Resilience in Healthcare and Chemical Production in Europe

Using Digital Twins for Sustainable Manufacturing Processes

In the last few years, any circumstances taken for granted were wiggled or even turned upside down. We had to learn that in a globally connected world, the sun does not rise more beautifully every day. We learned that the supply chains were disrupted. Many comfortable conditions we could have enjoyed during the last decades, and we conceived as being on solid ground, have been turned upside down. Thus, Europe needs to become more resilient. On issues of healthcare and our core industries, on which Europe's prosperity rests. We need to be more adaptable to influences on the European economy, where we do not have a direct impact.

Resilience Through Innovative Sustainable Manufacturing Processes

For over 20 years, many pharmaceuticals have been produced outside of Europe due to cost and existing intellectual property rights. Furthermore, many pharmaceuticals are produced in a batch-wise manner. This led to a situation in Europe where some pharmaceuticals were not available for patients. During the Covid pandemic, we, the Europeans, became aware of breaking supply chains, but we also learned that we are great innovators and able to invent safe vaccines within a noticeably short time if the pressure is great enough. This learning curve shall be used as a springboard in the future to become better in healthcare industry, chemical industry and other industrial areas across Europe.

Sustainable manufacturing is one of the most common demands industries, such as the pharmaceutical, chemical, and biotechnological industries, are faced with today. It defines a chemical process avoiding unnecessary compounds, hazardous initial substances, hazardous products and solvents, saves energy, reduces the complexity of synthesis and many more environmental principles for sustainable conduct. Extruder-assisted processes are well understood and can be optimized for specific educts and products with reduced by-products. Potentially, inflexible infrastructures and fixed distribution channels hinder the establishment of new sustainable processes and products.

So called "very old technologies" may be converted as more sustainable processes with new innovative insights, if the existing infrastructure can be customized and new distribution models established. These innovations can be protected by intellectual property rights, such as patents, and be exploited by Europe's industry. For example, the first German patent (DE 1) discloses a solvent free process. One could look up similar "old solvent free processes" and use them as a basis or inspiration for new processes. These new processes may integrate current state of the art technologies and sustainable manufacturing processes in a mixed synergistic innovation process.

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It is a fallacy to believe that to achieve these goals development of completely novel techniques is necessary. A holistic view is proposed, considering novel techniques, techniques used by nature, and sometimes old techniques in a new set-up with novel amendments and supplements that lead to sustainable manufacturing techniques.

A balanced and mixed IP strategy will also support the development, use and dissemination of greener chemistry with sustainable manufacturing, as patents protect the inventions of innovators.

In an objective way, factors that may hinder innovations should be

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considered. Some non-exhausting examples are the own subjective imagination of involved people, missing decisions of management or limited imagination of other participants, general framework conditions such as laws, regulations, directives and other guidelines, established infrastructure, rules of the market, cost etc. Important impediments for innovations are product policy aimed at product differentiation rather than product variation, that may dominate a company's innovation strategy. A corporate policy based on persistence, the commonly used "me-too-strategy", waits until a third-party innovation has established itself on the market for example. This strategy relies on tradition out of conviction and hinders a switch to sustainable manufacturing and resilience. Therefore, approved development costs and available equipment are key factors that frame innovations and inventors' possibilities.

These non-exhaustive obstacles are only intended to indicate possible difficulties solved by inventors with much optimism, persuasion, perseverance and technical, legal and rhetorical knowledge.

Valid IP rights secure the innovator a monopoly position in the markets and thus enable them to recoup their investments and make profits. Likewise, IP rights give the innovator or pioneer protection against imitators, such as companies that are considered early followers and late followers, or against companies that want to market detailed improvements such as a modification. Valid IP rights are also marketing tools proving the innovative spirit of a company, e.g., in social media, and are an enormously important part of the value of companies.

Setting the Course for Sustainable Innovations Using Digital Twins

Digital Twins (DigiTwins) are a large research initiative in Europe and beyond, aimed at revolutionizing healthcare and biomedical research for the benefit of citizens and society. They are computer models enabling a prediction of optimized chemical processes, costs and by-products.

Testing modular standardized connectable, continuously operated, small sized extruders or mechanochemical reactors, may allow a reduction of the plant size and a switch from batchwise production in the pharmaceutical industry to a continuous production as is typical for the chemical industry. Using digital twins for the estimation of a new process set-up, e.g., switching from solvent assisted batchwise production to a continuous, extruder supported production, enables development of nearly fully automated production processes in small sized reaction plants in movable scalable infrastructures. Moreover, the calculations of the digital twin can lead to heavily reduced production costs.

Setting the Course for Intellectual Property (IP) Strategy for Sustainable Innovations

Enabled through the intensified cooperation of EU member states, the European legislator will establish a more uniform and cost-effective patent system. This new system can be used from 1st June 2023 in participating member states of the EU through the Unified Patent System covering a Unitary Patent (UP) and Unitary Patent Court (UPC). The „unitary effect" of the new Unitary Patent avoids the previous fragmented protection in European Union countries, as all EU member states, except Spain and Croatia, want to implement the system in the future. The administrative and cost burden for all parties will be significantly reduced.

The European legislator has set a legal framework with the Supplementary Protection Certificate (SPC) Manufacturing Waiver (Reg. 2019/933 amending Reg. No 469/2009) that allows the production of specific generic pharmaceuticals during a certain time of the patent term, allowing stockpiling for the export of generic products outside the European Union, without patent protection. This is in addition to the former possible research privilege and Bolar-Roche Exemption.

These two legal frameworks will strengthen the resilience of availability of generics by reinstallation of the production of generic pharmaceuticals in Europe. As a side effect these frameworks will strengthen the resilience of Europe's healthcare system and create safe jobs, especially when combined with sustainable manufacturing methods which are optionally designed by digital twins.

On June 1, 2023, Routledge will publish the book" Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing." It contains, among other topics, a chapter on IP protection in the chemical sector, authored by Tanja Bendele. More info at: https://bit.ly/IP-Mechanochemistry

Setting the Course for Europe's Future

European institutions should foster natural science on all levels from school to work during the working lives of European citizens. They should check critically marketing costs that avoid real innovations, due to the above-mentioned obstacles. And importantly they should boot-up the implementation of innovative sustainable manufacturing. Utilizing and promoting the above-mentioned tools by market players, public institutions, research institutions etc. within the new European legislative framework, an innovative transformation of Europe's pharmaceutical industry and parts of chemical industry to a sustainable and resilient manufacturing, is possible.

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FDA Issues Continuous Manufacturing Advice for the Pharma Industry

On Mar. 1, 2023, the FDA issued the International Council for Harmonization (ICH) final guidance on the use of continuous manufacturing in drug production. As reported by Pharmaceutical Technoly, this marks the FDA's proactive steps to ease the pharmaceutical's industry transition to these advanced processes, states the announcement.

While not binding, the document covers the regulatory and scientific considerations needed for the development and implementation of continuous manufacturing in pharma, and the guidelines are meant for both new and pre-existing products.

This guidance was previously endorsed by the ICH Assembly in November 2022 and is regarded as an attempt to harmonize regulatory considerations surrounding continuous manufacturing. It adds to an overarching advisory framework established through other ICH guidelines.

For available products, the guidelines include considerations on the conversion of batch manufacturing practices to continuous manufacturing.

In the last few years, continuous manufacturing was cited as a solution to address the ongoing challenges facing pharmaceutical supply chains. The Covid-19 pandemic had highlighted the difficulties surrounding global supply chains and the reliance on manufacturers in other parts of the world.

In a June 2021 report following an executive order, the Biden administration called for more public investment into continuous manufacturing. Funding was also given to companies that would bolster US-based production of critical medicines. This method of manufacturing has been also highlighted as a way to mitigate the industry's environmental impact.

The document covers equipment design and process dynamics, among other topics, and features example of continuous manufacturing systems used to produce therapeutic proteins and tablet drugs in its annexes.

The guidelines also delve into quality control and process monitoring of continuous manufacturing. In one of the final sections, the document showcases some of the approaches than can be taken when managing disturbances that could affect material quality. Disturbances can harm the flow of a normal continuous operation and may result in a diversion of material.

In addition to the guidelines, the FDA shared a discussion paper on the implementation of artificial intelligence in drug production. However, this paper is not meant to offer recommendations, but instead will be used to source feedback from the industry.

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