SEQENS

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Flow chemistry for efficient and safe synthesis of APIs and intermediates

Approximately 2,800 active pharmaceutical ingredients (APIs) are currently marketed, 70% of which being synthetic chemical molecules.

Their complexity tends to increase: among the treatments approved annually by the FDA, there is a regular increase in average molecular weight and the number of chemical functionalities. Today, new drugs frequently contain several heterocycles, including classical elements of the periodic table such as nitrogen, oxygen, or fluorine. Those original structures are sought after to selectively address certain biological receptors, or to influence the drugs bioavailability. Successful synthesis of these complex molecules requires a high level of chemical expertise.

More than 35% of FDA approved drugs need at least one nitration step in their manufacturing process, and about 20% a fluorination step, to mention only these two reaction families. Such chemistry handles synthetic agents that are often highly reactive, sometimes corrosive or toxic, such as nitric acid, sodium nitrite, azides or hydrofluoric acid. Reactions themselves are often characterized by their exothermicity, and sometimes the energetic or unstable nature of the intermediates.

Over the last 20 years, the industrialization of such reactions has become rare in Europe due to the difficulty of maintaining their implementation in an acceptable environmental and safety conditions with regards to local regulations. In fact, a large part of the production of APIs has been exported to Asia: a crisis such as the Covid-19 is a clear indication of the fragility of the drug supply chain in western geographical areas. Notably, several drugs under clinical trials for CoVid-19 treatment require exothermic chemistry steps.

However, a great deal of work has been done to make industrial processes safer. Largely inspired by the large-scale processes used in petrochemicals or commodity chemistry, Flow chemistry is now part of the CDMO landscape and considered as an essential technological asset for controlling sensitive chemical reactions.

Continuous operation makes it possible to minimize reaction volumes: the quantity of unstable reaction mixture in the continuous reactor at a given time is greatly reduced compared to a conventional batch process, thereby reducing safety risks. The surface/volume ratio is also much more favorable, allowing a better control of the reaction temperature and exothermicity, and a safer operation.

Flow chemistry is also characterized by a gain in chemical efficiency: continuous plug flow or stirred-tank cascades of reactors allow a tighter residence time distribution than batch, and in many cases a better selectivity. All these elements contribute to minimizing secondary reactions and the formation of impurities: the quality of the products is correspondingly improved and the environmental footprint of such processes is reduced drastically.

Frédéric Schab, Seqens Innovation Director, explains : "*The key to mastering flow chemistry processes is to combine expertise in chemistry and process engineering. The complementarity of these two disciplines is essential to efficiently industrialize, on a continuous mode, a process developed in the laboratory*. " Seqens benefits from a long experience in Flow: chemical and process engineers have been designing, optimizing, and operating continuous processes for decades, whether on large scale building blocks or active pharmaceutical ingredients (APIs), such as GMP-grade salicylic acid.

The feasibility of Flow chemistry is systematically evaluated for all customers and internal projects of Seqens, in order to quickly identify the products that could benefit from such a technology. The experimental part is carried out in the R&D Center, Seqens Lab, in Porcheville (France), which is equipped with continuous bench reactors and analytical tools for appropriate data acquisition.

In order to complete its toolbox, Seqens Lab will be equipped at the end of 2020 with a new GMP pilot plant, capable of hosting nitration, diazotation or halogenation type reactions, and producing representative pre-commercial batches up to the ton scale. This flexible tool will enable to increase process robustness and accelerate scale-up and industrialization steps.

Pierre Luzeau, Seqens CEO, notes : "*Seqens leverages its range of scientific skills to deploy Flow chemistry and benefit from its advantages in terms of safety, reagents consumption, and efficiency, which now make it possible to envisage a massive repatriation of a certain type of difficult reactions, intermediates and APIs, to Europe. This reindustrialization will ultimately secure the supply chain for many medicines in Europe, provided that this effort is supported by an appropriate investment policy.*"

About SEQENS

Seqens is a world leader in pharmaceutical synthesis and specialty ingredients.
With 24 production sites and 3 R&D centers in Europe, North America and Asia, SEQENS develops tailor-made solutions and ingredients for the most demanding industries such as healthcare, electronics, cosmetics, food and home care. Driven by a culture of excellence and a strong entrepreneurial spirit, our 3,200 employees are committed to providing our customers with the highest level of service and quality while acting ethically in accordance with our Corporate Social Responsibility program.

press@seqens.com / www.seqens.com / Linkedin : SEQENS / Twitter : seqens_group