solvents. To do all this, the key lies in collaboration. We count on 15 excellent partners, highly specialised, that cover every facet of IMPACTIVE: from very specific techniques to crafting a sound IPR management of the project that ensures our results are commercially exploitable. We have a mixed team of people working in academia, industry and innovation hubs that works together. And this puts us in a unique position to tackle the challenges that come our way.

For this second year, I'm really looking forward to seeing two things: our first advertised results, and our first scaling-up trials. Let's hope and work towards a second successful year!



Evelina Colacino

IMPACTIVE Coordinator

Discontinuous & continuous processes



If you have ever tried to quit smoking, you'll know that letting go of old habits is hard. And it's especially hard at the beginning. We're just at that point with the pharma industry. We're trying to let go of the old, solvent-savvy processes, and develop new, solvent-free mechanochemical alternatives to manufacture APIs. **When scaled-up, these reactions could change the way we manufacture certain drugs.** And WP2 is where all starts. This WP is responsible for identifying viable alternatives at a lab scale. The partners in WP2 use a wide array of techniques like ball milling, resonant acoustic mixing, extrusion and many others.

One of the key goals of WP2 is to develop **greener and safer synthetic routes that sidestep the use of harmful gases and corrosive reagents.** During this year, our partners have been working hard at several synthesis routes. We cannot give you many specifics (we have to take IP protection seriously). However, you can glimpse a good example at the poster [we presented at IUPAC 2023](#). On it **we presented mechanochemical alternatives to three traditional, solvent-based reactions.** And this is just the beginning. You will hear more about this once we undergo the proper IPR protections.



From lab to scale

Our journey doesn't halt in the laboratory. WP2 works in close collaboration with WP4 (kinetics), WP5 (scale-up) and WP6 (LCA, safety & risk) to ensure the seamless transition from laboratory-scale experiments to larger production processes.

The continuous flow processing conditions, powered by reactive extrusion methods and beyond, bring a new dimension to pharmaceutical manufacturing. Furthermore, we are using cost-effective and recoverable catalysts, which adds an extra layer of innovation, making processes not just greener but also economically feasible.

Multicomponent forms & formulation



Multicomponent systems like cocrystals and salts, hold the potential to revolutionize drug formulation, enhancing the efficacy, solubility, and stability of APIs. IMPACTIVE runs at the forefront of pharmaceutical innovation, so we have devoted an entire Work Package to multicomponent systems. We do so with a mix of techniques: mechanochemical processes in batch and continuous modes, as well as spray drying. But it doesn't stop there. A rigorous characterization comes into play, ensuring that each new formulation aligns with quality standards and the desired properties.



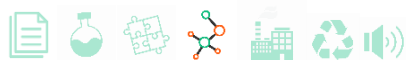
WP3 isn't just about innovation; it's about responsibility. Sustainability takes center stage. Together with WP6, the greenness of the systems and processes is quantified, through quantitative metrics and rigorous pollutant & impurity analysis.

undergo meticulous evaluation to prove their potential as game-changers in drug formulation. Their enhanced properties, from solubility to stability, paint a vivid picture of the future of pharmaceuticals.

During this first year, our team has been working on different approaches towards one-pot synthesis, since these reactions exemplify and how mechanochemical methods could simplify the manufacturing conditions for pharma. The rest of our work has been preparatory: mostly doing literature reviews for other target molecules.

As multicomponent systems materialize, the focus shifts to the world of formulation. The selected systems

Kinetics



In the intricate tapestry of manufacturing, time reigns supreme. Every cog, every process must mesh harmoniously to ensure products roll off the line punctually. In the pharmaceutical realm, this rhythm is no different. And so, **time plays an instrumental role in the reactions we're designing**. We want to produce APIs at the highest rate possible: this means that the reactions must happen as fast as possible, while producing as little waste as possible. For IMPACTIVE, that means that we have a dedicated group of partners working in chemical kinetics, to redefine the pace and precision of API synthesis.

Solving a collision puzzle

Our colleagues at CSGI are developing a novel form of spectroscopy, to unravel what goes on at a microscopic level when two ball mills collide. This unique experimental setup allows them to point a laser to the collision point of a ball mill, a mere square millimeter wide. It goes down to a temporal resolution of microseconds, allowing our team to extract valuable information about the chemical reaction.

Our team at WP4 looks at reactions really, really closely. We want to **understand how atoms and molecules behave** in ball mills, extruders and other mechanochemical equipment, to analyse reactions rates and optimise reactions. This involves tasks like doing numerical simulations of reactions or developing unique experimental settings to measure local reaction conditions.

To have a coherent methodology throughout the project, our partners at BAM have worked on a model

system to develop an experimental protocol. This systematic guide forms the bedrock for all partners within IMPACTIVE. **A unified approach ensures that insights from the molecular level resonate across the project**, enhancing the collective ability to harness kinetics for groundbreaking results.

On the more experimental side, our colleagues at MPI a collaborative force between academia and industry. Thanks to their access to industrial mills, they are able to perform experiments under different modes: cascade and cataract. Their aim? To find the best conditions for synthesising APIs: those that show the highest yield and conversion rates.

WP4 bridges the gap between theory and practice. By dissecting reactions at their core and formulating methodologies that ripple across IMPACTIVE, this team is instrumental in **transforming abstract concepts into tangible results**. Their joint work yields new methodologies and insights used by the whole consortium and is a testament to the collaborative spirit driving IMPACTIVE.

Scaling-up + Sustainability



Our Work Packages 5 and 6 merge groundbreaking mechanochemical processes with eco-friendly methodologies. Their mission? To **scale up, optimize, and enhance the pharmaceutical synthesis** developed in other WPs, while making sure they stay aligned with green metrics.

Work Package 5 (WP5) assumes the mantle of scaling up IMPACTIVE's most promising case studies from Work Packages 2 and 3, setting the stage for large-scale production. WP5's ambition extends beyond mere upscaling; it involves **integrating experimental evidence with modelling results** to automate production processes and optimize efficiency.

According to the initial plans, WP5's work didn't start until much later on the project. However, **different companies supported us and granted access to industrial milling**, which enabled our team to carry out experiments up to a kg range. One key feat achieved by WP5 is the upscaling of the synthesis of a pharmaceutical cocrystal, combining ibuprofen and nicotinamide. The results are promising: **we scaled things up to the kg range, at a conversion of 100%**. This remarkable achievement, which required collaborative efforts with industrial partners, showcased the successful transition from lab-scale to kilogram-range production.

WP6 is our guiding beacon, applying life cycle assessment, techno-economic analysis, and green chemistry tools to assess the environmental impact of IMPACTIVE's mechanochemical processes. Our partners champion the delicate balance between innovation and environmental responsibility.

One key tool in this WP6 is DOZN 2.0: Green Chemistry Evaluator developed by MERCK. One of the main achievements for this first year involves **applying the DOZN 2.0 Green Chemistry Evaluator to benchmark the batch process of pharmaceutical cocrystals** against the Twelve Principles of Green Chemistry. This systematic evaluation ensures that the most promising processes align with principles of sustainability and minimal ecological footprint.

Mechanochemistry means more than getting rid of solvents

At the very core of WPs 5 and 6 lies a keyword: metrics. We need to be able to measure the impact our reactions have in the outside world. Because we do more than *just getting rid of solvents*. Mechanochemical reactions use less energy and have, overall, less environmental impact. But to back up that with data, we need green metrics. Back in September 2023, part of our team published a paper reviewing the use of green metrics in mechanochemistry. So, if you want to talk about atom and real atom economy, E-factor, process mass intensity, Eco-scale, and much more, [head to the Chem. Soc. Rev. for a juicy article.](#)

Management & CDE



Without organisation and communication, research results get nowhere. These two workpackages are focused on making sure that our project runs smoothly and **amplify the IMPACTIVE's reach, fostering collaborations with diverse stakeholders** – from academia and industry to policymakers and the general public. A lot of the work in this first year has been preparatory: establishing clear internal processes, setting up a consistent communication plan, and start designing a to-the-market and Intellectual Property Rights (IPR) strategy.

IMPACTIVE brand was designed by AGATA and resonates across all the materials in the project. Its bright colour palette and bold typography, joined by clear design elements, sure make a lasting impact. Explainer animations, brochures, videos... the team has been busy preparing the initial pack of communications materials. All of them [available through mechanochemistry.eu](https://mechanochemistry.eu). Our online activity goes beyond the website. Our social media profiles of IMPACTIVE have been busy with **initiatives like #MechanoMondays**: small pills of mechanochemistry that you can enjoy every Monday – while you prepare for the working week ahead!

Since we're a collaborative bunch, we are building bridges with other projects. Overall, our team has attended over 5 different congresses, presenting IMPACTIVE results. Particularly meaningful for us was the joint PREMIER and Transpharm workshop, held in The Netherlands last April. Organised by two sister European projects, it showcases the project's collaborative spirit, yielding cross-project connections that strengthen the fabric of scientific innovation.



IMPACTIVE consortium at our yearly meeting

(Lisbon, 21-22 September 2023)

Icing of the cake, our partner SATTAs focus on nurturing the seeds of project exploitation and managing IPR. Their expertise guides us in charting a course for the future, **carefully identifying potential collaborators in the pharmaceutical industry**. The task's strategic significance is mirrored in the meticulous IPR management plan, which lays the groundwork for responsible and impactful exploitation.