

Brussels, 13 November 2018

COST 093/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action
“Mechanochemistry for Sustainable Industry” (Mech@SustInd) CA18112**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Mechanochemistry for Sustainable Industry approved by the Committee of Senior Officials through written procedure on 13 November 2018.



MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18112 MECHANOCHEMISTRY FOR SUSTAINABLE INDUSTRY (Mech@SustInd)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

- a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
- b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
- c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
- d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to create a multi-disciplinary, collaborative network of European and international scientists, engineers, technologists, entrepreneurs, industrialists and investors aiming to promote fundamental and applied research in mechanochemistry and its implementation in European industry, bringing mechanochemistry into the present and future technological framework of innovation and enhancing the competitiveness of European chemical industry. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 80 million in 2018.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary

The present COST Action focuses on the great promise, and unexpressed potential, shown by Mechanochemistry within the contexts of chemical, pharmaceutical industries, and process engineering.

Organic mechanochemistry has been shown to enable the reduction, or the elimination, of solvents, while ensuring increased yields and scope of substrates compared to solution-phase synthesis, better crystallinity of final products, and access to products that can be formed only under mechanical activation conditions. This COST Action aims at establishing a multi-disciplinary network of European scientists, engineers, technologists, entrepreneurs, industrialists and investors addressing the exploitation of mechanical activation in the production of chemicals through sustainable and economically convenient practices on the medium and large scales.

Specifically, this Action addresses the objective of harmonizing fundamental and applied research with technological innovation and industrial needs, representing the necessary step for enhancing the impact of mechanical processing onto organic synthesis and transferring specific knowledge into the industrial value chains. The Action aims to nucleate a critical mass of actors from EU research Institutions, enterprises and industries, bringing together different areas of expertise and application. The creation of an authoritative community to promote the study of mechanochemistry and encourage its utilization in production processes will catalyze strategic advances in European chemical industry. The favorable features of mechanically activated (organic) transformations is expected to enable the attainment of far-reaching objectives connected with the development of green economy, the improvement of European market competitors' capabilities, the innovation of process engineering, and the growth of a new generation of specialized researchers.

<p>Areas of Expertise Relevant for the Action</p> <ul style="list-style-type: none"> ● Chemical sciences: Green chemistry research ● Chemical sciences: Sustainability ● Chemical engineering: Sustainable engineering ● Chemical sciences: Chemical reactions: mechanisms, dynamics, kinetics and catalytic reactions ● Chemical engineering: Process chemistry and technology 	<p>Keywords</p> <ul style="list-style-type: none"> ● Green Chemistry ● Mechanochemistry ● Green Energy ● Sustainable Process Engineering
---	---

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

- The identification of specific mechanochemical reactions (condensations, multicomponent, cascade, domino, organo- or metal-catalysed, etc.) which are currently prepared by conventional solution based routes leading to common synthetic problems.
- The exploitation of mechanochemical transformations to enable the preparation of chemicals that cannot be prepared by thermal treatment in solution allowing to access to new compounds.
- The environmentally sustainable production of compounds and materials of industrial interest by solvent free or liquid-assisted grinding (LAG) mechanochemical procedures.
- The development of new solvent-free processing methodologies and the design of new reactors to allow the industrial scale-up of mechanochemical processes.
- The development of equipment and procedures to perform in situ real time ball milling.
- in silico investigation of ball milling reactions supported by further suitable experimental methods (e.g. single molecule force spectroscopy studies).

Capacity Building

- Entrepreneurs, industrialists, investors, decision makers and suitable research groups within this COST Action are invited to identify specific industrial needs, jointly propose and investigate the most convenient, viable and innovative mechanochemical routes to prepare the identified products at laboratory scale with a view to scaling up for the chemical industry.
- Integration of expertise and capabilities oriented at problem solving in specific areas of scientific and engineering research. The aim of this objective is to create multi-disciplinary task forces possessing the critical mass needed to overcome difficulties and provide responses to selected questions along the entire value chain for chemical production.
- Creation of a European Society for Industrial Mechanochemistry
- Education of young researchers, training of specialised scientists, engineers and technologists, promoting excellence and cross-fertilization among different fields of expertise. This approach is expected to raise awareness of innovation opportunities in the chemical industry which should result in new developments in mechanochemistry.
- Provide support to women in the field of mechanochemistry to take leading roles.
- Provide support to emerging groups from countries with less research capacity, despite the high potential of research development, and favour the involvement of under-represented gender in the topic of the Action.
- Discover and identify new opportunities for SMEs via the interaction with the ends of the value chains
- Facilitate growth, mobility and future leadership of Early Career Investigators, for example through Short-Term Scientific Missions (STSMs) and through the participation to Research Excellence Programs
- Involve new market sectors related to pharmaceutical, agrochemical, cosmetics, energy, food additives, polymers and biomass transformations.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The European Union (EU) is facing major challenges. Social, political and economic factors undermine the integration and the cooperation among EU countries. A range of pressures originating from global recession, slow economic growth, and high unemployment significantly depress the economy. The crisis is posing a serious risk to the industrial system. The rise of Asian and other emerging industrial powers has determined significant shifts in global trade and capital flows, altering the geography and inherent structure of value chains. Regulatory framework, volatility of demand in goods and services, access to international market and raw materials, trade negotiations, and energy prices and supplies definitely affect EU industry, requiring strongly cooperative securing strategies. The chemical industry is one of the largest manufacturing sectors in Europe, and a strategic enabling activity. EU organisations and programmes have repeatedly emphasized its pivotal role in providing innovative materials and technological solutions to enhance and support the competitiveness of EU industry as a whole. Presently, the chemical sector is undergoing rapid structural changes to meet the demand for innovation and competitiveness on the global level, thus maintaining the leadership in the development of Key Enabling Technologies in the attempt of providing strong solutions for societal challenges such as climate change, health, and nutrition. The Mechanochemistry for Sustainable Industry (*Mech@SusInd*) network is formed to face several challenges which are in the EU agenda. EU is presently calling for strong actions to stop, or mitigate, climate change via a suitable programme of measures. In chemical processes, the attention is focused on the reduction of solvent waste, the possibility to use less toxic solvents or reagents, atom economy to diminish the excess of reagents used and the number of steps involved in the synthesis and to prevent the need for purification processes. Another fundamental point is the quest for new raw materials which can be an alternative for critical raw materials or in anticipation of the possible reduction in global availability of certain materials. Finally, technological leadership, innovation, and integration represent the historical sources of competitive advantage for the EU chemical industry. In this regard, a significant opportunity is taking shape for EU to take the lead in a scientific and technological area that shows significant promise to beneficially impact the chemical sector in terms of product and process innovation, competitiveness and sustainability. This technological area is mechanochemistry. Mechanochemistry is the branch of chemistry focusing on the activation of chemical transformations by mechanical stresses in the solid state in the absence of solvents, though traces of solvents can be successfully used in this predominantly solvent-free reaction. Mechanochemistry can potentially accomplish in a solvent-free way the same reactions as currently are being performed in solution in laboratories and industry worldwide, with a drastic reduction of the solvent waste. Solid-state reactions allow the exploration of new synthetic pathways which can lead to new control over stereoselectivity, stoichiometric efficiency, atom economy and formation of nanotechnology products. Moreover, the different processes of the reactions lead to the investigation and access to poorly soluble, but cheaper reactants or new raw material. Europe is fully in the position to take lead of innovation in this area with crucial returns for other strategic sectors of chemical industry and manufacturing activities. Indeed, history of mechanochemistry roots in Europe and the largest community of researchers involved in mechanochemistry still resides in European countries. Physicists, chemists and engineers form a multi-faceted community with long tradition in mechanochemical studies and unique expertise to spend in enabling technologies. Beside them, a community of technologists,

entrepreneurs, industrialists and investors are ready to address the exploitation of mechanical activation methodologies in the production of chemicals. For Europe, taking the lead in mechanochemistry is a unique opportunity of scientific and technological growth that intrinsically bears the promise of sustainable innovation in chemical industry and definite stimulation of economy.

1.1.2. RELEVANCE AND TIMELINESS

Entitled Mechanochemistry for Sustainable Industry (*Mech@SusInd*), this COST Action aims at defining far-reaching objectives connected with the development of so-called green economy, the improvement of European market competitors' capabilities, the innovation of process engineering, and the growth of a new generation of specialized researchers and technicians in the area of mechanochemistry. *Mech@SusInd* addresses the establishment of a multi-disciplinary collaborative network of stakeholders from European research institutions, enterprises and industries with the objective of harmonizing fundamental and applied research with industrial needs and fostering technological transfer from research labs to industrial value chains. Following decades of study, mechanochemistry has been shown to have unexpressed innovation potential in the fields of materials science, process engineering, chemical synthesis and nanotechnology. Not only mechanochemistry shows the promise of enabling new materials solutions to strategic aerospace, automotive and energy industries, but also fostering technological advances in industrial processing and providing alternative and sustainable routes to specialty products for chemical and pharmaceutical industries. For instance, mechanochemistry by ball milling or screw extrusion offers a valid and inherently solvent-free green alternative to conventional solution based synthesis of organic compounds. It also allows safer processes, with simplified work-up procedures leading to reduced solvent waste and costs. In those applications, when ball mills, due to high impact forces, are too hard for a given reaction, the extrusion process allows enhanced finite control of the mechanical force being applied to the materials, particularly as the screw configuration is customisable, the mechanical force being applied can be modified based on the synthesis being carried out. As a result, there are mechanochemical alternative opportunities to ball mill for energy sensitive materials to be employed or synthesised using a continuous, predominantly solvent-free process. Overall, the knowledge in mechanical activation methods appear mature enough for helping re-thinking organic synthesis and for fostering innovation in small-medium enterprises (SMEs) and industry. A wealth of metallic and inorganic solids, organic-inorganic composites and co-crystals have already been prepared by mechanochemistry. Pilot-plant scale facilities for soil decontamination and biomass activation by mechanochemistry operate in Germany, Japan, New Zealand and United States.

The dissemination of the advances in mechanochemistry has been to date addressed by organising specialised international conferences. The International Conference on Mechanochemistry series [INCOME in Kosice (1993 and 2017), Novosibirsk (1997 and 2006) Prague (2000), Braunschweig (2003), Jamshedpur in India (2008), Montenegro (2011) and Krakowand (2014)] has seen a constant increase of participants. In USA, the Material Science and Technology conference (MS&T, 2016), the first Symposium in Mechanochemical Synthesis and Reactions in Materials Science attracted up to 45 presentations, the MS&T 2017 in Pennsylvania having similar success. Symposia more specific to organic chemistry in mechanochemistry inside the EU, are: *First and Second Symposia in Mechanochemistry and Solvent-free Synthesis* (Ireland, 2009 and 2011), *International Symposium on Mechanochemistry in Synthesis and Nanoscience* (Poland, 2013) and *Mech'Chem* (France, 2015). Outside Europe the *RSC Faraday Discussions 170: Mechanochemistry: From Functional Solids to Single Molecules* (Canada, 2014), *International Symposium on Mechanochemistry* (China, 2015), and *Pacificchem: Mechanochemistry and Solvent-free Synthesis* (Hawaii, 2015) had a broader view on mechanochemistry. In all these conferences, companies involved in the mechanochemistry have provided active support and have established strong collaborations with research groups. Special issues from Royal Society of Chemistry (RSC) («Mechanochemistry: fundamentals and application in synthesis» in *Chem. Comm.* **2012** and *Chem. Soc. Rev.* **2013**, *18*, 7487 and *Beilstein J. Org. Chem.* **2017**) and two books («Ball Milling Towards Green Synthesis: Applications, Projects, Challenges» *RSC Green Chemistry Series*, 2015 and «Mechanochemical Organic Synthesis» Elsevier, Amsterdam, 2016) have been published to highlight recent cutting-edge achievements in the field.

For Europe, taking now the lead in mechanochemistry is a unique and timely opportunity of scientific and technological growth that intrinsically bears the promise of sustainable innovation in the chemical industry and definite stimulation of the economy. The first step in this direction involves enhancing the cooperation within the existing community of researchers and coordinating their investigation via the creation of an authoritative, tightly bound network of stakeholders committed: (i) to promote the development of mechanochemistry, (ii) to address its application in academia as a synthetic tool, and

its utilization in industrial production, (iii) to innovate processing methods and catalyse strategic advances

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

The main research coordination objective of this COST Action *Mech@SusInd* is to create a multi-disciplinary, collaborative network of European and international scientists, engineers, technologists, entrepreneurs, industrialists and investors with the aim to promote fundamental and applied research in mechanochemistry and its implementation in European industry. This objective should bring mechanochemistry into the present and future technological framework of innovation and result in the competitiveness enhancement of European chemical industry. Specific objectives include (i) the identification of specific mechanochemical reactions (condensations, multicomponent, cascade, domino, organo- or metal-catalysed, etc.), which are currently prepared by conventional solution based routes leading to common synthetic problems. These problems are likely to be overcome by suitable mechanochemical procedures, (ii) The exploitation of mechanochemical transformations to enable the preparation of all types of chemicals that cannot be prepared by thermal treatment in solution allowing to access to new compounds, such as the coupling reactions of sulfonamides with carbodiimides (*Chem. Commun.* **2017**, 53, 901-904), (iii) the environmentally sustainable production of chemicals and materials of industrial interest by solvent free or liquid-assisted grinding (LAG) mechanochemical procedures, (iv) the development of new predominantly solvent-free processing methodologies [e.g. neat grinding (NG) and liquid-assisted grinding (LAG)] and the design of new reactors to allow the industrial scale-up of mechanochemical processes, (v) the development of equipment and procedures to perform *in situ* real-time studies of ball milling and (vi) *in silico* investigation of ball milling reactions supported by further suitable experimental methods (e.g. single molecule force spectroscopy studies).

1.2.2. CAPACITY-BUILDING OBJECTIVES

Mech@SusInd aims at exploiting the expertise, strengthening the skills, enhancing the competencies and improving the abilities of the whole community of scientists, engineers, technologists, entrepreneurs, industrialists and investors interested in the exploitation of mechanical activation methods for innovating the industrial production of chemicals. These objectives can be realistically achieved only if all the stakeholders involved in *Mech@SusInd* share innovative ideas and resources within a framework of full co-operation. Innovating the chemical industry working on specialty and niche applications is a challenging task. It requires the participation of a multidisciplinary, future-oriented platform facilitating the fruitful interaction between experts of fundamental chemical sciences, process engineering, technology transfer and manufacturing, all sharing an interest in innovation and sustainability. This COST Action will provide a unique opportunity for individual participants to be involved in all the different stages of the development of a mechanochemical project and should encourage the participation with Horizon 2020 and relevant International Cooperation Programs. *Mech@SusInd* defines the following list of priority objectives in order to build the capacities needed to drive innovation: (i) Identification of specific industrial needs which could be better manufactured by mechanochemistry, and strategies to transfer from lab research to market products on short, middle and long term. Entrepreneurs, industrialists, investors, decision makers and suitable research groups within this COST Action are invited to jointly propose and investigate the most convenient, viable and innovative mechanochemical routes to prepare the identified product initially at laboratory scale with a view to scaling up for the chemical industry. An additional set of expertise may be needed for the scale-up stage; (ii) Integration of expertise and capabilities oriented at problem solving in specific areas of scientific and engineering research. The aim of this objective is to create multi-disciplinary task forces possessing the critical mass needed to overcome difficulties and provide responses to selected questions along the entire value chain for chemical production; (iii) to create a European Society for Industrial Mechanochemistry; (iv) Education of young researchers, training of specialised scientists, engineers and technologists, promoting excellence and cross-fertilization among different fields of expertise. This approach is expected to raise awareness of innovation opportunities in the chemical industry which should result in new developments in mechanochemistry. This will be done by an extensive, systematic use of networking activities offered by this COST Action programme such as the organization of periodic meetings for *Mech@SusInd* participants. Organisation of conferences and workshops to pursue scientific excellence and enhance competitiveness of EU chemicals manufacturers would be open to external delegates to share expertise, disseminate results, attract new participants to *Mech@SusInd*, stimulate Round Robin activities, promote the exchange of interests between working

groups and researchers and strengthen collaboration with industry. *Mech@SusInd* will: (i) provide support to emerging groups from countries with less research capacity, despite the high potential of research development, and favour the involvement of under-represented gender in the topic of the Action, (ii) provide support to women in the field of mechanochemistry to take leading roles, (iii) discover and identify new opportunities for SMEs via the interaction with the ends of the value chains, (iv) design proposals for novel research and development involving scientific and industrial partners, (v) involve new market sectors related to pharmaceutical, agrochemical, cosmetics, energy, food additives, polymers and biomass transformations (vi) facilitate growth, mobility and future leadership of Early Career Investigators, for example through Short-Term Scientific Missions (STSMs) and through the participation to Research Excellence Programs.

1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

In the past decades, mechanical processing by ball milling has been subjected to intense studies in the light of its unique capability of inducing physical and chemical transformations. Successfully applied to broad areas of mineral processing, material science and engineering, biomass degradation and soil remediation, the methodology has attracted enormous interest in industry. Within this framework, scholars working in European countries played a primary role. Constituting the world largest community of researchers devoted to mechanochemistry, European scientists and engineers cover the entire spectrum of subjects within the field, with recognized excellence ranging from the preparation of materials to the design of novel ball milling and extrusion reactors and to niche industrial applications. For instance, at least 5 companies worldwide produce specialty materials by mechanical processing and 10 companies manufacture mechanochemical reactors of different scale. Mechanochemistry has been applied, sometimes just as a “proof of concept”, to most organic reactions currently being performed by solution chemistry, resulting in the formation of covalent bonds as well as supramolecular assemblies. A comprehensive compilation of all the mechanochemical reactions, covalent, supramolecular (co-crystals, rotaxanes, cages, MOFs, CPs) and COFS and functionalisation of fullerenes and graphite sheets, can be found in “Mechanochemical organic synthesis” (Elsevier, 2016). The capability of ball milling to activate strong covalent bonds in the solid state under mild conditions of temperature and reagents is resulting in the formation of carbon-carbon and carbon-heteroatom bonds (C-N, C-O, C-halogen, C-S, C-Se and C-Te) and disulphide exchange reactions. Examples of the formation of phosphorus, boron, silicon, bismuth and C-H bond has been also achieved by mechanochemistry. Crystal engineering also had its successes, achieving the synthesis of metal-organic frameworks (MOFs), covalent-organic frameworks (COFs) and coordination polymers (CPs). All these chemical transformations can be performed either by neat grinding (NG) or by liquid-assisted grinding (LAG) this latter is achieved by the addition of substoichiometric amounts of solvent which can lead to different outcomes from NG. LAG is considered solvent-free technology, as the amount of solvent used in LAG reactions is much too small to become an environmental concern. Generally speaking, when referring to mechanochemistry both NG and LAG reactions are considered. Examples of covalent bond forming mechanochemical reaction are dehydrogenative coupling, oxidation, reduction and organo-catalytic reactions, also in their asymmetric version. Ball milling is being used for the synthesis of nanocarbon materials like the functionalisation of fullerenes and graphite sheets. Because of different pathway of the reactions used in ball milling, these reactions can often be successfully performed to high yields and high purity sometimes even in the absence of catalyst unlike solution based synthesis. The formation of Active Pharmaceutical Ingredients (API) co-crystal can be better achieved by solid state reaction, instead of recrystallization from solution, to overcome the problem of poor solubility of the API. The pharmaceutical industry is interested in the pharmaceutical co-crystals to modify the API’s properties to improve poor bioavailability and/or other undesirable properties without altering the chemical structure of the API. In 2016, the FDA revised the guidance to the industry on the regulatory classification of pharmaceutical co-crystals elevating co-crystals to the status of APIs and classifying them in the same category as solvates and hydrates with the potential to be patented and therefore helping to extend the life of the drug. The milling equipment and vessels used by mechanochemists is imposing a limitation of scale as they are adaptation of milling equipment purposely manufactured for size reduction and homogenization; the scale (>100mg) is much too large for the laboratory synthetic chemists to consider mechanochemistry as a synthetic tool, and too small for industry to consider mechanochemistry for industrial scale. Fortunately, extrusion technology has found a niche for successful industrial scale of mechanochemical transformations forming covalent bonds and supramolecular assemblies (*Adv. Mater.* **2016**, *28*, 5747 and *Green Chem.* **2017**, *19*, 1507).

1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

European COST Member countries are in the position of leading breakthrough innovation of its chemical industry by exploring the significant potential of mechanochemical processes. This COST Action *Mech@SusInd* aims at becoming a strong platform to promote and disseminate mechanochemistry across Europe. This can be achieved by effective coordination of activities, a flexible organization of work packages and problem solving analysis, and a fully cooperative interaction involving all the different stakeholders in the mechanochemistry field across Europe. At least three broad areas of activity are susceptible of significant progress beyond the current state of the art. These include (i) the advance of scientific knowledge, (ii) the design and fabrication of innovative mechanochemical reactors and processing methodologies, (iii) the development of synthetic routes for specialty products for organic chemistry and pharmaceutical APIs. Specifically, work packages structured to advance scientific knowledge of mechanochemistry can be expected to provide improved understanding on the mechanisms and driving forces of mechanochemical transformations, the identification of possible thermal components, the definition of factors influencing the solid-state reactivity of organic system, the role of substoichiometric amounts of solvents (liquid-assisted grinding, LAG) in the distribution of products, the optimal purification strategies in the presence of by-products, discovery of new reactivity and new synthetic chemistry opportunities. This could include, for example, enhanced reactant scope, access to poorly soluble, but less expensive or less toxic reactants, new control over stereoselectivity or stoichiometric efficiency/atom economy. Mechanochemistry is not only a means to make chemistry greener, but also to investigate products and molecules and types of reactions that have previously been either unknown, or even considered impossible to achieve. *Mech@SusInd* is already moving to next-generation mechanochemical reactions, which combine activation by mechanical impact with thermochemistry or photochemistry widening the scope for synthesis of potential products. Since the transformation of simple organic chemicals and main group elements by mechanochemistry is well established, achieving product complexity is the next challenge – the formation of complicated, elaborate molecular architectures, such as rings, cages, and complex pharmaceutical ingredients. *Mech@SusInd* can be expected to identify the sources of inefficiency in the mechanochemical vessels and reactors, encouraging the manufacture of new lab equipment for fundamental studies, and for the scale-up of mechanochemical processes to industrial scale. Small- and large-scale pilot plants for the mechanochemical manufacture of chemicals should be designed to be compatible with existing facilities for chemical production in European countries. Finally, *Mech@SusInd* will promote new ways of thinking in order to tackle the challenges addressed by the EU. Industrial processes need to be constantly revised to decrease the CO₂ emission and reduce the cost. Using new reagents or new synthetic solvent-free reactions is a valid route to maintain the leadership, moreover an in-depth study of these processes allows to establish the Life Cycle Analysis (LCA) and to identify the best and most sustainable processes. The development of synthetic routes for specialty products fundamental to the organic and pharmaceutical chemistry and agriculture industry should focus primarily in the preparation of: i) 20 top seller generic drugs, medical and personal care products (therapeutically active nanostructured compositions), drug/carrier composites with improved properties when prepared by mechanochemistry, ii) fragrances and perfumes, prepared involving Schiff's base and condensation reactions, which are known to be easily reproduced by mechanochemical reactions, iii) discovery of new co-crystalline forms of APIs (to improve the solubility and bioavailability of drugs); iv) coordination polymers (CPs) and porous Metal-Organic Frameworks (MOFs) for energy storage and sensing or separations; v) new materials which are investigated for the emergent technologies which are expected to play a crucial role in future applications, such as rotaxanes, catenanes, cages, highly aromatic compounds, graphene-based materials and nanoparticles.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

This COST Action aims at fostering innovation in European chemical industry via an intensive networking programme involving scientists, engineers, technologists, entrepreneurs, industrialists and investors. *Mech@SusInd* aims at promoting technology transfer from research labs to chemical plants in companies and SMEs stimulating a strategic global re-positioning of EU chemical and manufacturing industries. Fundamental research will tackle the challenge of ensuring significant progress in the understanding of mechanochemical transformations, discovery of new synthetic processes thus providing the necessary background to engineers involved in the design of new and more efficient mechanochemical reactors. *Mech@SusInd* will focus on possibility to improve the production of already known compounds by a greener and more sustainable chemistry expect to result in the reduction of solvent waste, less reaction steps and the utilization of cheaper or less toxic reactants and the possibility of using alternatives chemicals for critical raw materials. This strategy should raise new market opportunities for SMEs and industries in Europe manufacturing selected chemicals and materials by

mechanochemistry technologies. *Mech@SusInd* will promote the manufacture of mechanochemical reactors using novel technologies to enable efficient processing at the different scale ranging from lab to pilot plant and to industrial ones. A significant role in the development of new, more efficient processes will be played by advanced mechanochemical methodologies that utilize additives or catalytic effects to achieve transformations of poorly reactive or inert substances. These methodologies will advance, induce or direct the mechanochemical transformations, as well as derived methodologies such as ion- and liquid-assisted grinding (ILAG), polymer-assisted grinding (POLAG) or seeding-assisted grinding (SEAG). In contrast to LAG, the ILAG methodology also utilizes a catalytic salt additive to activate reactivity of poorly reactive mineral substances, which would be of outstanding value for mineral processing, whereas POLAG utilizes small amounts of polymer additives to control polymorphism of organic substances, which is of outstanding potential in context of pharmaceutical form screening. Importantly, these modified methods are all very recently emerged and, while still poorly understood, they provide significant potential for advancing processes in pharmaceutical and mineral processing industries, as well as specialty chemicals and materials manufacturing. Part of this innovation is the incorporation in the ball milling equipment of real time on-line analytical equipment such as Raman. The involvement of companies will facilitate the development of new viable technical solutions and improved equipment, which will also encourage the use of mechanochemistry. This mechanochemistry approach will give access to new or existing products with high atom economy reducing environmental pollution which has a detrimental effect to climate change, and lowering cost resolving economic stagnation in Europe.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

European countries already host the largest community of researchers and experts in the world involved in the field of mechanochemistry and closely related technological areas. Scientists and engineers addressing the formidable challenge of innovating lab and large-scale production of organic chemicals and specialty materials by mechanochemistry, should no longer work separately from technologists, entrepreneurs, industrialists, investors and decision makers. The COST Action *Mech@SusInd* will enable the transition from the current sparse distribution of excellences in science, engineering, technology, entrepreneurship and industry into a collaborative community jointly cooperating to achieve strategic results. This is an ambitious objective. This COST Action, and the initiatives that it can give rise to, can well be expected to start this transition and finally provide the first stable nucleus of the mechanochemistry community. Joint transnational research programme initiatives involving scientists specialized in synthesis and crystallography, has lead already to a breakthrough for the real time in situ monitoring of mechanochemical milling reactions, using synchrotron X-ray Diffraction (see *Nature Chem.* **2013**, *5*, 66). Raman has recently joined this real time *in situ* monitoring techniques. There is a vast range of mechanochemically activated reaction types deserving deeper investigation through real time in situ techniques. The study of real time *in situ* reactions requires the collaboration of synthetic chemists, experts in solid state characterization and technologists to provide customized milling vessels and purposely build ball milling reactors to obtain improved signal to background from the *in-situ* detectors to enable good refinement of Power XRD data. This multidisciplinary approach requires an extended network between the different groups. Coordination at a European level will maximize results from the collaborations and will facilitate the exploration of new research directions involving both academic and industrial stakeholders. This should result in strategic advances in the European chemical industry, including niche sectors of excellence such as perfumes and fragrances. This stronger communication between transnational academic and industrial participants should result in improved success in the transfer of mechanochemical concepts from the laboratory into commercial products, therefore being able to tackle industrial difficulties with innovative procedures. Eight companies have already shown their interest in adopting mechanochemical procedures. This COST action will create an ideal scenario for the mobility and multidisciplinary training of Early Career Investigators (ECI). The COST framework will contribute/provide to the creation of flexible cooperation between eminent experts and young researchers around specific academic and industry-oriented aspects of mechanochemistry. The creative environment provided by the networking tools of this COST Action should assist in the emergence of new research groups and research programme initiatives within EU member states/COST Member Countries, developing their future leadership in the field. The benefit of such approach will be long lasting.

1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

This COST Action is complementary to a number of initiatives concerning individual European countries as well as EU as a whole. The Action will also facilitate the achievement of the objectives of the European Innovation Partnership (EIP) on Raw materials, and FP7 Public Private Partnerships (PPPs) on Nanotechnologies, Advanced Materials, Advanced Manufacturing and Processing, and Biotechnology, such as SPIRE (Sustainable Process Industry through Resource and Energy Efficiency, www.spire2030.eu/) and BBI JU (Bio based Industries Joint Initiative, <https://bbi-europe.eu/>), Factories of the Future (FoF, www.effra.eu). Potentially, this COST Action is synergistic with the *activities, surveys, discussions and overviews performed within the European Technology Platform for Advanced Engineering Materials and Technologies* (EuMAT, www.eumat.eu) and for Sustainable Chemistry (SusChem, www.suschem.org). This COST Action will be the forum for the discussion and development of theoretical and applied research topics in the field of materials science prepared by mechanochemistry. This COST Action should be complementary with the activities of the ETP EuMAT as it should be able to provide it with new scientific insights for process steps and mechanochemistry equipment/plants and to improve technology, to open and transfer know-how and technology between European countries, companies and branches, to reduce resource demand and costs, improve eco-efficiency and therefore maintain the economic competitiveness and environmental friendly solvent free processing and products.

This COST Action is aligned with the following relevant communications & documents: (i) **Communication from the Commission (2008) 699** “The raw materials initiative – meeting our critical needs for growth and jobs in Europe”, Document {SEC(2008) 2741}; (ii) **Annex V to the Report of the Ad-hoc Working Group** on defining critical raw materials- Enterprise and Industry Directorate General, EC; (iii) **MEMO/12/182** (Brussels, March 13, 2012) - “EU challenges China's export restrictions on rare earths” (copper, titanium and platinum group metals (PGMs), etc.) and high tech metals, essential inputs to chemical and pharmaceutical industry. The development of solvent free sustainable technologies and eco-innovative production processes will reduce the EU's consumption of raw materials, decrease the import dependency.

The COST Action *Mech@SusInd* is complementary to a number of European-wide research activities on raw materials research and innovation such as **CoPIRIDE** (Combining Process Intensification-driven Manufacture of Microstructured Reactors and Process Design regarding to Industrial Dimensions and Environment, www.copiride.eu/) or **F3 Factory** (Fast, Flexible and Future Factory, www.f3factory.com/) focusing on developing new technologies, processes and manufacturing concepts for the “plant of the future” for the Chemical Industry. Up to now, H2020 projects are dedicated to specific topics or specific application areas. The results achieved by running research projects that are funded by either Europe or national/regional programs in the involved countries will also be shared. For example: (i) **Croatian Science Foundation**: Mechanochemical reactivity under controlled temperature and atmosphere for clean synthesis of functional materials (2016-2019); (ii) **Slovak Grant Agencies: APVV** - Mechanochemistry of semiconductor nanocrystals: From minerals to materials and drugs (2015-2019); (iii) **H2020 FETOPEN-RIA**: New Technological Advances for the third generation of Solar Cells (GOTSolar), (2016-2018); **H2020 Marie Curie Action**: (iv) “Innovative Training Network”, Continuous Resolution and Deracemization of Chiral Compounds by Crystallisation (2016-2020); (v) “Career Integration Grants (CIG)”, Mechanically-Assisted Synthesis of Pharmaceuticals: A Greener Energy Input (2016-2018); (vi) **COST Action**: Alternatives for Critical Raw Materials in Extreme Conditions (CRM-Extreme), (2014-2018); (vii) **H2020 MSCA RISE**: Enhancing sustainable chemical technologies through the synergy of computer simulation and experiment (2015–2018) (viii) **ERC**: Mechanochemistry: a unique opportunity for oxygen isotopic labelling and NMR spectroscopy (2018-2022).

At the International Level, the **National Science Foundation of China** (NSFC) is currently funding the project: Green Synthesis of Cage Compounds and Covalent Organic Frameworks Under Mechanical Milling Conditions (2013–2017), while the **Russia and the Russian Academy of Sciences** is funding the projects: Basics of Mechanochemistry (2016-2020) and Complex research of mechanochemical reactions of molecular solids, (2016-2018). Finally the **US National Science Foundation** is funding the project: Highly Active Mechanochemically Generated Main Group and Lanthanide Complexes, (2017-2020).

Start-up Grants were founded by the Excellence Initiative of the German Federal and State Governments to develop “Photo-catalysed mechanochemical synthesis” (StUp_PD221-16, 2016-2017), showing the socio-economic impact of mechanochemistry as a new sustainable technology for eco-driven processes. Finally, the company MOF Technologies Ltd. which is the first company to implement the extrusion process as a mechanochemical route to the formation of MOFs has received extensive funding from QUBIS (the commercial arm of Queen's University Belfast), NetScientific and more recently

Excelsa, through this the company have brought several million of funding into the Northern Ireland economy, along with over 1.2 M of funding from Horizon 2020.

Mech@SusInd Action will spur a rationalization of the available knowledge on mechanochemistry and a harmonization of the nomenclature and procedures allow its popularization not only in academic settings, strengthening the European chemical industry's global technological leadership through faster, more flexible solvent free manufacturing methods.

2. IMPACT

2.1. EXPECTED IMPACT

2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

The adoption of mechanochemistry by industry and by research chemists in academia suffers primarily from a current lack of awareness of its technological achievements and secondarily from considerable resistance due to a persistent culture of liquid-based technology developed over 200 years this being exclusively taught at universities. **In the short term**, *Mech@SusInd* will focus on improving the understanding and performance of those mechanochemical organic reactions already published and apply lessons learned to a wider range of chemistry with a view to scaling them up for industrial use. The scaling up will be performed with tested and published technologies (see *Green Chem.* **2017**, *19*, 1507 and *Chem. Comm.* **2017**, *53*, 13067), identifying processes amenable to mechanical transformation so that significant time is not wasted on systems that will not succeed. Case studies that are susceptible amenable to industrial exploitation, concerns the preparation of green manufacturing process designs of APIs as alternatives to well established ones. The preparation of drugs containing imine bonds such as Furantin (antibiotic) and Dantrium (a muscle relaxant), and amide bonds such as paracetamol will be investigated by extrusion technology. Although their syntheses are among the most established manufacturing processes, many improvements can still be made in the search for green alternatives. The scale up of mechanical synthesis using extrusion technology, and the formation of an imine bond was one of the first chemical transformations to be investigated (see *Green Chem.* **2017**, *19*, 1507). Both Furantin and Dantrium are prepared through the formation of an imine bond, starting from commercially available reagents, so that they are highly suitable and feasible for scale up by extrusion technology. Currently, the research extruder available can carry out organic synthesis on a scale of 0.5 – 1.0 kg/h, however further collaboration with process engineers (some already established) can result in the ability to scale up from small to larger extruders (capable of processing ton/h quantities). The extrusion synthesis of paracetamol, involves the extrusion of 4-aminophenol and acetic acid at 100 °C, leading to the formation of paracetamol within two minutes. The preparation of the APIs mentioned leads to the formation of environmentally friendly by-products being water and, in the case of paracetamol, acetic acid (which can be removed by heating in the extruder). The syntheses of these APIs are green and completely scalable. In addition, co-crystals of drug compounds and the amorphisation of APIs are also of high interest to the pharmaceutical and chemical industries. Co-crystals can also be more quickly produced in the laboratory by ball milling or extrusion than by conventional solution based techniques and the amorphisation of paracetamol can be carried out by extrusion. Indomethacin, simvastatin, ranitidine, ketoprofen and naproxen, pharmaceutical market leaders can be prepared under solvent-free conditions and then render them amorphous. While the synthesis of APIs by extrusion will have great environmental and economic impact, the amorphisation of these APIs will have great biological impact, making drugs more effective.

Where mechanochemistry is likely to make **in the short term** the greatest impact to the outcome and yield of chemical reactions, is by eliminating processing steps. Mechanochemistry: i) gives more efficient routes to existing products because of the fundamental chemoselectivity under mild conditions; ii) leads to new products especially where the starting materials do not react in solution without the use of harsh chemicals; iii) allows to replace expensive catalytic systems with cheaper alternatives (such as in the diastereoselective cyclopropanation reaction using silver foil instead of expensive dirhodium (II) catalyst (*Angew. Chem. Int. Ed.* **2015**, *54*, 11084); iv) because mechanochemistry is a solvent-free procedure it will reduce the amount of solvents normally required in solution based procedures to dissolve the reactants; as mechanochemistry often results in the formation of pure and high yielding product, there is no need to use solvents for recrystallization or column chromatography to purify the reaction products. The post-synthetic treatments are therefore highly simplified, the risks of side reactions eliminated, the amount of solvents going to waste disposal and the energy consumption greatly reduced as compared

to current solution based procedures where bulk solvents must be heated or cooled). It is unlikely that mechanochemistry will replace in the short term all such solvent based reactions. Where the use of solvents cannot be eliminated in the short term, they could be replaced by a new generation of environmentally friendly solvents. Deep eutectic solvents (DESs) are a new generation of ionic liquids which can be used as a reaction medium and for precious metal extraction. One of the drawbacks of using these liquids industrially is the difficulties faced during conventional manufacture (thermal degradation, variable properties depending on the quality of batches). Extrusion has been demonstrated to overcome these problems, providing a continuous route to the manufacture of these ionic liquids. Therefore, it is now feasible to commercialise DESs, and with further scale up using large extruders, chemical industrialists may be interested in taking these DESs to a commercial stage. As a consequence, there may be a domino effect in that not only is the manufacture of DESs more effective, but also, employed as reaction mediums, the DESs can make synthesis and processing more environmentally friendly, reducing the need for toxic solvents. **On the long term**, in addition to the impact discussed, (i) mechanochemistry has the possibility of rewriting the procedures used in the chemical and pharmaceutical manufacture. With the utilisation of extrusion, the potential to introduce mechanochemical routes into the manufacture of a great number of chemicals and APIs is possible. Solvent-free synthesis which is typically carried out on small scale can be scaled up into a continuous process, and in many cases the synthesis can be optimised so that post-synthetic purification is no longer required. The availability of expertise in the mechanochemistry industry and the already established collaborations of chemical engineers, mechanical engineers and process engineers with industry means that solvent-free industrial synthesis is no longer 'blue sky' thinking and it is now a feasible strategy for the long-term future. With this, there is also the obvious environmental and economic impact of continuing with this work. Globally, there is a drive towards climate control and to preserve the environment. Depending on the jurisdiction of the country it is possible, that government funding will be available to help incorporate this mechanochemical technology into manufacturing processes as an incentive to mitigate current trends. Secondly, by eliminating unusable by-products, materials (often toxic) being sent to incineration or land fill, waste will be obviously reduced. To be realistic, some of the solvent going to waste disposal is incinerated to produce energy or returned to be refined. Another challenge/impact of mechanochemistry **on the long term**, is to achieve product complexity to prepare complicated, elaborate molecular architectures, such as rings, catenanes, rotaxanes, cages, and complex pharmaceutical products. This potential will be a huge attraction to pharmaceutical companies, also considering the recent emergence of "*medicinal mechanochemistry*" (see *Chem. Comm.* **2016**, 52, 7760). *Mech@SusInd* will allow to address the new, emergent technologies based on highly aromatic compounds – such as nano-graphenes and fullerenes.

Developments in these areas will impact both the application of mechanochemistry in industry but also advance the science; it will enable greater understanding of the fundamental processes through reaction monitoring, analyses and characterisation of the product from mechanochemical transformation and the development or refinement of theoretical models of the processes involved. Replacing solution based chemistry for solvent-free mechanochemistry technology will require cross industry and academic effort, but the benefits could be substantial environmentally and financially. *Mech@SusInd* initiatives are expected to recruit more scientists to work in mechanochemistry and disseminate this discipline in all universities in Europe. The success of the *Mech@SusInd* network will facilitate the potential for Europe to lead the world in mechanochemistry, extending its practice in other industrial sectors additional to material science (e.g. pharmaceutical, fragrance and skin care settings).

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The advantages and limitations of the adoption of mechanochemical techniques, where appropriate, are clear. It is also clear that there is a barrier to their adoption as mentioned in the introduction, namely the existing 200 years old technological development and culture of solution based synthetic chemistry procedures. It is also apparent that despite significant progress being made in academia by some research groups, very little of this is being transferred to industry. *Mech@SusInd* will address these shortcomings by bringing together all the relevant stakeholders to discuss problems and challenges and pinpoint where mechanochemistry can be immediately applied, where technology is lacking, where progress can be made and where this technology is likely to have impact in the short and long term. The goals of *Mech@SusInd* will be to: i) Educate industry and policy makers in the recent advances that have been made in mechanochemistry; ii) Educate academics and policy makers in the barriers facing its adoption such as the lack of presence of this topic in university teaching and research activities; iii)

to encourage technology companies to develop custom technologies for mechanochemistry; iv) create a European Society for Industrial Mechanochemistry. The most relevant stakeholders for the activities addressed by *Mech@SusInd* can be identified as follows:

- *the scientific communities* working on organic and organometallic synthesis, spectroscopy, molecular modelling, solid-state synthesis and chemical process engineering. This COST Action will leverage the networking tools made available by COST to achieve otherwise unreachable scientific breakthroughs, as well as attracting researchers from the other fields where mechanochemistry could solve some common scientific issues already addressed by *Mech@SusInd* Action. While key scientists in the mechanochemistry field from diverse locations, with different levels of experience (newcomers, emerging groups and leading teams) and backgrounds are already participating in this COST Action, there is an expectation to identify in future other scientists related to the thematic of *Mech@SusInd*.

- *Industry players* active in the pharmaceutical, agro-food chemical, skin-care and energy sectors will be prioritised. Industries are already supporting the Action with diverse letters of intent. Representatives from industries will participate on an Advisory board of the Action and will be invited once a year to attend a dedicated session of the MC meeting with the aim of strengthening the collaboration between industry and researchers and inspiring new applications of mechanochemistry to the industrial sector. The Action will proactively involve current and new stakeholders as in response to the extensive dissemination plan described in Section 2.2.2. In addition, dedicated workshops or thematic business day events targeting pharma and fine chemical industries will be organized every year involving leading organisations representing industrial production, policy makers such EU agencies (ECHA), European Chemical Industry Council (CEFIC) and National Federations of Chemical Industries across EU.

- *EC and funding agencies*: several aspects of *Mech@SusInd* research are priorities of current EU/Horizon 2020 programmes (e.g. nanotechnology, KETs) Several proposers are active in ERC, FET and Marie Curie projects. *Mech@SusInd* will therefore plan a “raising awareness” and “information exchange” in order to explore further funding in Horizon 2020 or the upcoming FP9.

- *General public*: European citizens should be addressed as potential stakeholders of the Action (see *J. Bus. Ethics* **2004**, 53, 107 and <http://www.eltis.org/guidelines/activity-23-plan-stakeholder-and-citizen-involvement>). Therefore, *Mech@SusInd* will develop material for the general public and encourage public engagement (e.g. through liaising with public media for its workshops/conferences).

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

Dissemination is the fundamental role of the *Mech@SusInd* COST Action, promoting the practical development of mechanochemistry within and outside the network. Therefore, a sub-group will be charged with developing and implementing a dissemination plan including, for example, the *Mech@SusInd* Action's website. This sub-group will be selected from within the Core Group (CG). In addition, an *Mech@SusInd* partner for each country will be appointed to identify appropriate national events (workshop, conferences, meetings) in which *Mech@SusInd* will take an active interest and to generate a mailing list of media and potential stakeholders in his/her country. The audience so identified will be targeted with different approaches: (i) **Publications in leading scientific journals**, mainly encouraging collaborative joint articles (minimum 5 papers/per year) from the partners of the *Mech@SusInd* COST Action; (ii) **Fostering the edition of special journal issues** focusing on mechanochemistry, acknowledging the *Mech@SusInd* COST Action. This will support the impact of mechanochemistry on the scientific community in general; (iii) **Participation in appropriate National and International conferences** and workshops on organic synthesis, solid state chemistry, process engineering, material science and technologies, etc.); (iv) **Participation in Training and Scientific Missions** (STSMs); (v) **Organisation of *Mech@SusInd* COST Action Annual Meeting**, not only for COST Members and the Advisory board members but also for the stakeholders and the entire scientific community not-necessarily involved in the field of mechanochemistry, to present research results within the Action; (vi) **Creation of a Webpage** and easily recognised branding (logo etc.) dedicated to the activities of the Action for the entire period, containing information about members, challenges, objectives, annual reports, news, announcements, meeting schedules, working opportunities within the Action, etc. A private area for information only for the partners will be created. (vii) **Use of Social Media** (web channel on You Tube, Facebook, Twitter, Research Gate, LinkedIn) will be integrated into the website to facilitate the dissemination of the Action activity to the general public. Additionally, the *Mech@SusInd* COST Action will be promoted using the website of each Principal Investigator (PI) or through a broad-casting; (viii) **Improving the existing Wikipedia webpage** on mechanochemistry (<https://en.wikipedia.org/wiki/Mechanochemistry>), including its translation in all the languages of the

participating Member Countries of the *Mech@SusInd* COST using language and arguments understandable, not only to scientists but also to the general public; (ix) **Promotion of a textbook** dedicated to *Mech@SusInd* COST Action among all the participants in electronic format, with special editing addressed to the Universities, for pedagogic purposes. In addition, all MC and Action members will participate in local and national activities and publicity campaigns. The partner contract will include a section that will protect developments being made within the partners' organisations where that development is proprietary whilst promoting sharing and collaboration and the generation of shared knowledge. With regard to exploitation issue, in the interests of meaningful discussions on the status of current research efforts and in compliance with article 8 of the grant agreement, WG meeting participants will be asked to sign non-disclosure agreements, allowing presentation of results with actual or potential commercial interest. Extrusion of fine chemicals and APIs is already set up as a pilot process and therefore Industrial Clinics can be provided to companies considering incorporating this technology. The clinic would involve meeting with mechanochemistry and extrusion experts, with a demonstration of a fine chemical synthesis with real time *in situ* characterisation. Funding from the COST Network would provide a means to finance the travel of chemical and pharmaceutical industrialists to the clinic.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

The application of mechanochemistry as technology for scaling-up organic synthesis within industrial settings has been relatively limited. Because this COST Action puts together several highly-experienced workers in field of mechanochemistry it has great potential to generate important ground-breaking innovations (e.g. in paragraph 1.3.3) including finding solutions to some of the problems already outlined (see paragraphs 1.3.2 and 2.1.1). By including both chemists and process engineers with diverse competencies, a strong practical network will be developed with the common objective to increase the application and knowledge of mechanochemistry. The impact of these innovations is expected to change the fundamental way process chemists consider producing products, developing new specialised companies in process mechanochemistry and new supporting technology companies, such as SME and larger entities. Potential risk factors can be highlighted in the translation of lab-scale concepts to large-scale facilities (e.g. heat transfer from exothermic reactions, stability of reagents and catalyst to grinding, isolation of products from reaction mixtures). To overcome these risks, it is important to entail a strong interaction between technologists and chemists for the conception of new grinding equipment, although this innovation breakthrough can be achieved in the long-term. Mechanochemical reactions on large scale will be also explored by Twin Screw Extrusion (TSE), an already established technique employed in the food, pharmaceutical and polymer industry and it is well understood. This means that the uncertainty of employing an unknown process or a novel process is removed. Extrusion has already proved successful in many mechanochemical reactions and so there is great potential to further this work and drive to convert industrial processes. As the pharmaceutical and polymer industry (also readily employed in the chemical industry) have extruders implemented for alternative uses in their manufacturing processes, they are more willing to embrace this technique and rethink their production processes. The purchasing of new equipment is unnecessary as they already have the equipment, at most, they may wish to invest in more of similar equipment.

The request for in-situ real-time monitoring of the industrial process (e.g. the temperature/pressure control and calorimetric profiles during grinding) could prevent the adoption of mechanochemistry in large scale facilities, although examples of thermal recording of large industrial mills are already described and other technological solutions could well be achieved to some extent through engineering design and funding. However, in-situ analyses developed at lab-scale level with synergic use of chemometric approaches should be improved and adapted to satisfy these needs.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

This COST Action will be organized in three Working Groups (WGs) focusing on mechanochemistry for green and sustainable syntheses, to acknowledge the broadness of the field.

WG1 Lab-scale syntheses. WG1 will bring together experts in mechanosynthesis with the aim to design mechanochemical protocols that can offer advantages over existing solution-based methods to advance capability in this area. Furthermore, WG1 will work side by side with the other WGs in order to discover and study new types of reactivity (with WG2) and to identify suitable reactions for scaling-up (with WG3). Additionally, the direct involvement of engineers at this early stage will allow the conception of processes working at lab scale that can be realistically scaled them up.

Objectives. The objectives of the WG1 will include: (i) the identification of specific mechanochemical reactions (condensations, multicomponent, cascade, domino, organo- or metal-catalysed, etc.) that allow synthesising specialty products avoiding common problems arising in conventional solution routes, (ii) Designing the strategy to evaluate the reproducibility of specific mechanochemical reactions; (iii) Evaluate the effect of liquid-assisted grinding on controlling chemical reactivity and selectivity, (iv) Discovery of organic molecules and new compounds (CP, co-crystals, catalysts, MOFs) accessible only under mechanochemical conditions, studying their unique reactivity together with the WG2.

Milestones. (M1) Identification of different reactions leading to compounds of industrial interest such as generic APIs, catalysts, CP and MOF for energy storage and pharmaceutical co-crystals to be investigated for the scale up process (in collaboration with WG3); (M2) Identify one or two benchmark reactions to understand the mechanistic aspects underlying the reactive event and the role of liquid-assisted grinding in mechanochemical reactions (in collaboration with WG2); (M3) Identification of technical parameters allowing to optimize the reactions.

Deliverables. (i) Technical report on different reactions, which can be tested for scale up process, including Guidelines, Good Practice and practical skills for mechanochemistry; (ii) Technical report on the achieved objectives will be presented to the annual meeting; (iii) Publication in leading scientific journals and open access journals.

WG 2: Mechanistic investigations and in situ monitoring. WG2 will aim to provide mechanistic background and the study of driving forces of mechanochemical milling reactions and will work closely with all other WGs. All of the methodology described in the *Mech@SusInd* Action has an associated and often unknown mechanistic component and the understanding of driving forces of the reaction and thus all research groups have a keen interest and buy-in into this area. WG2 will focus on a combination of computer simulation and *in situ* monitoring methodologies, based on both powder X-ray diffraction and spectroscopy for solid phase composition. In-situ monitoring of mechanochemical reactions is complemented by fundamental studies of reaction mechanisms based on single-molecule force spectroscopy of mechanophores and advanced quantum chemistry. Technologists and experts able to provide tailor-made process automation solutions (including thermal recording of large industrial mills) in this challenging environment will be involved.

Objectives. (i) Identify reaction mechanisms for solvent-free reactions and Liquid-Assisted Grinding (LAG) *via in situ* analyses. We will also seek parallels with currently existing mechanistic frameworks of corresponding solution reactions (with WG1); (ii) Conceive general methodologies for the *in-situ* analyses; (iii) Examine the influence of the reactor in size and geometry for the final product (with WG1 and WG3)

Milestones. (M4) Optimization of monitoring of in-situ reactions and develop of multivariate analyses for the on-line monitoring of the reactions; (M5) Perform molecular dynamics simulations of the grinding process under a variety of conditions and develop methodologies to analyse structural and thermodynamic properties of the phases formed during molecular dynamics simulations and establish a standard protocol for covalent single molecule force spectroscopy. (M6) Develop multi-scale computational methods to address the kinetics of formation of the final products of mechanochemical reactions;

Deliverables. (i) Technical report on detailed identification and better understanding of patterns and trends in reactivity; (ii) Technical report on the achieved objectives will be presented to the annual meeting; (iii) Publication on automatic routines for analysis of large analysis data sets; (iv) Procedures for *in situ* monitoring of mechanochemical reactions; (v) New laboratory equipment for the *in situ* analyses (vi) modification of the milling vessels and equipment to incorporate the *in-situ* equipment.

WG3: “the engineering perspective”: Mechanochemical reactions are often regarded as green or sustainable alternatives to classical synthetic methodologies. One aspect of sustainability is the assessment of reactions and / or methodologies from ecological and economical viewpoints.

Optimization of developed reaction protocols often needs engineering knowledge allowing not only to find optimized reaction conditions but also to provide improved reactor concepts. Mechanochemical syntheses developed in WG1 and mechanistically investigated in W2 will be selected for scale-up by twin screw extrusion (TSE), not only for the gram to multi-kg h⁻¹ production of (pharmaceutical) materials. In the case of APIs, TSE will be also used for improved formulation.

Objectives. (i) the environmentally sustainable production of compounds and materials of industrial interest in large scale; (ii) the development of new processing methodologies and the design of new reactors to allow the industrial scale-up of mechanochemical processes and (in collaboration with WG2); (iii) Provide general guidelines for the scale-up of mechanochemical reactions in general and specifically for mechanochemistry in ball mills for industrial relevant products. This includes an assessment of several parameters and in special cases also the development of test equipment at mini- and / or pilot plant scale; iv) Connect academia to the market and industry through the involvement of entrepreneurs, industrialists and investors, to bring on the market the mechanochemically synthesized products; v) Identify the process having the lowest impact for the environment, compared to currently used manufacturing processes.

Milestones. (M7) Life Cycle Analysis (LCA) assessment; (M8) Assessment of the important parameters during the scale- up process; (M9) Development of reactors to perform reactions isothermally at adjustable temperature levels to overcome the inhomogeneous and non-stationary temperature behaviour during the mechanochemistry reactions; (M10) Evaluation of the environmental impact and energy consumption for large scale manufacturing by twin screw extrusion of one or two (pharmaceutical) materials, to help make a decision compared to how the product(s) are usually manufactured.

Deliverables. (i) Prototypes of reactors for: scale-up process, *in situ* monitoring, temperature control and guidelines and protocols for scale up process; (ii) For one or two (pharmaceutical) materials, provide Good Manufacturing Practice (GMP)-certification for large scale manufacturing by TSE, complemented by LCA-based labels.

The objective on the harmonization on the nomenclature is common to all WGs, and it will be pursued by a strong collaboration among the participants of this COST action. During the final meeting a report summarizing the guidelines for the mechanochemistry reaction (nomenclature, good laboratory practice, critical parameters, etc.) will be presented to the community.

3.1.2. GANTT DIAGRAM

Legend: M = milestone (please see technical annex); A = annual technical report; P = paper / publication; G = Guidelines for mechanochemical reactions; WG = working group meeting; MC = management committee meeting; S = semester.

Objectives	S1	S2	S3	S4	S5	S6	S7	S8
KEY DELIVERABLES								
Working Group (WG) 1: Lab-scale syntheses		A		P/A		A	P	A/G
Identification of different reactions leading to compounds of industrial interest (organic, material, co-drugs)		M1		M2				
Identification of technical parameters allowing to optimize the reactions					M3			
Discovery of new compounds								
WG2: Mechanistic investigations and in situ monitoring		A		P/A		A	p	A/G
Identify reaction mechanisms for solvent-free reactions via in situ analyses.						M5		
Conceive general methodologies for the in situ analyses			M4					
Examine the influence of the reactor in size and geometry for the final product						M6		
WG3: the engineering perspective"		A		A		A		A/G
Identification of different reactions leading to compounds of industrial interest (organic, material, codrugs)		M1						
the environmentally sustainable production of compounds and materials of industrial interest in large scale					M7			
the development of new processing methodologies and the design of new reactors to allow the industrial scale-up of mechanochemical processes				M8			M9	
Provide general guidelines for the scale-up of mechanochemical reactions in general and specifically for mechanochemistry in ball mills for industrial relevant products.							M10	
MANAGEMENT								
Meeting	Kick Off	WG		WG		WG		MC Final
Annual Work & budget plan and Risk and contingency plan			MC		MC		MC	
Stakeholders engagement strategy and updates								
Communication and dissemination:								
Website launch and social media pages logo and communication materials								
Capacity building								
Short Term Scientific Missions (STSMs)								
Training Schools				TS1		TS2		
Workshops, seminars								

3.1.3. PERT CHART (OPTIONAL)

3.1.4. RISK AND CONTINGENCY PLANS

The Chair, the vice-Chair and the Managing Committee (MC), in coordination with the WG leaders will be responsible for managing risks and taking corrective actions as necessary while a sound monitoring of the activities will be performed by each WG leader, the DC and his/her vice. A Risk Assessment and Contingency Plan at the beginning of the Action will be prepared to minimize possible deviations from the expected results and timelines will be drawn, while a more complete list of risks will be developed. A first indicative list of risks and risk-mitigation measures is foreseen as follows:

Risk 1. The objectives of the Action are not achieved at the end of the time scheduled. *Odds:* low. *Contingency Plan (CP):* regular meetings, taking any necessary corrective actions to meet the plan, pre-checking of results (against the objectives of the Action) and ensuring their internal distribution. Risk can be also minimized by selecting less challenging, well-known transformations on lab-scale before transposing them to large-scale settings. Overview by the MC. All the Proposers have a very good track record of delivering all the activities to a high-level standard and on time.

Risk 2. Lack of communication among Proposers. *Odds:* low. *CP:* an internal communication plan will be developed and use of effective communication tools (skype calls, dropbox repository, etc...) encouraged.

Risk 3. Schedule and budget under/over spending. *Odds:* low/medium. *CP:* the MC chair will monitor the schedule and the work progress tightly. In particular, he/she will work in strict collaboration with the GH manager to timely and effectively monitor forecasted expenditures. In case, the MC will be timely informed and involved in order to deliberate appropriate solutions.

Risk 4. Delay in submitting deliverables (e.g.: publications). *Odds:* low. *CP:* each WG will be driven by a WG leader, appointed by the MC, who will be responsible for setting a detailed schedule and work-plan, to ensure the risk of delay is minimized.

Risk 5. Low participation in the activities, especially STSMs and TSs, and in particular of women and ECIs. *Odds:* low. *CP:* specific actions will be targeted to timely communicate the opening of calls for STSM and encourage participation of these two groups. The whole network will be involved in this activity under the coordination of an STSM and TS coordinator. All partners are committed to advancing the field and believe that networking will facilitate this. However, as a last resort, partners may be removed or replaced. However, with the level of enthusiasm existing, this is unlikely.

Risk 6. Failure to reach the necessary number of stakeholders and not having the promised impact. *Odds:* low/medium. *CP:* interactions with SH will be under a close scrutiny of each WG meeting on dissemination. Pre-work/pre-meetings will be planned with the necessary number of stakeholders. A tailored stakeholders' engagement plan will be elaborated to make use of the Action Members' resources network in relevant fields of expertise, as well as to strengthen information and dissemination procedures for a more attractive or targeted communication.

Risk 7. Failure in strong collaboration between academic and industrial partners. *Odds:* Medium/High. *CP:* this is a "high risk high gain" situation. It is believed that the chosen academic partners (having already experience in the technology transfer) and the industrial and SME partners (which are innovation oriented), are strongly committed to achieve the objectives of the COST, thus minimising this risk.

The *Mech@SusInd* network failing to advance the science and its application is also a risk but not facilitating the networking and exchange of ideas, ensures the science and application will continue to advance slowly. By bringing together the leaders in Europe in the *Mech@SusInd* network with small and large companies, and drawing in other participants in the resulting actions, there is a greater likelihood that advances will be made.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The management and organisation of this Action will be set up in compliance with COST Rules. The Management Committee (MC), chaired by the Action Chair (AC) and a Vice-Chair (AVC), will steer and oversee the activities, supervise the correct allocation and use of the budget, guarantee and promote proper gender balance and effective dissemination, decide on the participation of Working Group (WG) members and ad hoc participants (with emphasis in ECI, the under-represented gender and researchers from Inclusiveness Targeted Countries and Near Neighbour Countries), so that the Action is correctly implemented according to COST rules. The initial consortium combines all the necessary expertise to engage in this network but further partners with complementary skills are anticipated to join to maximize the results. MC will also prepare MC meetings, agendas and meetings. Overall, the MC will be milestone-driven and supervise the successful completion of Action Activities. During the first MC meeting, a Core Group (CG) will be appointed, Working Group composition and work plans defined, to ensure successful networking. The CG will be composed by the Action Chair (AC) and the Vice-Action Chair (VAC), WG leaders (WGLs) and Vice-Leaders (WGLVs) who coordinate each WG and report progress to the MC. The CG will be supported by specific tasks coordinator: i) the Grant Holder Manager (GHM – responsible for the sound administrative management of the Action); ii) a Dissemination Coordinator (DC) and Vice Coordinator (DVC) (working on the coordination of dissemination activities - see section 2.2.2.); iii) Short Term Scientific Mission Manager (STSM) and a Training Coordinator (TC) coordinating the organization of training schools and training opportunities, especially involving the Early Career Investigators (ECIs), allowing them to obtain international research experience in other groups or nominating them as national delegates (whenever possible) and in leading roles; iv) two Industrial Representatives (IRS), who will discuss the needs of the industry and translate the information about potentially exploitable outcomes. MC will include also an Advisory Board (AB) of observers and external experts - also from the industrial sector - to control the compliance of the work plan according to the milestones and deliverables foreseen, proposing adjustments of the Action scientific work plan or activities if necessary and help to re-orient the WGs towards research lines most appealing and profitable to present and future market scenarios for chemical and pharmaceutical industries. Moreover, individual MC members will be appointed as Coordinator of Gender Balance (CGB) and Vice Coordinator (VCGB), in charge to monitor an appropriate gender balance in all the activities. Special attention will be devoted to the gender balance in the management structures and in the participation in activities. There will be a strong cooperation between all the members of the CG. MC and CG will meet once a year to discuss progress, define and re-define operational guidelines and organize future activities, meanwhile maintaining fluent communication by e-mails, conference calls, videoconferences or similarly. Other management structures will be adapted if necessary by the MC during the lifetime of the Action.

3.3. NETWORK AS A WHOLE

The network, which had set up this Action, comprised of research groups belonging to 20 different COST Member Countries – with 65% of COST Inclusiveness Target Countries (ITCs), 1 COST Near Neighbour Country (NNC) and 5 COST International Partner Countries (IPC). The participants from the international partners (COST International Partners Countries) are scientists with a strong background and knowledge in mechanochemistry having provided milestones, breakthrough and strong advancement in the field. It is worth noting that some of them have been formed in Europe and they continue to share their expertise with their former collaborators in the COST Member Countries, maintaining a strong link to their European roots. All the participants (from Cost Member Countries and ITCs, NNC and IPC) are already actively working in the field of mechanochemistry in complementary areas of expertise. They constitute already a whole entity built to treat scientifically and technically the topic of mechanochemistry applied to organic synthesis and scale-up with different competencies and cultural inputs. Their affiliations are from academia, (85%), Government or Intergovernmental Institutions (5%) to private research institutions, including some companies (12% of the network). COST members are distributed among sectors of Chemical (85%), and Physical Sciences (4%), Material Sciences (7%) and Chemical Engineering (2%) and nano-technology (2%). The initial network has 44% female partners – with the aim of 50% to respect gender balance, with both men and women having equal opportunities in all activities (including management, promoting excellence, research, networking and scientific integration). The initial consortium has already the critical mass, expertise and geographical distribution needed for addressing the challenge and objectives. 20 Early Career Investigators were involved (almost 30% of the proposers) but this number will increase once the Action is launched with the opportunity of recruiting other qualified participants (also to reinforce specialists in Process and Chemical Engineering), to address answers for specific problems not possible to be solved within the initial network. The Action has gathered groups dedicated to the development of methodology in organic, organometallic synthesis and crystal engineering, solvent-free preparation of advanced porous materials, providing technological solutions for *in situ* and real time reaction monitoring, mechanistic investigations of mechanochemical reactions, theoretical calculations, and structural determination by spectroscopic techniques. The network had gathered 2 experts from 2 large companies and 6 experts from Small to Medium Enterprises (SMEs) devoted to crystal engineering for the pharmaceutical industry. The participation to the network of a 'Big Skin Care Group', which is a large Company, and a worldwide leader in grinding solutions on industrial scale and six SMEs, strengthen and demonstrates the high socioeconomic impact and positive effect of the Action, indicating that the consortium has already the right skills for the successful achievement of milestones and objectives. The IPC institutions in this COST Action will welcome collaboration possibilities and will do all what they can to support the Action. The mutual benefit from their participation stems from: (i) Advanced technologies for *in-situ* monitoring of the reactions; (ii) Experts in crystal engineering and aging problems with crystals formed by ball milling; (iii) Mechanochemical reactivity using purposely build reactors for synthesis and catalytic reactions performed by ball milling; (iv) Expertise in designing and producing large scale equipment for mechanochemistry, to transfer the lab-scale concept to large-scale facilities, including safety assessment, energy costs and risks assessments of failure by a case-to-case study, and crucial studies for maximising the technological applicability at industrial level. The collaboration of researchers to increase the efficiency of mechanochemical devices through the use of Twin Screw Extrusion (TSE) as an alternative approach for the productions of 20 top seller generics and APIs in general will attract the interest of the pharma industry (see paragraph 2.3.1).