Panel Discussion on Flow Chemistry

Commentary article

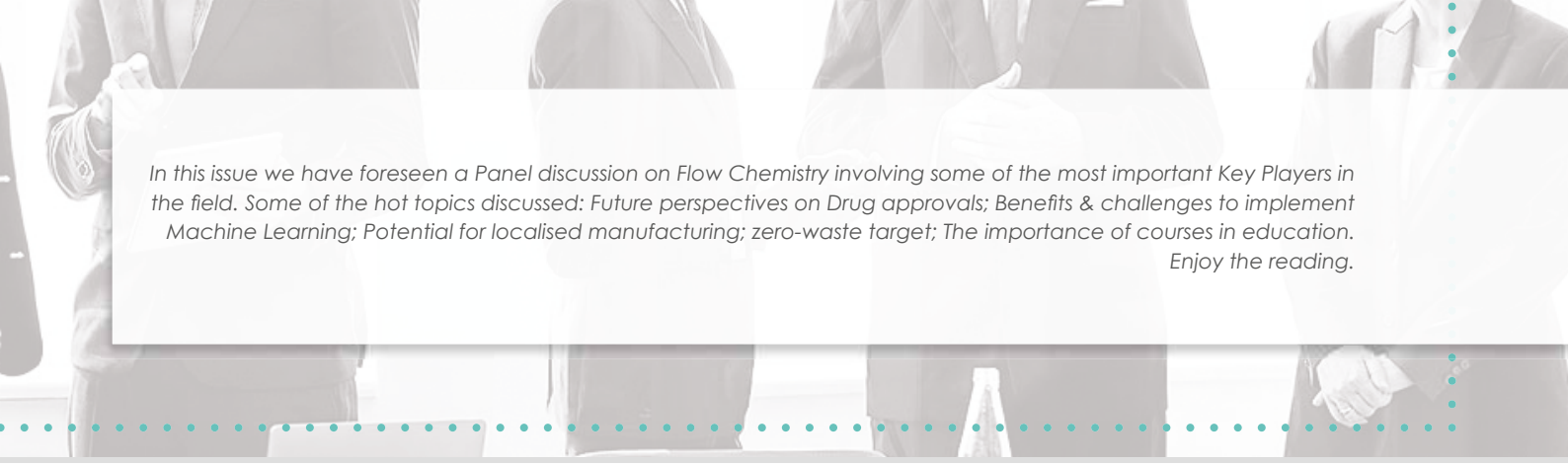
GIANVITO VILÉ
Group Leader of the Innovation Lab for Sustainable Process Intensification & Professor in Flow Chemistry, Politecnico di Milano

In June 2002, a research article containing for the first time the words "continuous flow chemistry" in the title was submitted and accepted in a peer-reviewed journal. After 18 years, it is now time to look back at the developments and celebrate the success of flow chemistry and continuous manufacturing in bringing industrialization and automation, major drivers in most of the modern branches of industry, into the chemist's dictionary. Flow chemistry is today an established enabling technology that can drastically improve the safety of hazardous chemicals, reducing handling of highly energetic intermediates, enhancing yield, reducing solvent and other raw material inputs, and lessening the environmental impact of a pharmaceutical process. This is key for a sector that has been historically suspected of generating the highest amount of waste and pollution. In particular, flow technology has advanced substantially from library synthesis to manufacturing, and it is not surprising that high temperature/pressure reactions, hazardous chemistries, flash methods involving organometallics, polymerizations, photochemical or electrochemical reactions, and multistep syntheses of APIs can all be accomplished effortlessly. Besides, novel process windows have facilitated the conduction of reactions which could not be traditionally done in batch due to safety concerns. This has widened the IP space and, from the answers of this year panelists, it emerges clearly that this has made possible that 5 drugs approved by the FDA could be manufactured in flow under GMP conditions. Panelists mention that it is difficult to predict whether this trend will continue to increase, but current evidences suggest that there is now a great number of molecules in the pipeline relying on at least one flow chemistry step during manufacture. Some panelists have highlighted that the trend seems to correspond to the increasing number of CMOs and CDMOs supporting today large pharmaceutical companies with efficient and cost-effective continuous processes at commercial scale.

While the field continues to gather importance, it has also started to embrace new technologies. According to this year panelists, machine learning can have a tremendous impact to assist experimentalists in predicting conditions and proposing reaction schemes. Complemented with DoE tools for process development, it can enhance the power of feedback-based optimization and validation methods. In addition, the now widespread use of real-time, non-invasive methods, such as IR and NMR, help triggering commands when parameters go out-of-range, saving significant material of high cost. 3D-printing is now becoming essentially important with regard to rapid prototyping of novel reactor geometries. The outstanding work done by some of the panelists in creating novel 3D-printed photoreactors has shown the true power of additive manufacturing to accelerate the design of reactors with optimal fluid-dynamic characteristics. As correctly stated, such novel technologies can help today improving product and process understanding, based on new scientific evidences, with the overall aim of expanding the use of micro- and millireactors while ensuring a safe drug supply to the consumer and improve manufacturing performance.

At industrial scale, a trend remains in preferring flow chemistry due to the small-scale nature of the systems compared to traditional batch reactors. This seems to change the perspective of producers, since there is no longer a need to build large facilities to accommodate batch vessels. Such reduction of the manufacturing footprint can enable manufacturers to respond on demand to production needs. And, in the age of pandemics, this aspect is key. It is, in fact, dangerous to rely on international trade only, and localized (European) production can become increasingly important to ensure local production facilities. All panelists agree that this can happen only embracing flow chemistry.

An important aspect which has emerged from this year answers concerns sustainability. As policy makers continue to apply pressure towards sustainability, the eventual carbon footprint of processes may well push chemical development in the direction of continuous manufacturing. Flow chemistry can in fact contribute significantly to achieving a zero-waste target.



In this issue we have foreseen a Panel discussion on Flow Chemistry involving some of the most important Key Players in the field. Some of the hot topics discussed: Future perspectives on Drug approvals; Benefits & challenges to implement Machine Learning; Potential for localised manufacturing; zero-waste target; The importance of courses in education. Enjoy the reading.

Finally, transitioning from batch to flow requires a broad mind-set change. And this can only be done with education. It is, thus, wonderful to see that all panelists have stressed the importance of having "flow chemistry" and "process intensification" courses in the chemistry and chemical engineering curricula. Theoretical and practical trainings on these industrially-relevant topics are fundamental and should be a mandatory part of undergraduate education. In fact, failure to be aware of the opportunities that continuous manufacturing brings, means that those entering the workplace only consider age-old toolbox options. Politecnico di Milano, the Eindhoven University of Technology, the University of Graz are offering already flow chemistry courses; and we expect that this trend will increase in the years to come, as more professors will establish independent groups in academia. By teaching the next generations the skills required to transform batch processes into flow mode can help challenge the status quo, leading to a wider implementation of this unique technology.

ABOUT THE AUTHOR

Gianvito Vilé *studied Chemical Engineering at Politecnico di Milano and obtained his PhD at ETH Zurich. From 2016 to 2019, he was a Lab Head at Idorsia Pharmaceuticals, coordinating R&D activities to transform batch pharmaceutical processes into continuous mode. In 2020, he moved back to Italy, accepting a faculty position at Politecnico di Milano funded by Bracco. He is developing novel flow processes to increase the sustainability of the pharmaceutical industry.*

Panelists

Franz Amann, Senior Scientist Development and Samuel Bourne Scientific Specialist - **CARBOGEN AMCIS**

Martin Elliott, Chief Commercial Officer - **Centillion Technology Limited**

Charlotte Wiles, CEO - **Chemtrix BV**

Stephen Houldsworth VP, Global Platform Management & Marketing - **CordenPharma International**

Alessandra Vizza, Regional Business Director Corning Reactor Technologies - **Corning**

Hannes Gemoets, Head of R&D - **Creaflow**

Srividya Ramakrishnan, Head - API Process engineering and **Rakeshwar Bandichhor**, Head of Chemistry, API, PR&D - **Dr Reddys**

Anne Kaaden, Head of Marketing and **Joachim Heck**, Managing Director, **Ehrfeld Mikrotechnik**

Timothy Noel, Associate Professor, **Eindhoven University of Technology**

Michael Nonnenmacher, Senior Project Manager, Innovation Management, Business Line Health Care - **Evonik Nutrition & Care GmbH**

Rui Loureiro, Process Chemist Development - **Hovione**

Dirk Kirschneck, Strategic Director, **Microinnova**

Xiong-Wei Ni, FIChemE, FRSC, Founder and CSO - **NiTech® Solutions Ltd**

David Lovett, Managing Director - **Perceptive Engineering**

Johannes Khinast, Professor at University of Graz and CEO / Scientific Director of **Reseach Center - Pharmaceutical Engineering**

Bill Dubay, Global Head of R&D and Olivier Dapremont, Process Technologies AMPAC Fine Chemicals, an **SK pharmteco company**

Mark Muldowney, Head of Technology and Innovation - **Sterling Pharma Solutions**

FRANZ AMANN[1], SAMUEL BOURNE[2]
1. Senior Scientist Development
2. Scientific Specialist
CARBOGEN AMCIS

DO YOU SEE CHALLENGES WITH THE CLEANING VALIDATION OF CERTAIN TYPES OF FLOW REACTORS, FORMULATION AND TABLETING STEPS ETC FOR PHARMA APPLICATIONS?

A general challenge associated with cleaning flow reactors is the limited ability to visually inspect small tubes and other internal structures. Identifying parallel flows or dead spots within fittings and valves is critical and can be considered during the initial design of the reactor. If classical rinsing is insufficient due to the type of deposits or any geometrical complexities then most reactor modules can be easily disassembled to perform an initial gross decontamination; however, this is ideally avoided as it requires additional time and requires specialist knowledge of the equipment.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

Over the past 15 years there has been a steady increase in flow chemistry related research and a corresponding increase in publications from academia. The use of lab flow chemistry equipment should be part of the practical undergraduate education. Not necessarily in special courses but as one tool within synthetic chemistry. Accordingly, the general theoretical education, especially at the universities, should give some insight to basic concepts of chemical engineering including flow chemistry as an established technique.

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

It's difficult to put an exact number on this; although, the evidence suggests that there are now a great number of molecules in the pipeline that rely on at least one flow chemistry step during their manufacture. The trend is clear - as the pharmaceutical industry, particularly CMOs and CDMOs, move towards more efficient and cost-effective processes for commercial manufacture, the number of filings that contain flow chemistry steps will continue to rise.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

The advent of machine learning is clearly new to many industries and the advantages for the chemical industry are yet to be fully realised. For the time being, QbD and DoE continue to be the most effective tools for process development, optimisation and validation at CARBOGEN AMCIS. However, it is possible to envision more AI based approaches being used across the industry in the near future as relevant applications of the technology are developed and perfected.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

The control strategy for a continuous process also differs very little from the control strategy of a batch process. The final critical quality attributes of the API must be met and the robustness must be demonstrated using the specified equipment over a series of runs or batches. The greatest advantage of continuous manufacturing is the availability of real-time parameter data and in-line analysis using non-invasive methods such as IR, UV/Vis and NMR. The ability to automatically trigger a divert to waste command if any parameters go out-of-range or in the event of an equipment failure gives ultimate control over the quality of product included in a run or batch. In contrast, an equipment failure during a batch manufacturing process can easily result in the loss of significantly more material at much greater cost.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow chemistry can dramatically improve the safety of hazardous chemicals by means of the make-and-consume principal; whereby the inventory of highly energetic intermediates is reduced by continuously forming then destroying them in the subsequent chemical transformation. Many well suited reactions also benefit from improvements in yield; as a result, energy, solvent and other raw material inputs can be reduced, lessening the environmental impact of the process.

THE ROLE OF FLOW CHEMISTRY IN HELPING COMPANIES ACHIEVE THEIR SUSTAINABILITY OBJECTIVES, PARTICULARLY WITH REGARDS TO CARBON FOOTPRINT.

The pharmaceutical industry is beginning to take small steps towards sustainability but there is still a long road ahead. By improving the efficiency of reactions, flow chemistry techniques can reduce the carbon footprint of a process through reduced raw material and solvent consumption. Intelligently designed continuous processes can reclaim chemical energy and recycle solvents. Such processes already exist but they are rarely, if yet, to be applied to complex pharmaceutical synthesis and have only limited potential for cost saving but bear a certain risk of contamination. As policy makers continue to focus in on sustainability the efficiencies offered up by flow chemistry will make the technology even more attractive.

MARTIN ELLIOTT
Chief Commercial Officer,
Centillion Technology Limited

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

The earlier that future generations of scientists, engineers and technicians get exposed to flow chemistry, the better. The frame of mind that you go from a test tube to flask to a kettle and then to a larger kettle needs changing. Having flow chemistry equipment in both research and teaching laboratories in University's is a start but we need to bring it forward into the classrooms and lecture halls. That means engaging with the respective professional bodies and those who influence and compile the teaching curricula.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Our control strategies can incorporate real time data and both-in line and at-line analytics that brings a level of control that is beyond the capability of batch systems. Should any parameters slip outside of specification, then the quantity of product affected can be immediately isolated and limited to a particular segmented time period rather than be ruinous of an entire batch.

One area of opportunity through monitoring performance parameters is greater accuracy in predicting the need and timing for maintenance, so minimising operational downtime and interruption to supply. Also, by continuous monitoring it is feasible to run the CM process in as lean a mode as possible thus making valuable savings on reagents and consumables.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

Elsewhere, I have spoken about the benefits to a company's Carbon Footprint by reduction in the transport element. It can go beyond this, bringing smaller manufacturing plants to markets and utilisation of local raw materials. This could well be an important step in bringing new products and manufacturing opportunities within the reach of emerging economies.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow Chemistry has the capability of bringing considerable benefits in the areas of Health, Safety and Environmental matters.

The degree of enhanced control that it brings to the reaction will inevitably lead to higher yields as well as lower bi product and impurity manufacture with the associated reduction in need to rework or dispose. The reduction in quantities of flammable solvents required will also result in reduced risk.

The ability to rapidly shut down the smaller size of reactor required for the manufacture of hazardous products and intermediates minimises the risk of experiencing a thermal runaway should a reaction go out of control, as well as any potential atmospheric releases through easier containment.

Some extreme chemistries such as Azide chemistry can now become more economically viable as the cost of the safety measures that are required will be considerably less and more viable for a reaction of kilogram scale compared with what would be required for tonnage quantities.

THE ROLE OF FLOW CHEMISTRY IN HELPING COMPANIES ACHIEVE THEIR SUSTAINABILITY OBJECTIVES, PARTICULARLY WITH REGARDS TO CARBON FOOTPRINT

Much has been made of the resource and energy efficiency that Flow Chemistry brings to manufacturing from a cost element but equally of importance is how the minimisation of energy consumption impacts upon a company's sustainability targets, particularly with respect to Carbon footprint. The superior surface to volume ratios that flow reactors bring compared to batch equipment, achieve superior energy transfer rates as well as the ability to attain optimum operating conditions in a shorter time period.

The control I referred to earlier in leading to higher yields and less bi product and impurity formation will also contribute significantly to achieving a zero-waste target.

There is also the flexibility in business planning that the smaller footprint and modular nature of plants bring that allows for multiple plants being sited closer to end markets reducing the footprint associated with transport.

WHAT APPLICATION AREA DO YOU SEE THE MOST RAPID UPTAKE FOR YOUR SOLUTION?

I think we will see an increase in activity in both the synthetic chemistry and formulation environments (personal care, food technology, surface coatings etc). Decisions will be driven by enhancement of company performance both financially as well as in implementing its commitment to sustainability.

One further area that particularly excites me is Industrial Biotechnology. Although this may not be where the most rapid uptake occurs, it is an opportunity to embed the technology from the very earliest stages of development.

CHARLOTTE WILES
CEO, Chemtrix BV

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

Continuous manufacturing (CM) is gaining global significance, not only as a research tool but also as a production tool. With an increase in advanced process control strategies, these flexible, modular units afford opportunities to disrupt conventional supply chains via strategies such as point of use & just in time manufacturing. Small, turn-key units lend themselves to replication to scale output & since the location of such units is not fixed, CM enables rapid deployment of manufacturing capabilities to new locations - without conventional chemical infrastructure. When combined with PAT/model-based automation, modular & flexible CM will increase productivity in Companies focussed on complex formulated products such as pharmaceuticals, chemicals & personal healthcare products. Recent global events will undoubtedly change the way we manufacture fine & speciality chemicals, through to APIs, with supply chain management favouring distributed manufacturing models.

THERE ARE CURRENTLY 5 PHARMACEUTICALS APPROVED USING CM, HOW MANY API APPROVALS DO YOU EXPECT IN THE NEXT 10 YEAR?

Whilst there are currently five OSD (oral solid dosage) forms approved by the US FDA, it is hard to put a number on how many API approvals can be expected in the next 10 years, this is largely due to the complex development pipeline & high attrition rate for API's. Just over a year ago, the US FDA published a draft guidance 'Quality Considerations for Continuous Manufacturing'. Hesitation on how different regulatory bodies will act has been addressed by the initiation of a new International Council for Harmonisation of Technical Requirements for Pharmaceuticals & Human Use (ICH) working group, for the development of ICH Q13 Continuous Manufacturing – anticipated in 2021. This move has certainly had a positive impact on the number of Companies actively scaling CM – the result will be filings at the US FDA.

STEPHEN HOULDSWORTH
VP, Global Platform Management & Marketing
CordenPharma International

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

Although flow chemistry is an important tool in the arsenal of the modern pharmaceutical chemist, many in the field still do not take full advantage of its capabilities and possibilities. It is imperative that newly trained apprentices joining the workforce have a grasp of the flow chemistry skill set and a basic understanding of how and when to apply those skills. With each new development or advancement there is a learning curve that must be gone through before the development is embraced as mainstream. By teaching the next generation those skills in academia, they can help challenge the status quo, leading to wider implementation. Flow chemistry is not the panacea of all that ills the pharmaceutical industry today. Yet it does, when used appropriately, solve some fundamental challenges with respect the classic batch approach, whilst also providing a potentially improved control aspect through prudent use of PAT.

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

The number could be limitless. With the proposed accelerated review being offered by the FDA, the potential

If we break down opportunities for API CM, we have; 1) new products, 2) second generation processes by originators & 3) new process development by generic companies. New products present a perceived risk since additional work is required for QA Teams to file a new product using a new technology. Whilst there are technical & operational benefits to CM, there is a reluctance to change an existing batch process to CM since this requires a new filing. To mitigate this risk, we see increased activity in the parallel development of batch & CM processes, first filing the batch protocol & following with a second generation filing for the CM process, a trend that will continue. Not unsurprisingly, the area that receives the most attention is generic manufacturing – a trend that will continue as Countries look to secure their pharmaceutical supply chains. I expect that generic Companies will be the growth area for CM API approvals. Many generic Companies are seeing the opportunities that CM brings to reduce manufacturing costs, through increased control & reduced batch failures, resulting in an increased competitiveness. So, whilst we have seen positive movement in the CM of API's, with several Companies filing processes with the US FDA & approvals pending, I feel that that the CM API approvals will continue to lag behind those of OSD drugs.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

An often-underestimated part of introducing a new technology is how to navigate the transition from its use as a curiosity into one that is an integral part of a process. The first step of this is widespread awareness of the pro's & cons of use. Education & training are fundamental, without a knowledge of a new technique, it will not be considered as a viable option. Consequently, theoretical & practical training is an essential part of undergraduate education. Failure to be aware of the opportunities that CM brings, means that those entering the workplace only consider age-old toolbox options.
Our view is that a multidisciplinary approach is required to achieve the project goals of safe, efficient, cost effective manufacturing & should involve a mixed Team from the outset, obtaining the much needed 'departmental buy-in' to accept a 'new way' of doing something. Through education & training, the shift from a chemists' world to one led by chemical & mechanical engineers, then beyond to operators & quality personnel, will be more easily realised.

time saving will most likely prove very beneficial to the biotech industry. The possibility of more rapid scaling of processes to produce larger quantities of API and intermediates via flow chemistry will also offer potential time saving in the long run as well. With time to market being a critical consideration for cash-strapped development organizations, there are many incentives to consider flow chemistry within the manufacturing supply chain, including the overall improvement in process knowledge and built-in quality control. We will surely see the number of processes using flow chemistry increase, which will also drive up their associated drug product approvals.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Flow chemistry, or continuous manufacturing, only truly bring advantages when used hand in hand with Process Analytical Technology (PAT). The ability to receive almost instantaneous feedback on your process using appropriate PAT techniques means an immediate demonstration that operations are under control at all times, assurance that quality is built into your product, and the elimination of product recalls due to quality oversights or mistakes. When your process approaches the limits of the quality envelope, corrective actions can be taken in real time to create a process adjustment and bring the process back in line, well before a critical failure leads to batch failure.
The days of re-processing may become a thing of the past. However, this can only be possible via a complete understanding of the process, and development of appropriate PAT methods that give an accurate picture of the process in an appropriate timeframe. Without that PAT feedback loop, the process will be executed in the same uninformed scenario that often characterizes current batch processing methods.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

One advantage that flow chemistry brings to the industry is the "skid" concept of manufacturing. Instead of investing huge sums of capital in massive batch chemistry infrastructure, smaller, more agile "skids" can be developed that run around the clock in flow mode to produce large quantities via small footprints. Need to increase capacity? Simple. Either run the "skid" for longer, or duplicate the "skid" and double your capacity. The recent COVID-19 pandemic has put incredible pressure on the already strained global pharmaceutical supply chain, where either environmental, quality or trade war issues had, even before the crisis, already led numerous companies to question their existing global supply chain and consider "local" or "regional" manufacturing solutions. Flow chemistry and the small footprint "skid" concept could enable companies to have multiple small, but identical flow manufacturing "skids" located in appropriate regional areas, creating local product supply options for their drug products.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow chemistry has the possibility of increasing the size of the current tool chest for the pharmaceutical process chemist. Its ability to reduce the volumes of reactions, and more accurately and rapidly heat & cool solutions through the increased surface area that flow reactors provide, ultimately results in process chemistry with a wider group of reagents or technologies. Hazardous materials or reagents that would never be considered in batch processes due to their inherent instability or latent reactivity can now be considered. Thanks to the minimized risk resulting from reduced volume, easier handling, better reaction monitoring and the ability to correct a "runaway" reaction scenario before a failure mode is reached, will see more reactive chemistry being utilized. However, it is not just not hazardous or reactive chemistry that will be incorporated, but we will also see a rise in chemistry that did not originally lend itself well to batch processing. Chemistry concepts such as photochemistry that offer elegant solutions on a small R&D scale, but could not be applied to a larger scale because the "batch mode" approach was too limiting, can now be considered.

ALESSANDRA VIZZA
Regional Business Director Corning Reactor Technologies - Corning Incorporated

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

The capability to add flow chemistry education to university curriculum is a must for academia and for the chemical processing industry as a whole. The more students learn about the many advantages of continuous flow reactor technology, the more likely they will be to implement it in their future careers. Corning is dedicated to educating future generations and provide them with the latest innovations and products available on the market.
Since introducing Corning® Advanced-Flow™ Reactors more than a decade ago, Corning has worked closely with academic institutions to support students' use of our reactor technologies as a tool to better understand chemistry and/or chemical engineering. In November 2019, we expanded our product portfolio to include Corning Nebula™ Education Kits to help develop talent for the pharmaceutical, fine chemical, specialty chemical, and new material industries. Our goal is to be able to work with universities worldwide to give students exposure to inherently safer continuous flow reactors. With our Education Kits we are building a practical and interactive foundation for these technologies in classrooms and labs that could open the door to related careers. Therefore, for us, the future is built by working directly with students as future users and experts.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

Among the many advantages of flow chemistry technologies, I would highlight their continuous and small-scale nature, which allows for much lower reaction volumes (holdups) than traditional batch reactors. Consequently, this changes the perspective of production units – there is no longer a need to build new facilities to accommodate large batch reactors. Corning's reactors require one-third less space than batch reactors, which can drastically reduce manufacturing footprint and enable manufacturers to respond on-demand to production needs. Additionally, this represents an important saving on transportation and logistics costs since production can be done close to the end producer or user. Today the industry requires equipment manufacturers to have a fast response to market needs, geographical proximity to our customers, the ability to switch processes quickly, and the capacity to work by campaign or on demand. We also observe (due to the macro economic situation) a real need to have dedicated small production units in more locations. Flow chemistry is a valuable process intensification tool that is a clear response to meet those needs.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow chemistry is a process intensification tool that can enable more sustainable processes through higher yields, lower waste, and inherently safer, more efficient equipment. Corning has worked over the past 20 years to make available to the industry products that enable the incorporation of hazardous chemicals with less risk as compared to conventional batch production systems. Our continuous flow reactor technology is recognized as an inherently safer technology that enables the use of hazardous materials and intense reactions, particularly at industrial production scale. This is possible thanks to the improved heat-transfer and mass-transfer our technology provides compared to batch reactors, as well as narrow residence time distribution, all of which enable excellent process efficiency (reaction times of a few seconds with Corning Advanced-Flow Reactors versus several hours in batch reactors) and yield higher quality products with better performance – meaning the transfer to production is no longer an issue for the industry.
Corning AFR recently worked with a customer in China to help them speed up production of PAA (peracetic acid), which is an example of how using our technology enables our customers to respond quickly to real needs while also considering the HS&E impact. In this case we worked closely with our customer to finalize process development in the lab in a few days to enable customer to make PAA solution at 6 tons per day with the same reactor system to meet urgent demand. With this example I would like to highlight how flow chemistry is a real tool to make chemical processes more efficiently and more safely.
We do have experience handling hazardous reactions, particularly nitration and reactions involving energetic compounds. We have multiple reactor installations running continuously for the last two years that produce more than 10,000 tons per year. Those few examples are a confirmation of the many benefits of flow chemistry.

HANNES GEMOETS
Head of R&D - Creaflow

DO YOU SEE CHALLENGES WITH THE CLEANING VALIDATION OF CERTAIN TYPES OF FLOW REACTORS, FORMULATION AND TABLETING STEPS ETC FOR PHARMA APPLICATIONS?

Despite the plethora of continuous-flow reactors available on the market nowadays, I believe there are still limited options when it comes to the flow devices 'suited for GMP production'. Since the lion share of current flow reactors are based on the tubular 'closed-shell' configuration, cleaning validation (which is a required operation in GMP production) becomes strenuous or even impossible. At Creaflow we have tackled this challenge by developing our flow photoreactor as an assembled 'open-shell' configuration, in combination with a transparent window covering the process channels. During off-cycles, the window allows the operator to easily asses the reactor internals by visual inspection through the window. In addition, the lid can be disassembled effortlessly for physical cleaning and/or swab sampling purposes.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

There's more to chemistry than the round-bottomed flask, and I believe Universities such as Eindhoven University of Technology and University of Graz are prime examples of how to act swiftly and accordingly to successfully implement flow

chemistry themed courses in the undergraduate curriculum. I believe education is key in order to expedite growth and innovation in the field of flow technology. I believe that in case we want to enable the next generation of chemists and engineers to intensely communicate and push the boundaries of our field, we have to implement the latest research and flow technology in every layer of the curriculum.

VERSATILITY AND CONVENIENCE OF USING 3D-PRINTED REACTORS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS, USING FLOW TECHNIQUES

Latest additive manufacturing technologies have triggered even the most sceptic of us. I truly believe that 3D printing will become more and more a 'go-to technology' to solve our current unmet needs in reactor development. As with subtractive machining methods (e.g. CNC milling), we were mostly limited to the so-called 2.5D. This refers to the projection of a 2D plane into a 3rd dimension, while the resulting object is 3-dimensional, there are no overhanging elements that are possible to be created, therefore limiting the reactor's complexity. On the other hand, 3D printing methods expand the chemical engineer's toolbox, allowing to completely re-think and re-design their reactor concepts and design configuration that were previously out of the question. At Creaflow, we have now embraced this technology as we have in our currently development pipeline the implementation of 3D printed reactor parts, in order to increase structural complexity for optimized output.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

Disrupted supply chains have often been the root cause of reported drug shortages globally. The traditional methods of batch-wise manufacturing approach at multiple locations may lead to mismatch in delivery times, require larger inventories, and eventually results in prolonged lead times of the end product. In fact, delocalized batchwise manufacturing its biggest challenge is to accordingly respond to sudden changes in demand, such as during epidemics and pandemics, which are a most relevant topic nowadays. Owing the capacity for localized end-to-end continuous manufacturing would allow companies and/or governments to address such issues.

THE ROLE OF FLOW CHEMISTRY IN HELPING COMPANIES ACHIEVE THEIR SUSTAINABILITY OBJECTIVES, PARTICULARLY WITH REGARDS TO CARBON FOOTPRINT.

The ever growing population and our standard of living has taken its toll on mother nature, as we are witnessing the first consequences of global warming. And where the environmental impact of the chemical industry has been higher than for other industries, it is our responsibility and duty to act and explore 'greener' chemical solutions in order to create a more sustainable manufacturing landscape. Flow chemistry has attracted our attention, by offering lower build footprints, greater reliability and enhanced safety profiles, leading to more efficient performing chemical reactions. In addition, flow technology allows us to tap into the field of these so-called 'forbidden chemistries', referring to what we consider dangerous or 'difficult-to-perform' transformations at the preparative scale. However, once mastered, such chemistries open pathways for intensified processes that eventually translate into significantly reduced carbon footprints.

WHAT APPLICATION AREA DO YOU SEE THE MOST RAPID UPTAKE FOR YOUR SOLUTION?

I believe that innovation in flow technology will have significant impact on the commercializing of largely unexploited chemistries such as photochemistry and electrochemistry. These chemistries (which utilize alternative energy inputs) possess intrinsic limited scale-out capabilities (due to light attenuation effect and ohmic drop respectively), but can be circumvented by the implementation of continuous-flow reactor technology. At Creaflow, we have developed a truly scalable flow photoreactor, which is capable effortlessly scaling photochemistry from the laboratory to the pilot and production scale.

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1. Head - API Process engineering
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FLOW TECHNOLOGY HAS THE POTENTIAL TO BECOME A SUPERIOR MANUFACTURING ALTERNATIVE FOR COMPLEX SYNTHESIS

The syntheses of complex pharmaceuticals require enormous efforts right from R&D to manufacturing, and call for advanced technologies to make processes eco-friendly and sustainable at scale. Flow technology is such an emerging platform for synthetic chemistry that has been developed extensively and has now started to find its place in academic and industrial research. During centuries, synthetic chemists used to conduct reactions in classical glassware and were unfamiliar with the use flow technology in routine synthesis. Flow technology has now advanced to an extent where high temperature and pressure reactions, hazardous reactions, flash chemistry, polymerization, photochemistry, electrochemistry and multistep syntheses of APIs can be accomplished effortlessly. Flow technology has potential to accommodate all kinds of transformations e.g. organometallics, organocatalysis, solid supported, couplings, oxidation, reductions etc. Novel process windows have opened up enabling reactions which cannot be traditionally practised in batch due to safety considerations or inadequate control on the kinetics. As more and more chemists start understanding the capabilities and limitations of flow technology and work together with chemical engineers for synergistic development of manufacturing processes, the advantages and flexibility of continuous manufacturing would become apparent. Batch mode operation to manufacture APIs is becoming unenduring due to various reasons e.g. most of the operations are space-intensive, some pose safety challenges, poor process-control, degradation of starting materials and products, batch to batch variability, difficult chemistries that cannot be scaled up etc. Transitioning from batch to flow would require a mind-set change and would turn out to be a game changer in the area of pharmaceutical production.

Flow technology has elegant features by virtue of high surface area that enables good heat and mass transfer, excellent process control, safety during operation, smaller footprint etc. Typically, in flow systems, reactants are continuously pumped into micro-reactors where they mix, react and give rise to the desired product that gets continuously collected or transitioned to the next step. Higher surface to volume ratio of micro reactors result in high heat and mass transfer rates along with precisely controlled residence time, enabling the entire system to provide higher yield and selectivity. In other words, we see that continuous flow manufacturing is emerging as an innovative and significant technology platform in the pharmaceutical industry.

Despite the key advantages, the major challenge for the industry is to establish flow technology applications to commercially relevant molecules. Another challenge is the identification of opportunities to apply flow technology to process intensification of current processes. Overcoming these challenges are found to be critical to the success of this technology in pharmaceutical operations. There are certain limitations of flow technology e.g. 60% of the reactions contain solids either as reactant, catalyst or product and current flow technology handles solids very poorly (inconsistently). Sometimes, clogging due to heterogeneous reaction mixtures poses certain degree of challenges, however some more advanced technologies are coming up to address these constraints. Alongside flow operations, a few essential batch operations such as reagent preparation, precipitation, distillation, work-up, filtration drying etc…are still required. Despite of these challenges, there are plenty of opportunities to develop novel reaction conditions e.g. new thermal windows for reaction, solvent selection considering limited lifetime of unstable or hazardous intermediates that provide safety, improve yield and selectivity to ensure quality, reduce waste generation to safeguard environment and control the cost, automated optimization to accelerate processes time and last but not the least, consistent scale-up(out) of the optimised reaction.

The increasing demand of generics and expiring IP of key medicines have forced the pharmaceutical industries to enhance their productivity in every sense. Flow processes are being developed to make large quantities of raw materials, key starting materials, intermediates of finished products to improve safety, quality, throughput and economic attributes. Potentially, all difficult reactions are carried out under flow chemistry conditions to maximize the throughput with minimal impurities. Cryogenic reactions, which require low temperatures in batch to batch production, can be performed at relatively higher temperatures in a very short period of time, which potentially lowers the operating expenses while also replacing space-intensive and expensive reactors. The distinctive advantage of flow operation is that once the optimized conditions have been identified on a small scale there may not be further process development required at scale and similar processes can be run in parallel. Despite all the advantages, flow chemistry is not suitable for every reactions and new creative thinking is required to further bring down the costs of production, improve the quality of drugs. In essence, flow technology undoubtedly has the potential to become an important manufacturing alternative in the very near future.

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WHAT APPLICATION AREA DO YOU SEE THE MOST RAPID UPTAKE FOR YOUR SOLUTION?

Currently there is a development in process industry to product portfolios which are more customer-specified. For this reason, micro- and millireactors can offer great benefits compared to classical batch processes. Key words are modularization, surface to volume ratio and continuous production processes as a pathway to optimized future production concepts. Even on an industrial scale of some thousands of tons of product per year first success stories are available and can be shown. With microreaction technology (MRT) absolutely new ways of production can be mastered, because of optimized process conditions like mixing and heat exchange and corresponding enhanced process control.
To give a short overview, further important benefits of micro- and millireactors are:
- short defined residence times
- easy process control due to low system inertia
- minimal hold-up
- short development times

Especially highly exothermic reactions including toxic or explosive reagents, profit of microreaction technology. Small hold up and enhanced process control is a great advantage over traditional batch reactor technology. High pressures and high temperatures can be achieved easily in MRT and offer a large variability during process development.

Implementation of micro- and millireactors in production processes results in strong economic benefits:
- higher yield
- lower formation of by-products
- improved product quality
- sustainable plant safety
- lower energy consumption and lower carbon footprint

Unfortunately, micro- and millireactors are not yet established in the market and a really underestimated topic in the market worldwide. Several very well-known companies in the segments of fine & specialty chemical production as well as in pharmaceutical production use micro- and millireactors in R&D and sometimes in pilot scale. This means that the paradigm shift Batch-to-Conti is still in progress. Hurdles to be taken are missing visible examples in production scale and education focused strongly on batch processes.

To finally answer the question, in our opinion attractive market segments for this technology are peroxides, sulfonation and ethoxylation, hydrogenation, lithiation, ozonolysis or the production of AI / APIs, to name just a few attractive options. Obviously potential is broader and a screening of internal product portfolios should be beneficially. Especially thinking of the economic benefits its now on the decision-makers to take on the baton to enter the pathway of next generation technology platform: micro- and millireactors.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

As already mentioned above, one of the hurdles of implementing micro- and millireactors from lab scale to

production scale in fine & specialty or pharmaceutical companies could be education and training. A lot of people still think in round flasks and do not even know the second, maybe advantageous, option. In future two options will become a natural mandatory requirement – Batch and Flow. This is the only possibility to decide for the optimal approach right from the beginning. Whether it is study or training or school education, everybody should get an idea about all important potentials in process technology.

In chemistry, chemical engineering or process engineering systematic training on the topic of flow chemistry must be included. Some universities already work on this topic, but not yet across the board. And this would be the idea for further inclusion of flow chemistry in academic education. Practical training must be obligatory for all named courses, chemistry, chemical engineering and process engineering. If everybody passes such a practical training, everyone has equal conditions and same competences. And this might even help to overcome misunderstandings between chemists and process engineers. This means double achievement, if both talking the same language when working together in industries.

TIMOTHY NOEL
Associate Professor, Eindhoven University of Technology

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

If we really want to ensure the uptake of flow chemistry, we have to embed the technology in every layer of our curriculum starting with the bachelor years. Only then will continuous-flow technology be considered as a viable alternative for current batch technology and will we be able to overcome that initial resistance.

I think a good suggestion would be to start with including flow experiments in the practical courses. In that way, students will experience the technology and see its added value to synthetic organic chemistry.

I also believe it is even more important to embed it in classical chemistry majors, since chemical engineering students are already decades aware of the technology. If you look at the background of most 'engineers' in pharmaceutical companies, they are not chemical engineers but organic chemists which have been repurposed. These people have never learned a course on chemical reactor engineering and are thus not trained to handle continuous-flow reactors. Hence, I believe that it is crucial to start such courses in chemistry curricula over the world. From what I experience, this is slowly starting but more will be needed.

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

That is hard to predict. However, I do expect many more flow applications to pop up in the coming decade. We see now more flow chemistry being used in early drug discovery, e.g. to speed up the making of med chem compounds. Also the popularity of electro and photo chemistry will create a need to use flow chemistry, even on a production scale.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

The advantage of ML is that you can reduce the amount of experiments by carrying out some of the screening in silico. However, in recent years, ML has been overhyped. For sure it will have a tremendous impact but we should be careful to overstate the capacity of ML. In my opinion, it is a great tool to assist the experimentalist, nothing more, nothing less.

VERSATILITY AND CONVENIENCE OF USING 3D-PRINTED REACTORS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS, USING FLOW TECHNIQUES

3D-printing is essentially important with regard to rapid prototyping to test a couple of reactor designs. Especially for challenging reactions, 3D-printing can enable the construction of tailor-made reactors.
Also in the laboratory environment, 3D printing has revolutionized the way we do things. Instead of ordering the right part and wait for the delivery, you can now easily print that part in no time and continue your work. I am sure that 3D-printing will further accelerate the collection of results in the future.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

I think that flow chemistry allows to make exactly the right amount at the right time. Most of the flow plants are substantially smaller (e.g. container size production units) which can be readily deployed. Localized production is going to become increasingly important. After the COVID pandemic, it is clear that it is dangerous to rely on international trade only. For key APIs, Europe should ensure its own production facilities and this can happen with flow chemistry.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow chemistry can keep the inventory of hazardous materials small when they are made in situ and immediately reacted away. This off course addresses the issue of safety quite effectively. Also, less dead zones are encountered in flow. It is in these dead zones where hazardous material could accumulate and subsequently explode.

WHAT APPLICATION AREA DO YOU SEE THE MOST RAPID UPTAKE FOR YOUR SOLUTION?

I think that a lot of flow chemistry is readily implemented for those chemistries which are dangerous to carry out, e.g. exothermic reactions. Also the popularity of photoredox catalysis and electrochemistry in synthetic organic chemistry will result in new synthetic routes which will need to be scaled. For these challenging reactions, continuous flow equipment are the reactor of choice.

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THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

The adoption of continuous manufacturing (CM) processes is rapidly gaining momentum across the industry due to the excellent groundwork done by academia, pharma companies, CDMOs and regulatory authorities over multiple decades. While there were only a handful of commercial drug products utilizing CM in 2019, the large size of the pipeline suggests that significant growth will occur the coming few years.

The use of continuous manufacturing processes for APIs offers several major advantages over traditional batch manufacturing. These benefits can include higher levels of quality and safety, and better efficiency. When the increasing synthetic complexity required to manufacture many pipeline APIs is also taken into account, we expect the number of processes that generate added value from CM will increase significantly over the next decade. The magnitude of investments being made in CM by many pharmaceutical companies, as well as CMOs such as Evonik, underlines the positive direction of this market shift.

One particular area that's driving demand for CM is the opportunity to accelerate development workflow and reduce capital investment during commercial implementation through the application of modular concepts. Here, Evonik has designed a Modular Continuous Pilot Plant (MCP), setup in Hanau, Germany to support flow chemistry under cGMP.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Manufacturing in flow is characterized by a continuous output of material. This compares to batch operations which are defined by cycle-time and batch size. CMC for batch processes is fully built on the definition of a batch, allowing control over defined raw material input, reaction conditions and product amount with quality release. However, steady-state continuous processing requires a different understanding, as feeds are constantly converted and characterized by the nature of the setup and residence time distribution. This explains the importance of process analytical tools (PAT) that facilitate continuous, nonstop process monitoring and automation. The benefit of continuous manufacturing clearly lies in enabling process windows that allow a fully QbD driven control over selectivity without the heat and mass transfer limitations imposed by large scale batch reactors.

At Evonik, teams of process design, engineering, analytical, quality and regulatory experts are efficiently collaborating to ensure quality focused process development and implementation.

VERSATILITY AND CONVENIENCE OF USING 3D-PRINTED REACTORS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS, USING FLOW TECHNIQUES?

Sintering laser melting (SLM) technologies represent an important tool in the box for reactor-design, process development and scaleup. Real benefits include flexible structure design that allows complex flow patterns and efficient mass and energy transport as well as rapid access to prototypes. Importantly, printing can make a more efficient use of high value materials of construction. For implementation in a GMP environment and commercial production, the legal and regulatory framework also needs to be considered. Evonik has established a 3D printing and SLM competency center that works with relevant development, manufacturing and quality functions, as well as local authorities, to rapidly advance projects into commercial applications.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

Most of today`s academic research is not focused on the industrial implementation of processes. While scientists starting out in the industry are well trained in organic chemistry, they can often need additional coaching in process scale-up as well as other technical aspects. It would be desirable if academic institutions could further emphasize the importance of technical process implementation based on thorough physicochemical process understanding. State of the art methodologies applied especially in flow development such as CFD or concepts of self-optimizing systems should be discussed in universities in any case.

THE ROLE OF FLOW CHEMISTRY IN HELPING COMPANIES ACHIEVE THEIR SUSTAINABILITY OBJECTIVES, PARTICULARLY WITH REGARDS TO CARBON FOOTPRINT.

The access of novel process windows that cannot be used in batch, and the application of optimized tailor-made flow reactors and equipment, allow flow processes to be developed exactly based on the kinetic network and thermodynamic requirements. This can lead to reductions in energy consumption, optimized mass intensity factors and a lower carbon footprint compared to multipurpose batch plants where process adaption to equipment capability is required in many cases. Evonik is steadily reviewing opportunities to reduce emissions. We remain on track for the efficient use of materials to achieve a 50% CO2 emission reduction goal by 2025. Continuous processing is regarded as excellent technology for this.

RUI LOUREIRO
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WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

The knowledge of flow chemistry in school is very important to have a young generation of chemists thinking about its use in the pharmaceutical industry. We all understand the benefits of using continuous chemistries, but we need the new generation to have a great grasp of how to apply this technology to open synthetic pathways that so far were prohibitive to the industry. The basic knowledge of how to understand how flow chemistry can be used to speed up process development is of great importance. In this area understanding physical chemistry (reaction kinetics, interaction between molecules …) combine with basic engineering knowledge, in my view, will be very important as the chemistry occurs very quickly and most of the time will be spend on setting up the equipment and therefore understanding mass transfer issues, how pumps and back pressure regulators work and other equipment will significant help the chemist talking with the engineers. Another very important aspects is the knowledge of PAT and how they can be used to help developing the flow chemistry process. After all a flow chemistry process that does not uses PAT tool will never take the maximum possible benefit out of flow chemistry.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

I believe that the use of machine learning in the pharma industry is the next big thing. Thus, the use of all data generated in the past and in the coming years will open the door to speed up development. This has already shown its first results and synthetic routes designed by computers have been demonstrated to be more efficient than those design by chemist for the same API. Thus, ML will help reducing the number of pathways followed to develop an API and at the same time will ensure that the most effective synthetic route has been chosen.

The use of QbD in the pharmaceutical industry has the ultimate goal of achieving API quality through process control and not based on testing, which can also be seen as having real time release as the product quality is ensured by the process. The use of ML will not replace QbD but it will help the industry to achieve this goal of real time release. I expect that ML will support the better connection between the CPP and a product CQA through the use of past experience and with this achieve a faster development while ensuring the product quality throughout the entire chain of manufacturing.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

The end goal is always to ensure product quality, and the principles of QbD lead closer to the objective of having quality built in-to the product instead of by testing its quality at the end of the process. This is only possible if we have ways to demonstrate the product quality control. In a CM rig this is only possible if we implement PAT tools which will allow a significant different control strategy from the batch approach. In API manufactured, in a batch approach, the control strategy is based on controlling process parameters that impact the product CQAs and this is the same when we move to a continuous process. Nevertheless, there are difference between the two approaches; in a continuous process, quality is constantly monitored through PAT, and the process parameters can be adjusted in real time to ensure product quality and part of a batch can be segregated if some parameters falls out of control. This is not possible in a batch as we treat is as one single entity and therefore if an excursion occurs the full batch is only tested at the end to ensure product quality. One of the most critical aspects in the control strategy when doing a batch process, is control over the scale dependent variables as we increase production scale. In flow because we can scale-out instead of scale-up we remove the scale dependent variables and we can ensure a better product quality even when producing large product quantities.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

I believe this is the area where flow chemistry can have the larger impact in the pharmaceutical industry. Flow reactors are small and therefore they allow that the combination of dangerous reagents to be done all in small quantities which therefore reduces risk in case of any failure. As an example just imagine you need to carry out a reaction that is exothermic and can add to a run-away reaction. In this situation if we use a batch reactor, we are talking probably of having more than 1000 L or reaction mixture that will need to be well mixed and cooled down. In case of an accident this will lead to a serious situation. On the contrary if you consider that we have the same reaction but that the maximum we mix at one time is 1L this immediately reduced the potential impact safety. Additionally, flow chemistry allows a continuous reaction quench and separation of the reaction by-products which again if quench is exothermic the amount of cooling required at any moment in time is considerably lower than the one required by a large production vessel. Another change that flow chemistry allows is the use in continuous of membranes or other equipment that continuously reduces the content of organic solvents in water allowing a faster return of water to the ecosystems with a very reduced time. Thus, the potential impacts of flow chemistries in HSE is one of the major drivers for the pharmaceutical industry to make efforts to move from batch to continuous.

DIRK KIRSCHNECK
Strategic Director, Microinnova

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

The subject of reaction technology is a key competence for the exchange between chemists and engineers. The continuous chemical plant in the lab needs chemical competence, as well as reaction technology competence to use the plant in the best possible way.

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

I expect a strong impact of COVID-19 on the flow chemistry and continuous processing community. Governments have realized that API manufacturing capabilities are a key resource, since some countries have blocked the export of APIs in the period of the highest demand. The ability to have access to modular, flexible pilot plants and manufacturing units offer the option to take action, especially in crisis situations. Sourcing medical diagnostics, treatments and items such as reagents and intermediates are critical for crisis management. The response to a dramatically changing demand contains a high value, especially in cases where the supply from other parts of the world is not stable. Modular plants using continuous manufacturing can deliver a minimized time-to-produce and can therefore save lives.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

I do not see a conflict between these two approaches. The aim is to develop a robust and reliable process with high level of process capability (six-sigma-level). Quality-by-Design is a Quality Management Tool, while the implementation of Machine Learning algorithms helps to find the best possible window of operation. A useful combination makes sense.

XIONG-WEI NI
Founder and CSO, NiTech® Solutions Ltd

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

The number is rather small, given that significant R&D efforts have put into this space in the last 10 years. Companies who have already embarked continuous manufacture tend to implement continuous approaches on a product by product basis, rather creating an overall platform strategy. While substantial investments have been made, these have been scattered and far from harvested to its potential. The added fact is that there is a lack of personnel expertise and training, and crucially, insufficient support at the corporate-level. As a result, the numbers for production units do not match the investments, efforts and governmental drives in the past decade. In order to accelerate the adoption of continuous manufacturing in

VERSATILITY AND CONVENIENCE OF USING 3D-PRINTED REACTORS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS, USING FLOW TECHNIQUES.

Every chemical transformation is different. 3D-printed reactors can enable an easy adjustment of the reactor to the needs of the chemical transformation. That means that 3D-printed reactors reduce the time to market.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Control strategies of Continuous Manufacturing can lift chemical processing to precise processing. This means that every molecule is exposed to the same conditions during processing, while in Batch, the molecule can be in a concentration spot at the inlet, at the hot wall of the vessel or in shear zone of the stirrer. That means continuous processing provides a process with a level of uniformity or in other words a high process capability.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

The highest value for society is good availability of key APIs, medical diagnostics and medical treatment in a crisis like COVID-19. That means local manufacturing of APIs is a key resource to secure the supply of medical treatments.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Of course, it can. Since reactor volumes decrease dramatically, the impact of a potential accident is on a much lower level. Hazardous reagents can be manufactured on-demand, which eliminates the risk of transport and storage. New business models can support the on-demand supply.

THE DEVELOPMENT OF AGILE, CONTINUOUS MANUFACTURING (CM) SYSTEMS WILL BE ONE OF THE MOST SIGNIFICANT CHANGES IN THE PHARMACEUTICAL INDUSTRY IN THE NEXT 10 YEARS. CONTINUOUS PROCESSING IMPROVES THE QUALITY OF PHARMACEUTICAL END PRODUCTS: BY FOCUSING ON QUALITY DURING THE WHOLE PRODUCT LIFECYCLE AND BY UNDERSTANDING THE CAPABILITY OF THE PROCESSES, MANAGING SOURCES OF VARIABILITY AND DECREASING ANY ASSOCIATED RISKS.

I support this statement. This will transform the way of processing in the pharmaceutical industry fundamentally.

the coming years, government supported incentives are necessary in a world-wide basis, including tax incentives and streamlining regulatory processes.

For continuous crystallisation, the one bottleneck is how effectively to make seeds, as continuous seeding is required in continuous crystallisation, no matter what crystallisation platform is used. Right size and correct mass of seeds is the successful combination of Seeding Operation (1). Traditional methods of generating seeds involve either dry or wet milling, both of which are notoriously labour and time intensive processes, do not render scale up operation.

Wet milling

A fraction of the product crystal stream can be directed to a seed preparation tank. A Raman spectroscopic probe or FTIR probe can be installed at the end of the product stream, the concentration of crystal solids in a solvent or solvent mixture can readily be determined. If the solid concentration is equal or higher than the required percentage for seeding, the slurry is ready for milling. If lower, a known amount of dry crystal products of any size must be added into the solution to make up the desired concentration before milling. A proportion of solvent can be added after the milling if it is higher.

The same mechanical device for wet granulation can readily be used here without the bonding or adhesive liquid agent, involves a high shear impellor, in either a batch or flow set up. For crystal size during milling, a FBRM probe gives the online information, or samples taken and analysed periodically the offline data. The batch set up resembles a kitchen smoothie machine, foams are often formed when air is entrained into the solution when operating at high rotational speeds; majority of the crystals are migrating into the foams, affecting the determination of crystal sizes and defeating the purpose of milling. Antifoam agent can be used to alleviate this phenomenon, but the removal of antifoam brings about more problems. When the rotational speed of the impellor is too low, it would take weeks to complete a batch. A compromised speed could only be found through experimentation. As a rough rule of thumb, it would take about 1 week to make a batch of 5 L seeds of 15w/w% with a mean diameter of 50 µm.

The flow set up necessitates pumping and recycling the solution containing crystals from a tank through a rotor-stator type of high shearing device (2) or using a turbulent jet (3). Seeds generated this way often undergo agglomeration, but an ultrasonic device can be used to control and reduce this effect, although lengthen the process (4). The overall time take to prepare a 5 L seeds of 15w/w% with a mean diameter of 50 µm would still be 3-4 days.

Wet milling can also be done using sonication, an ultrasonic device is inserted into the tank, appropriate intensity is selected, the crystal slurry is bombarded by the ultrasonic waves, achieving the size reduction. The advantage of this method is that it can produce very small size, albeit take much longer time. The disadvantage is that ultrasonic device must be switched on throughout the process, or agglomeration would take place when sonication is stopped. For a batch of 5 L seeds of 15w/w% with a mean diameter of 50 µm, this method would take the similar time as the above.

The wet milled crystals can also be filtered out, dried and weighed, made up of the seed slurry offline as the dry milling method does.

Dry milling

Dry milling literally involves 'pedal and mortar' type of devices to grind crystals, either manually or by machines. This breaks up crystals and the required crystal sizes are obtained by sieving. The grinding process is repeated for oversize crystals, while the fines so generated are re-dissolved for recrystallisation. Once the desired seed size is achieved, the slurry is made up with a known mass of crystals per litre of solvent based on solubility at a seeding temperature. It would take a few hours to grind dry crystal particles to a mean diameter of 50 µm for a 5 L batch of 15w/w%.

Continuous seed generation

Are there any ways of generating seeds continuous? While labile region is to be avoided at all costs in cooling crystallisation in a continuous oscillatory baffled crystalliser (COBC), operating antisolvent crystallisation in COBC at labile region presents an elegant means of generating seeds of small crystal size and large crystal mass, the two essential criteria for seeds. It has shown that the steady states of crystal sizes were achieved in the COBC crystalliser of 700 mm long, 884 g of seed crystals of uniform size (45 ± 3.01 mm) were produced over 6.25 h (5). These particles are perfect for seeds and are sufficient to make up 12 times of 5 L seeds at 15w/w%.

Generally, the smaller the seed crystal sizes, the larger the surface areas, the less the seed crystals to be used, the more effective the seeding method. In terms of producing seeds of <100 µm, the process is not only more problematic, but also takes days and requires significantly more energy to achieve the size reduction. By assuming growth only, the product crystal and the seed crystal sizes (diameters) follow the formula below:

$$\left(\frac{Diameter\ of\ seed\ crystal}{Diameter\ of\ product\ crystal}\right)^3 = \%\ of\ seeding$$

As the desired product crystal size for majority of pharmaceutical compounds is generally about 150 µm, using the above formula and taking 5% seeds, the corresponding required seed size is about 50 µm. The above method thus provides a faster, scalable and continuous means of generating seeds.

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BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

Quality-by-Design (QbD) defines a systematic approach for end-to-end development that begins with predefined objectives and emphasizes product and process understanding and process control, based on scientific investigation and statistical analysis. The overall aim is to ensure a safe drug supply to the consumer and improve manufacturing performance. There is scope to insert Machine Learning (ML) algorithms into the QbD process to expedite development activity. ML can be leveraged in a number of ways, including; smart data generation, similarity analysis and quality prediction. While the benefits of these approaches can be speculated, the challenges are more apparent – firstly, a large amount of structured data is generally required to train and refine algorithms, this is not always freely available. Secondly there is a lack of a defined regulatory framework for these algorithms, which is made worse by the perceived "black-box" nature of some ML models. However, modern computational Design-of-Experiment (DoE) already demonstrates the potential to reduce experimental work required to deliver process models reliable for scale-up and analysis of product integrity.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Control strategies for Continuous Manufacturing (CM) need to be based on rapid feedback, based on measurements accurately reflecting the process state, with adjustments to maintain precise control of all aspects of the process, rather than infrequent measurements taken in a batch process which may not be homogeneous and not indicative of the system state. Continuous processes typically allow measurements closer to the point of interest and adjustments which directly affect the process behaviour and final product characteristics. CM presents opportunities to ensure an overall higher quality of product. Eg if product quality is measured at regular intervals, Advanced Process Control (APC) can be employed to automatically update the process parameters in response to process and raw-material disturbances. A well-designed APC system implemented on a continuous process ensures that everything leaving the manufacturing line is the highest possible quality. In batch manufacturing (BM) a single quality measurement with wider limits measured at the end of the batch time leaves no scope for remediation if there has been quality-creep during the process. Of course, this brings challenges such as "how to measure quality in-line?" and "how to define the control space if a process is under closed-loop control?". Fortunately, increasing maturity of CM within the Pharmaceutical industry combined with knowledge transfer from other high-value manufacturing industries allows these questions to be answered.

CONTINUOUS WET GRANULATION AND DRYING HAVE LONG BEEN A HOT TOPIC IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D) AND INDUSTRY. WHAT IS YOUR SOLUTION?

Perceptive Engineering has developed a software solution to enable rapid, robust implementation of Continuous Process Verification (CPV) for pharmaceutical direct compression and wet granulation processes. This provides interfaces to processing equipment and associated analytical devices, allows visualisation and statistical monitoring of Critical Process Parameters (CPPs) and critical quality attributes (CQAs). It simplifies development of monitoring and diversion strategies using soft-sensors, residence time distribution (RTD) models and/or chemometric methods to ensure the process remains in a state-of-control during manufacturing. Product quality and process efficiency can also be optimised by including our APC method providing model-based control of process CQAs. All methods are backed-up with configurable model maintenance workflows and management of measurement uncertainty for robust operation.

THE DEVELOPMENT OF AGILE, CONTINUOUS MANUFACTURING (CM) SYSTEMS WILL BE ONE OF THE MOST SIGNIFICANT CHANGES IN THE PHARMACEUTICAL INDUSTRY IN THE NEXT 10 YEARS. CONTINUOUS PROCESSING IMPROVES THE QUALITY OF PHARMACEUTICAL END PRODUCTS: BY FOCUSING ON QUALITY DURING THE WHOLE PRODUCT LIFECYCLE AND BY UNDERSTANDING THE CAPABILITY OF THE PROCESSES, MANAGING SOURCES OF VARIABILITY AND DECREASING ANY ASSOCIATED RISKS.

While this statement is true, the industry has made significant progress in developing continuous manufacturing (CM) systems in recent years and there is no sign of progress stopping. Improvements in sensor technology, spectroscopic and otherwise, have allowed democratisation of development. This coupled with the prevalence and relatively low cost of data storage means that now, more than ever, process data is being recorded, catalogued and analysed to understand the impact of variability from raw material to finished product. The final piece of this grand puzzle lies in the way the industry collaborates to develop standardised solutions, shared material databases and develops a Quality by Digital Design approach to shared challenges

WHAT APPLICATION AREA DO YOU SEE THE MOST RAPID UPTAKE FOR YOUR SOLUTION?

In addition to the CPV platform, we have developed an "Optimised Experimental Design Platform (OEDP)". This provides connectivity to lab and pilot scale process equipment and associated PAT devices (Process Analytical Techniques) allowing users to automate processes such as DoE (Design of Experiments) execution, data fusion and chemometric modelling. The platform can be extended with "Smart" and "Modern" DoE designs combined with the implementation of advanced ML algorithms and APC for rapid, automated process development. The platform is designed to be process agnostic so the same approach is applied across all process units, helping to standardise workflows, data generation and data storage. OEDP is being evaluated across many advanced manufacturing applications from food to personal care to pharma. It is hoped this will go someway toward mitigating the challenges of ML discussed earlier.

JOHANNES KHINAST
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BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

Machine learning is powerful when there is an availability of lots of data, even noisy data, and when these data can be used to detect complex interdependencies that are not accessible otherwise. Process control, image and data analysis are a few examples, where useful applications can be envisioned. Nevertheless, one needs to be aware that machine learning is a tool that can be used for detecting structure in data but not for extrapolating or gaining insight in a process. Yes, it can be used to screen molecular libraries and even to identify new molecules if the targets are known, but an understanding of the biomolecular basis of diseases will always be gained by hard "mechanistic" work. In our field, i.e. formulation and process development, we thus count mainly on mechanistic models that are derived from a sound understanding of the underlying physics and chemistry.

Mechanistic approaches allow the design of new formulations and processes even if few data are available, early on in a development process. Thus, I believe that machine leaning will be useful for some applications but will not be useful in all areas.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

Continuous manufacturing is built on real-time process control via sensors and soft sensors. That means that what is applied is dynamic control strategies, not end-of-pipe testing, so the requirements are very different. Note, however, that the tools developed for CM can also be applied in batch manufacturing and can enhance the quality. Thus, in our mind the main progress that was achieved by the "CM-movement" is better real-time process analytics and process control. In some way the pharmaceutical industry was forced to arrive in the 21st century.

BILL DUBAY[1], OLIVIER DAPREMONT[2]
1. Global Head of R&D SK pharmteco
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DO YOU SEE CHALLENGES WITH THE CLEANING VALIDATION OF CERTAIN TYPES OF FLOW REACTORS, FORMULATION AND TABLETING STEPS ETC FOR PHARMA APPLICATIONS?

Cleaning is always a challenge for the pharmaceutical industry. However, the great advantage of continuous flow reactors is that equipment can be small and can be dedicated for a product. Therefore, cleaning can become less problematic. In addition, a cost benefit analysis needs to be conducted to evaluate using single use equipment versus performing a difficult and often time-consuming cleaning procedure.

THERE CURRENTLY ARE 4 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

There are actually more APIs using continuous processing already – not flow but continuous purifications using Simulated Moving Bed (SMB) and continuous falling film distillation. Therefore, the regulatory authorities are quite familiar with these processes. There is definitively a growing interest in developing continuous processes for either one-step or multiple steps of chemistries. It would not be surprising to see the number of APIs using CP to ramp up in the next 5 to 10 years. However, the economic pressure and the scarcity of equipment available may be slowing down the development of CP versus batch processes.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

The development of continuous processes requires a significant amount of work upfront to understand the chemistry and the physics of the process. However, every process can be boiled down to a few parameters; stoichiometry, pressure and temperature and maybe a couple of additional very specific parameters. If the ranges for these parameters are well understood and well controlled, then the output of the process should be consistently within specification. Understanding what can go wrong and the speed at which this can happen is very important and control strategies, much be put in place to alleviate these potential events. A Failure Mode and Effect Analysis (FMEA) should be performed early on, during the process development, and the chemists/engineers should focus their efforts in reducing the high-risk events identified by the FMEA. The FMEA should be re-evaluated regularly to manage the risks associated with the process. These parameters can be easily controlled using various forms of Process Analytical Technology (PAT).

WHAT ADVANCES ARE MADE IN THE AREA OF FILTER-DRYING & WHAT REMAINS TO BE SOLVED FOR CM APPLICATIONS?

Filter-drying is to this day inherently a batch process. Continuous drying methods are being developed, this is for example something we at RCPE are working on, yet it is not an easy process to be converted to continuous manufacturing. Lots of challenges have to be solved (e.g. particle agglomeration and breakage), especially for the mass throughput rates in continuous manufacturing which typically are in the range of 1-50kg per hour.

CONTINUOUS WET GRANULATION AND DRYING HAVE LONG BEEN A HOT TOPIC IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D) AND INDUSTRY. WHAT IS YOUR SOLUTION?

At RCPE we use continuous extrusion (both wet and hot-melt) to produce granules in a continuous manner.

WHAT ADVANCES ARE MADE IN THE AREA OF FILTER-DRYING & WHAT REMAINS TO BE SOLVED FOR CM APPLICATIONS?

So far semi-continuous filter/drying processes are being used in the pharma industry of small molecules. This conveniently provides a "batch" of homogeneous quality and therefore it is going to be quite difficult to move away from that. One of the main challenges would be to perform continuous filtration and drying. However, pumping solids efficiently and consistently with minimum equipment failure is by far the most difficult aspect of filter/drying. Some technical solutions from other industries should be considered and implemented with the caveat that this has to be done within a strict cGMP environment.

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Currently there is very little capacity installed for continuous manufacturing especially compared to the vast batch reactor capacity installed worldwide. The current approach is to develop a process, optimize it and then build the required equipment to match the desired annual production need. This can take 16 to 24 months depending on the complexity and the number of unit operations involved and requires as well a significant amount of capital. Comparatively for a batch process, the process is modified to fit in the already existing (installed) equipment – even if sometime process efficiency is sacrificed. Multiple size reactors are available, and the process can be scaled-up rather rapidly. Ideally, manufacturing suppliers should have existing CP equipment and tools to develop the process at small scale with "simple" scale-up rules available to fit the process to the existing, installed, equipment. This will allow for a much faster development and implementation of a continuous process. For example, at SK pharmteco, we can quickly screen chiral separation (2-3 weeks) and based on the outcome of the screening and our experience, we can quickly calculate, with modelling tools, the daily production

rate we can achieve for the various size of Simulated Moving Bed (SMB) units installed at the plant. This allows us to quickly provide the customer with cost estimates and production solutions. It is not unprecedented that a process developed at g scale, reaches 100's kg scale within a year. The process will go through clinical phases up to commercial within a few years.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

The use of CP significantly reduces the risks associated with hazardous chemistries. At any moment in time only a small amount of reagents are in contact. Some chemistries can be done in flow at significantly higher pressure allowing the use of solvent at higher temperature than their normal boiling point, increasing the choice of solvents (more environmentally friendly solvents can be used), solubility and process kinetics. Reaction can even be performed using supercritical CO_2, making the process more environmentally friendly (CO_2 is extracted from the air or is the by product of other industries) as the material produced will be simply collected after the CO_2 is returned to its gas state by reducing the pressure downstream.

Because the ratio of the reactor surface area to the volume of solution is most favorable, it is easier to provide high cooling to allow a better control of the reaction and avoid runaway reactions.

Finally, it is easier to have automated procedures in place to safely shut down the process to avoid further supply of reagents to the process (fail safe mechanisms).
These types of solutions have been in place for over 70 years at companies such as Aerojet for the manufacturing of highly energetic materials (rocket fuels and explosives).

MARK MULDOWNEY
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Sterling Pharma Solutions

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

There are a number of challenges facing the pharmaceutical industry when it comes to utilising continuous manufacturing (CM) to bring more APIs to market. These start with the education of chemists and engineers and go all the way to educating quality and safety departments in industry.

It is significantly harder to gain knowledge and experience on new technologies once you have left academia; in industry time is precious and unless you can put dedicated resource aside then learning new ways of working is often restricted to specific projects.

When it comes to ensuring sufficient academic teaching around CM, it's important that we ensure students from different disciplines learn the basic principles of CM and have an appreciation of the different perspectives. We should broaden teaching to groups that wouldn't initially be considered, for example a significant majority of Quality Managers in the pharma industry started their careers as analytical chemists. Also, it's important to teach that what is theoretically possible is a good start but following up with known examples from industry and gaining an understanding of how those theories had to be modified, for example when they met scale up issues, will give students additional insight that can be applied later on in their careers.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

Another topic that should be taught to students in academia is quality by design (QbD)and what this could mean for a continuous process. A good example here is that one of the benefits of a continuous process is the ability to optimise a range of parameters using fewer reactions when compared to performing a full factorial QBD batch process study. When undertaking a Design of Experiments (DOE) study multiple standard runs must be performed to remove the challenges associated with human reproducibility. However, machine learning coupled to online analysis has been demonstrated to be a powerful tool in optimisation of continuous processes. Provided the continuous system performs consistently then optimisation can be achieved without an operator and so process parameters can be explored 24/7 without the need for a person to be constantly reviewing data.

VERSATILITY AND CONVENIENCE OF USING 3D-PRINTED REACTORS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS, USING FLOW TECHNIQUES

When looking at the different types of reactors now available the new technique of 3D printing a bespoke reactor, which is gaining popularity in academic labs, is of great interest. Whilst a 3D printed reactor will obviously have certain limitations, based on materials of construction and size, it does have the potential to quickly optimise both design and function. In my opinion, the potential for using cheap replaceable 3D printed reactors is something that will become of more interest as projects move from discovery and into bulk manufacturing, particularly for low cost drugs.

The ability to generate a reactor quickly from an approved and qualified design will mean that these reactors can be discarded at the end of the campaign so prolonged and expensive cleanouts can be avoided. In addition, if a company has the ability to print their own reactors it will minimise the time required to set the equipment up and replace parts if they become blocked and cannot be cleared.

WHAT ARE THE BENEFITS THAT FLOW CHEMISTRY AND LOCALISATION OF MANUFACTURE OFFER TO PRODUCERS AND MARKETS?

Finally, when customers are looking for suppliers to manufacture products in flow the proximity of good local Universities who have experts in flow technology is a major benefit. Combining the academic skills of invention and the understanding of manufacturing practices is the best of both worlds and something we at Sterling believe we are well situated to do. ■