# Panel Discussion on FLOW CHEMISTRY

*In this issue, we present a Panel Discussion on manufacturing using **flow chemistry**. This topic is of particular interest as the importance of micro reactor technology and flow chemistry in industrial manufacturing is rapidly rising; we have testimony of this because of the high number of companies that showed willingness to participate in this discussion around a virtual table.*

*The following players have joined the initiative:*

## PANELISTS

**Ulrich Wietelmann**, *Manager Business Development & Innovations Lithium Specialties and Battery Materials* - Albemarle

**Boris Gorin**, *Senior Scientific Advisor, Research & Development* Alphora Research

**Jacopo Buzzanca**, *Custom Synthesis BD* Angelini SpA | Fine Chemicals Division

**Paul Quigley**, *Head of Drug Substance* and **Samuel Bourne**, *Process Development Chemist* - Arcinova

**Miguel Angel Gonzalez**, *Sr. Director – Chemical Engineering* Asymchem

**Marcel Vranceanu**, *Research Engineer Formulation Processing Technologies* and **Christian Holtze**, *Senior Research Engineer Formulation Technology* - BASF

**Franz Amann**, *Senior Scientist* - Carbogen Amcis

**Charlotte Wiles**, *CEO* - Chemtrix

**Guillaume Gauron**, *EMEA Technical Sales Manager* Corning® Advanced-Flow™ Reactors

**John Tsanaktsidis**, *Research Director* - CSIRO Manufacturing

**Tony Warr**, *Head of Process Technology* Dr. Reddy's Laboratories

**Jochen Becker**, *Global Project Manager* Evonik Nutrition & Care

**Torfinn Haaland**, *Research Coordinator* - GE Healthcare

**Flavien Susanne**, *R&D Drug Substance Continuous Processing Lead* - GSK

**Silvia Werner**, *Project manager* Heraeus Pharmaceutical Ingredients

**Rui Loureiro**, *Director, R&D Process Chemistry Development* Hovione

**Steve Pollington**, *Research Leader* - Johnson Matthey

**Pierre Giuliano**, *Managing Director* - La Mesta - Yriel Group

**Rajiv Khatau**, *Managing Director* - LODAAT

**Amanda Evans**, *Scientist* - Los Alamos National Laboratory

**Dirk Kirschneck**, *Managing Director* - Microinnova

**Steven T. Perry**, *Senior Product Manager* Parr Instrument Company

**Ryan Seongho Oh**, *Vice President, Head of R&D* - SK Biotek

**Matthew M. Bio**, *President & CEO* - Snapdragon Chemistry

**Frank Gupton**, *Department Chair* Virginia Commonwealth University

**Ulrich Wietelmann**, *Manager Business Development & Innovations Lithium Specialties and Battery Materials* - Albemarle

**Why change from batch to flow?**

Flow chemistry serves to achieve process intensification and it is an efficient tool to implement green chemistry principles. Frequently, the reaction concentration can be increased and higher room/time yield be achieved hence. Besides process intensification, there are safety advantages for the case of toxic or thermally labile materials involved and/or high exothermicity of the reaction. Energy savings are realized due to less specific cooling needs.

Finally, there are yields improvements, better product purities, a higher degree of process stability and reduced solvent utilization possible. All these advantages have been recognized by the industry and pharma processes are currently converting from batch to flow in a high rate. The US FDA (Federal Drug Administration) has recognized the strong impact of continuous manufacturing on product quality and therefore supports the conversion from batch to flow. Novartis expects that continuous manufacturing in the pharmaceutical industry has the potential to cut drug manufacturing time by 90% and drug manufacturing costs by 30-50%. (https://www.novartis.com/stories/discovery/new-drug-manufacturing-tools-change-pharma-chemistry). As an example, we have found that butyllithium processes (bromo/lithium exchange and deprotonations) are significantly improved by simply using butyllithium in higher concentration (> 2.5 mol/L).

Such processes save hydrocarbon solvents and can increase reaction concentration by a factor of 2-10 and this goes along with significantly reduced danger of clogging microstructured channels.

**Approaches for minimizing risk when implementing a new technology / technique?**
For the case of flow chemistry processes, there is flexible, profound lab equipment from different producers available. Typically, these can also supply a useful software, which minimizes errors in experimentation and a quick screening of key reaction parameters like stoichiometry, temperature, solvents etc. This systematic approach allows for detecting optimum conditions and mitigates safety, product purity and the like pitfalls.

**What role can modelling play in flow process development?**
Kinetic and thermodynamic parameter estimation modelling is a vital tool in order to compute essential data for the design of microreactors.

**Does one size fit all or should we consider integration of technologies / techniques?**
The various kinetics and physical requirements ask for dedicated equipment, when it comes to scale-up and commercialization of chemical processes.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Flow chemistry is primarily applied in areas, where a high, constant product quality is required and the products need a flexible, and/or low-investment cost process. This is the case in the product development phase, e.g. when similar, but chemically slightly different products are under investigation or when the user expects short product lifetimes. These are areas for specialty chemistry, typically in the pharma, electronics and agrochem field.

**How important is collaboration?**
There are several highly experienced companies specialized on the field of microreaction and flow chemistry technologies. For a newcomer it makes perfectly sense to cooperate with such, typically small, start-up-type companies. We have recognized that challenges in details (e.g. construction materials, pumping technology, microreactor selection) are vital aspects determining the commercial viability of a flow process. A "guiding hand" from such an experienced enterprise can minimize pitfalls and ensure straight-forward process development.

**What challenges remain?**
Specific reactions, e.g. gas/liquid and all reactions involving solid raw materials need tailored process technology. This is typically not available from off the rack

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
We have no experiences in this area, but: why not?

## COMPANY PROFILE

**Albemarle Corporation** (NYSE: ALB), headquartered in Charlotte, NC, is a global specialty chemicals company with leading positions in lithium, bromine and refining catalysts. We power the potential of companies in many of the world's largest and most critical industries, from energy and communications to transportation and electronics.

Working side-by-side with our customers, we develop value-added, customized solutions that make them more competitive. Our solutions combine the finest technology and ingredients with the knowledge and expertise of our highly experienced and talented team of operators, scientists and engineers.

**Albemarle** is one of the world's leading suppliers of Lithium compounds like Butyllithium, Hydrides, Alkoxides, Amides and Lithium metal. With this expertise, the company also supplies other organometallic compounds as versatile tools for organic synthesis, such as Grignards. Furthermore, **Albemarle** supplies Cesium compounds as well as metal products based on Barium, Strontium, Zirconium, or Titanium.

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**Boris Gorin**, *Senior Scientific Advisor, Research & Development* - Alphora Research Inc

**Why change from batch to flow?**
Flow processing offers substantial advantages over batch processing in pharmaceutical manufacturing (in particular, in the manufacture of synthetic pharmaceutical substances). Just to name a few, it's a significant improvement of process safety associated with lesser volumes of chemicals processes per time and volume units; reduction of energy consumption and environmental footprint improvement due to much better heat and mass transfer in flow processing and lesser waste streams volume, and significant cost reduction (30-50%) as an overall result of other advantages.

**Approaches for minimizing risk when implementing a new technology / technique?**
One of the major challenges during implementation of continuous processing in pharmaceutical manufacturing relates to its intrinsic regulatory requirements and, in particular, to monitoring and controls of product quality. Implementation of Process Analytical Technologies (PAT) along with Continuous Flow processing as well as appropriate validation of new technologies helps to minimize risks associated with innovation.

**What role can modelling play in flow process development?**
Process engineering and computer modeling is an essential part of designing robust and efficient continuous flow processes for chemical manufacture of synthetic pharmaceuticals. Understanding critical process parameters and design space for any chemical process is not only a key to successful implementation of the flow processing, but also a regulatory trend of these days in our pursuit of Quality-by-Design approach.

**Does one size fit all or should we consider integration of technologies/techniques?**
Chemical manufacturing of the synthetic pharmaceutical substances depends to large extent on the nature of those substances and complexity of chemical processes associated with their manufacture. As such, the "one size fits all" concept doesn't work in our industry and integration of various technologies is a must. Different chemical processes require different processing conditions construction materials (compatibility issues), controls of processing parameters, product isolation and purification, etc. Combination of various CF platforms (microfluidics, plug-flow, CSTR, etc.) as well as associated process analytical technologies (IR, UV, NMR spectrometry, conductivity measurements, etc.) is absolutely required for designing robust and efficient continuous processes.

**What challenges remain?**
In my humble opinion, the main challenge for introduction of any innovation is always human and business inertia. Businesses and scientists should be more openminded to new technologies.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
Rapid uptake of foto-redox chemistry in organic synthesis over the last decade demonstrates great potential of this synthetic methodology and opens wide-ranging opportunities of its application. Photo-redox chemistry is a perfect fit for exploration in flow processing. This has been demonstrated in multiple publications from academia recently and it's time to start exploring this technology in industrial settings. There are many equipment manufacturing companies these days that offer flow reactors made of UV-transparent materials that allows to use such modules in manufacturing plants.

**In which markets will flow processing have the greatest impact?**
Being a veteran of pharmaceutical industry, I strongly believe that pharmaceutical manufacture (both pharmaceutical substances and finished dosage forms) will see the greatest impact in the next decade or so. Recent success in regulatory approval of several pharmaceutical products manufactured via continuous processes in just a few years (Orkambi™ by Vertex in 2015, Prezista™ by Janssen in 2016, Verzenio™ by Ely Lilly in 2017, and Symdeko™ by Vertex in 2018) indicates substantial uptake of continuous manufacture in pharmaceutical industry. One of the most popular quotations among process chemists these days is what Mrs. Janet Woodcock, director of the CDER at the FDA said about 8 years ago speaking about the trends in pharmaceutical industry: "*In the next 25 years pharma will shift from batch to continuous manufacturing and make current production methods obsolete*". I may be not as optimistic as Mrs. Woodcock, but I am quite positive that continuous flow is the future of pharmaceutical manufacture.

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**Jacopo Buzzanca**, *Custom Synthesis BD*
Angelini SpA | Fine Chemicals Division

**Why change from batch to flow?**
Flow chemistry is playing an increasingly important role in API process development and manufacture in the pharmaceutical and fine chemical industry nowadays. A confluence of factors is driving the need for a paradigm shift in pharmaceutical manufacturing strategies, from batch to flow. Movement towards tailor-made drug therapy, rising generics competition, dramatically higher clinical trial costs and timelines, the shift away from blockbusters to niche products, and the growing number of candidates with accelerated development designations (Fast Track, Breakthrough Therapy, Orphan Drug) are all placing pressure on API manufacturers to eliminate inefficiencies and increase productivity in order to reduce development costs and get new therapies to the pharmaceutical market more rapidly.

The small size of the microreactor, either PFR or CSTR, offers high surface-to-volume ratio which translates into more efficient mixing, heat and mass transfer than traditional batch reactor, ultimately leading to higher yields and better product profile with fewer impurities. This feature is especially useful in handling reactions that are highly exothermic (e.g. hydrogenation, oxidation, nitration), or require hazardous or unstable chemicals (e.g. halogens, cyanides, carbon monoxide, ozone). Dealing with toxic chemicals is also safer – cytotoxic APIs can be produced in inexpensive, dedicated, and disposable equipment sets for production of low volumes of these compounds in the laboratory fume hood.

Moreover, important process parameters such as mixing, temperature, pressure, flow rate, reaction residence time are under rigorous control, allowing fast parameter screening and process optimization. Due to the tiny volume and high controllability, flow chemistry permits to access to novel chemical spaces on large-scale, opening the opportunity to develop new chemical reaction under conditions that are considered difficult or even impossible in batch reactors (e.g. flash chemistry, high temperature/pressure). Additional advantage offered by flow chemistry is fast and simple scale-up strategies. The production capacity of a microreactor can be increased in three ways: [1] Increasing the capacity/size of the microreactor (scaling up), [2] Increasing the number of reactors running in parallel (numbering up) and [3] Run the reaction for longer (scaling out) reactor will improve yields. Therefore, for flow chemistry, scale-up from microgram to kilogram quantities up to multi-tons scale often require minimal chemistry modifications or reactor engineering, leading significantly time / cost saving for scale-up studies and manufacturing of APIs.

Another impetus for increasing adoption of continuous manufacturing strategies has come from the major international regulatory agencies, such as EMA, FDA and PMDA (just to name few). Since 2014, the regulatory agencies have been encouraging the adoption of continuous manufacturing for small / large molecules and biologicals as one of several approaches to speed up drug development and commercialization to market.

**What challenges remain?**
Although much progress has been made in the development and use of continuous flow reactor in the pharmaceutical industry in the last decade, the transition to continuous manufacturing is occurring slowly. The number of flow steps during development remains stubbornly below 5%. Not surprisingly, given the conservative nature of the pharmaceutical industry, adopting continuous flow manufacturing is still a challenge in an industry where for over 100 years everything has been done in batch production. This requires a change in mind-set, a whole re-education of our chemists, and a re-kitting of our manufacturing facilities.

For the flow chemistry to be harnessed more widely in pharmaceutical industry, it is imperative that this discipline, along with other new technologies, be taught at an academic level utilizing in the first instance manual flow equipment, giving the next generation of chemists the skills required to truly benefit from automated flow platforms. In the next 5–10 years, I predict that growth in the pharmaceutical industry for the use of flow chemistry will be at the interface between drug discovery and process development; with the technique facilitating the preparation of the first milligrams of a material, then used to prepare grams to kilograms for clinical assessment up to commercial production on multi-tons scale per annum.

**Paul Quigley**, *Head of Drug Substance*
Arcinova

**Samuel Bourne**, *Process Development Chemist*
Arcinova

**Why change from batch to flow?**
Flow chemistry offers several advantages over batch methodology, including better heat and mass transfer and greater control of process parameters that lead to improved yield and selectivity. These benefits are leading scientists to move towards continuous processing, particularly for fast and highly exothermic or cryogenic reactions that can be difficult to handle in batch. Technological advances in flow chemistry are opening up new areas of organic chemistry for API development and manufacturing, along with the ability to compress multi-step processes.

**What approaches should be considered for minimizing risk when implementing a new technology / technique?**
One of the risks associated with implementing flow chemistry within the pharmaceutical industry is simply the limited expertise available, in comparison to the vast knowledge and experience accumulated for batch processing. This risk has been overcome by the new influx of PhD and post-doc students with flow chemistry experience. At Arcinova, we utilise the expertise of this next generation to bridge the experience gap and confidently implement flow chemistry.

**Does one size fit all or should we consider integration of technologies / techniques?**
Integration of technologies and techniques is critical for success. API manufacture requires a flexible approach and technology should be chosen depending on the individual application. Flow chemistry is well suited to hazardous and fast reactions, whereas batch reactors are preferred for processes with long reaction times or for manufacturing crystallised products. It is important that technologies are used appropriately and will benefit the processes they are used for.

**Which sectors have seen the fastest uptake of flow chemistry and why?**
Continuous flow manufacture is not a new technique. Bulk chemical sectors have used variants of flow chemistry for a long time to produce products in large volumes. The contemporary application of flow for smaller quantities is growing, especially for APIs, specialty chemicals and agricultural chemicals. Although the fine chemicals and petrochemical industries have utilised flow chemistry for over a hundred years, the technique has only seriously been applied to complex molecular synthesis in the last two decades.

**How important is collaboration in this industry?**
The application of flow chemistry in the pharmaceutical industry has enabled an unprecedented level of collaboration. Companies and academic institutions are sharing their discoveries and working towards the common goal of improved API manufacture. Collaboration is also important to CDMOs as we can take advantage of the experience within third parties to co-develop flow chemistry technologies, which are used to enhance offerings to clients. At Arcinova, we have been collaborating with the University of Nottingham on a £2m Innovate UK project to develop novel continuous flow technology for producing patient-specific medicines.

**What challenges remain?**
There still needs to be a change in attitude within the pharmaceutical industry. Companies with large assets in batch processing are often more hesitant to implement new technology and may not have recruited flow chemistry experts. It is easier for younger and more nimble companies, such as Arcinova, to invest in the technology and hire new talent.

Nonetheless, there has been a dramatic change in how flow chemistry is viewed within the industry. Regulatory barriers have been all but removed and the adoption of continuous manufacturing in the pharmaceutical industry is now being actively encouraged. This is evident by the FDAs recent Guidance for Industry guidelines on the subject of emerging technologies.

**Miguel Angel Gonzalez,** *Sr. Director – Chemical Engineering* - Asymchem, Inc.

**Why change from batch to flow?**
Is a matter of choice and flow is not always the answer to all questions. Implementation of flow depends on the business need, maturity of the process, and what you are trying to accomplish; but opportunities are endless in flow! Side benefits from adopting flow include: enhanced heat and mass transfer, easy scale-up, better process performance & quality, attractive e-factor, and improved throughput. This relatively "young" technology has emerged to enable transformations that have been difficult or almost impossible to do it in the already centennial batch platform. While in batch you are secluded to certain unit operations, in flow you can tailor those operational units to whatever is needed. This inherent flexibility makes flow a game changer technology, a powerful tool that really balances the business needs and the speed of bringing significant solutions to our patients.

**Does one size fits all or should we consider integration of technologies / techniques?**
No, one size does not fit all; integration of technologies and different techniques is a must to be successful! The ability to integrate new technologies and perhaps develop new operational units is what makes flow technology so attractive and flexible. On the early stages of adapting flow, the scientific community focused more on the reaction portion of the process while still making the workup in batch mode. Nowadays, you can see the integration of all operational units working in tandem to set end-to-end processes capable of making Kg or Metric Tons a day of intermediates or API's in a very small footprint. The successful adaptation of technologies like photochemistry, electrochemistry, and even mechanochemistry as tools for molecular synthesis, demonstrate the continuous evolution and flexibility of flow in the Lab and Industry. The creative mindset of the scientist is one of the main drivers for integrating all these technologies and different techniques into an efficient process; as we know, possibilities and creativeness are endless.

**How important is collaboration?**
Collaboration is an intrinsic part of been successful on adapting flow technology. Working in silos will take you nowhere if you want to really excel on implementing flow. Similar to any process in batch, the synergy between the different type of scientists with specific expertise is critical to be able to properly conceive the process and scale it up. The communication between the different groups: chemistry, engineering, analytical, facilities, quality, supply chain, is key to be successful. Even outside of your own company, these collaborations have shown to be successful when the expertise for a specific task is non-existent among the internal teams. A recent example was the enablement of a high energetic reaction using a powerful oxidizing agent (tert-Butyl HydroPeroxide: TBHP) where its storage and handling at bulk quantities is prohibitive due to safety.
A collaboration between Asymchem, Pfizer, and Compact Membrane Systems resulted in the successful implementation of a pervaporation system that was integrated into an end-to-end process to generate multi-kilos of an intermediate. (*Continuous Production of Anhydrous tert-Butyl Hydroperoxide in Nonane Using Membrane Pervaporation and Its Application in Flow Oxidation of a g-Butyrolactam* - https://pubs.acs.org/doi/ipdf/10.1021/acs.oprd.8b00083)

**What challenges remain?**
Flow technology will keep evolving and making new strides by adapting novel technologies that fit the purpose of a process. However, one of the main challenges that still remains is the regulatory aspect due to flow been relatively new in the pharma industry. People are embracing more and more the adaptation of this technology into their processes but the lack of standards make it a bit difficult to adapt. The regulatory agencies are working together with the industry (e.g. FDA Emerging technology Team {ETT}) to make the filing process less cumbersome; but it still a work in progress. Nevertheless, the collaboration is already ongoing, then it will be a matter of time for standards to be available that will help to overcome this challenge.

**Marcel Vranceanu**, *Research Engineer Formulation Processing Technologies* BASF SE

**Christian Holtze**, *Senior Research Engineer Formulation Technology* - BASF SE

**Why change from batch to flow?**
Chemical industry considers different types of costs. During the R&D stage time cost and probability of success matter. Flow processing can help in speeding up screening by sequentially carring out hundreds of reactions per day. Online analytics, automatization and even artificial intelligence can further speed up product development. Moreover, scaling up is often more straightforward in flow than in batch. Capital expenditures are related to setting up a production facility and strongly correlate with space time yield and most importantly safety aspects. Flow chemistry is attractive in this respect as it features small hold up volumes of the reactor and can make an inherently safe operation possible by providing conditions

in which runaway reactions cannot occur. Finally, operating expenditures of continuously operated processes are generally lower than those of batch processes. In this respect flow chemistry is attractive as it makes the use of highly reactive species possible by in-situ generation. Moreover, yield and selectivity can be increased by providing better control of the operating conditions of a continuously operated process. Due to better heat and mass transfer in flow reactors new processing windows can be accessed that may translate in reduced side-product generation and even in saving specific separation steps that would be needed in the corresponding batch process.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
While flow chemistry has been highly attractive in the late 20th century it has taken another 25 years to have been applied considerably in industry. The reason for the recent renaissance is associated with technological development and most importantly with the availability of suitable lab equipment on the market. This has set the foundation for both academic and industrial research on flow chemistry. In academia scientists are attracted by the possibility of accessing novel processing windows, e.g. very fast mixing, heating and cooling. This has led to many inventions and publications exploiting the possibility of accessing novel reaction pathways. The merits of straightforward scalability and room for generating novel IP are most important in the start-up world. Finally, pharmaceutical research and production benefit from the promises of shorter time to market. As volumes of active pharmaceutical ingredients are generally low compared to the specialty chemical business it is not surprising that most of the industrial applications still take place in the pharmaceutical area.

**What challenges remain?**
Organic synthetic chemistry has been carried out in round bottom flasks for more than 150 years and it is still "the standard procedure" for university and industrial chemists around the world. Moving from batch to continuous operation has classically been the domain of chemical engineering. Consequently, chemists and engineers need to work together to realize a true flow chemistry R&D workflow. Moreover, to use flow chemistry to its full potential, modern digital methods of extracting information from data have to be considered. Therefore, currently the predominant challenge is associated with interdisciplinarity. This will require novel ways of teaching at university and building up competence in industry.
A major change in mindset is prerequisite for the acceptance of flow chemistry and its wide spread application. Moreover, flow chemistry requires different infrastructure in labs, in pilot facilities and in multipurpose production plants, which entails major investment, training and time to fully equip the facilities with the required infrastructure. Eventually it will be necessary to be persistent in change management as the users of flow chemistry discover the boundary conditions by failure e.g. when solids form in a fluidic setup.

**Franz Amann,** *Senior Scientist*
Carbogen Amcis

**Why change from batch to flow?**
Flow chemistry can circumvent scale-up issues such as mixing problems, heat transfer, and scale dependent safety risks. It also can increase the capacity of a given production plant. The decision to switch from a batch to a flow process depends on the individual problem being addressed and in some cases flow chemistry is not applicable.

**Approaches for minimizing risk when implementing a new technology / technique?**
New technology should be introduced step by step. Full design of the final device, system or plant from zero will increase the effect of mistakes and reduces the optimization potential. The steps may include proof of concept, evaluation of alternatives, scale up, stress tests, and qualification of individual modules.
Specific new know-how needs to be shared within a group of people and not only rest on the shoulders of one specialist. At the same time, individual responsibility, however, and room for individual engagement must not suffer. On the basis of existing or anticipated challenges, the organization must embrace implementation of the new technology. Customers will then also be convinced of the benefits. And, it should be fun.

**Does one size fit all or should we consider integration of technologies / techniques?**
Flow chemistry set-ups should be integrated into existing plants - not only in terms of devices and conditions, but also in regard to personnel and procedures. The average flow reactor is designed for an individual process and therefore more adapted to the chemistry than a stirred vessel. Thus, it is less versatile and at least so far not a good equivalent for a set of stirred vessels in a typical plant. But, it is a valuable add-on.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Large scale production with the ammonia process as the flagship example within the bulk chemical industry. Here, continuous plants dominate. Lower volumes, short cycle times and the quest for variable use of the investment usually favor batch processes. But the border is shifting. More literature examples, more experience/education and more off-the shelf equipment allow setting-up continuous flow processes with less effort, making them attractive for the fine chemical and pharmaceutical industry, too.

**How important is collaboration?**
For large projects, collaboration is indispensable. For smaller projects or proof of concept all necessary means should be onboard to allow competitive delivery. Competitive in this sense means in comparison with the development of a batch process.

**What challenges remain?**
There are specific technical aspects such as handling of solids and fouling, pumping and chemical resistance. Continuous work-up has a potential comparable to the reaction itself but is even more challenging as it is often based on heterogenic systems and requires additional techniques for phase separation and filtration. Acceptance is no longer a real issue but you still have to demonstrate that there is a clear benefit of the transition to a flow process.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
It could be one factor that will allow the potential of these reactions to be exploited. However, many possible advantages of flow chemistry are already incorporated in specialized batch reactors e. g. rapid circulation of the reaction mass through a lamp-loop to optimize the homogeneity of the irradiation and the parameter control. Thus, the possible gains are reduced.

**In which markets will flow processing have the greatest impact?**
In those markets where flow chemistry traditionally was not present, such as in pharmaceuticals.

**Can developing counties exploit flow processing to start new industries?**
The threshold is lower due to lower capital costs.

However, this is only one aspect and probably not the most important. Cost of labor and political stability have been more important in the past. There might be more flexibility in developing countries but foreign partners might also request certain standards e.g. GMP, environmental protection or labor regulations that need to be achieved.

**Charlotte Wiles,** *CEO*
Chemtrix BV

**Why change from batch to flow?**
The advantages of changing from batch to flow are widely publicised to include increases in safety, process efficiency & product consistency; however, the reasons for a Company to change are varied, often depending on the sector, process type of interest, scale of operation & location of activities. As a result of this variety in application space & the emerging nature of the technique, close partnering between vendors & end users is needed to ensure correct tool selection & implementation strategy is employed from the outset.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Whilst conference presentations feature widely activities within the pharmaceutical space, the sectors that have demonstrated the most significant uptake of continuous manufacturing in terms of project number & manufacturing volume, in our experience, have been CMO's (contract manufacturing organisations) & those operating in the specialty chemicals space.

Rationale for this can be that these sectors have established markets & product demands (specification & quantities) that are often met by challenging chemistries – increases in production rate & distributed manufacturer are therefore sought *via* new production techniques to maintain safe operation & to achieve target specifications.

**Does one size fit all or should we consider integration of technologies / techniques?**
When operating in such chemical space, the product is key – how it is made is a choice based on the chemistry, cost of goods, volume & hazard profile – as a result, no single solution fits all scenarios. Modularity & flexibility are key to the success of continuous manufacturing as this enables changes to be made to hardware where reaction characteristics require this – as a result, you will see examples emerging that employ multiple pump types & / or reactor types (static & active) to realise multi-stage transformations.

**Approaches for minimizing risk when implementing a new technology / technique?**
Over the past decade, approaches for minimising risk when implementing a new technique have centred around partnering – this can be with a knowledge partner / scientific institute or vendors in the particular application space of interest; why re-invent the wheel when you can go to the sector expert(s)?

## COMPANY PROFILE

Continuous flow is a rapidly emerging technology that enables researchers to develop processes & manufacture using conditions that would otherwise be inaccessible using conventional techniques. Established in 2008, **Chemtrix BV** combines expertise in the field of chemical / mechanical engineering & synthetic chemistry to assist our Customers to harness the benefits of flow chemistry which include increased safety, efficiency & sustainability. Our expertise enables us to offer scalable & flexible flow chemistry solutions from mg to multi-metric tonne scale & we focus on delivering our Partners higher profits by accessing safe & reliable scale-up from lab to production.

In addition to the supply of turnkey equipment, **Chemtrix BV** can assist the customer in maximising the benefits of flow reactor technology for their chosen synthetic application by accessing close to twenty years of flow chemistry expertise in the form of feasibility studies & contract research. Our engineering experts are also on hand to advise on the development of innovative, customised flow solutions. We also provide training for Companies, to facilitate knowledge transfer & to accelerate the adoption of this emerging technology.

Contact the experts at **Chemtrix BV** to discuss your flow chemistry requirements **info@chemtrix.com**

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Pre-competitive consortia have also been an extremely valuable, highlighting common challenges faced by the Industry, trialling out potential solutions / prototypes & together pushing boundaries with a common goal to accelerate developments & uptake. Another instance where Partnering is key, is between hardware suppliers to deliver on the needed modular, flexible & future proofed systems – with the process outcomes of such joint activities far outweighing any one individual's contribution.

**In which markets will flow processing have the greatest impact?**
When considering which markets flow chemistry / continuous manufacturing will have the greatest impact, my personal view is that this will remain a broad application space as we address a range of chemical challenges – as a result, applications will be found across the pharmaceutical, fine chemical & specialty chemical sectors. Uptake will continue to increase within the pharmaceutical space, however the long cycle time from NCE through clinical trials to the manufacturing of an approved drug will mean that for the foreseeable time, manufacturing activities will be in the generic or second-generation process space.

**Can developing countries exploit flow processing to start new industries?**
The technology also presents an interesting option for developing countries, we see this most pronounced in the API space where examples of activities in the private & public sector are emerging to address the need for local control of anti-retroviral & anti-malaria medication supply – with local manufacturing of the API not just its formulation becoming a real option.

**What role can modelling play in flow process development?**
We are just at the beginning of demonstrating what continuous manufacturing has to offer & of course challenges remain. Modelling has a more significant role to play in flow process development than it currently does, not only from the perspective of gaining process understanding, but in the definition of design space, the characterisation of how to deal with process upsets & the development of an overall control strategy.

**What challenges remain?**
Embedding these techniques into the toolbox of researchers, process developers & manufacturers is needed, together with a reduction in the silo's within organisations. Wider promotion of case studies showing successes & failure (including reasoning behind application type & solution fit) are also needed to stimulate ideas on when an organisation should consider the use of flow. I look forward to a time when people are no longer discussing 'moving from batch to flow', but simply considering what is most appropriate for the process in hand – we are seeing more cases of flow first time & only flow routes being developed for new products – but there is a long way to go before this becomes the norm!

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**Guillaume Gauron**, *EMEA Technical Sales Manager* - Corning® Advanced-Flow™ Reactors

**Why change from batch to flow?**
Based on our experience, I think that the better question is WHEN to change from batch to flow. Today we should consider flow as an additional process tool for the chemical industry's tool box and not think of it as a replacement technology. The idea is to consider which part of a process will take advantage of flow technology rather than trying to convert a whole process to flow.
In a market where personalized medicine is becoming the rule, you can no longer build a full dedicated continuous system for one process. You need more flexible tools with multiple units you can select and rearrange as needed.

This is even more true when you want to implement new technology. Trying to change a whole process is a big risk. I recommend going slowly and starting with a critical part of a process that will directly benefit from the new technology. Later one can address the rest of the process to see if the technology makes sense. Implementing a new technology provides many different challenges and the technical part is probably the easiest part to deal with. Training, mindset change, and getting buy-in from operations up to the management, those are the things that will take the most effort.

The integration of technology is a key to success. Flow technology allows one to optimize the process at lab scale and scale quickly to production. Other technologies should also be quickly scalable. It is important to integrate scalable techniques and equipment as soon as possible during the process development.

Analytics or downstream processes can help save time and money, but they must not add additional complexity to the process.

Although the fine chemistry sector has clearly seen the advantage of the technology and remain the leading sector, pharma is now taking the lead. The FDA has been promoting continuous processing's advantages of better quality, safety, etc.. The new guidance provided by the FDA last February is a clear message for the pharmaceutical industry.

The mindset is changing and more companies are actively experimenting and producing with flow chemistry technology. But convincing old industries deciding invest in new CAPEX is still a big challenge. This is less true for the Asian market where process intensification and higher safety level are strong drivers for competitive advantage for their chemical industry.

**How important is collaboration?**
To help industries examine flow technologies, collaborations remain important. Academics and industries are talking to each other now more than ever. Equipment suppliers are working together to improve the value proposition and to help the community select proven solutions.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
As a final word, the combination of LED and a micro-reactor, is shaking up the old world of photochemistry. This very old chemical process is now a really hot topic. The technology has made big strides since the days when mercury lamps were the light source. The industry set the technology on the "back burner" for many years because of cost and safety issues, but this is changing and really fast. Glass micro-reactors combined with LEDs allow for the seamless scale-up of new synthesis routes that nobody wanted to explore before.

**John Tsanaktsidis,** *Research Director*
CSIRO Manufacturing

**Why change from batch to flow?**
While there are numerous reasons for considering the adoption of flow over batch processing when implementing a chemical manufacturing process, including, scalability, better process control, shorter reaction times, less waste generation, and reduced operating & maintenance costs, the overwhelming consideration should be *safety*! If nothing else, the development of a flow process, wherever possible, will result in lower process risk profile through reduced exposure, and the effective elimination of catastrophic events.

**Approaches for minimizing risk when implementing a new technology / technique?**
One approach to minimizing the risk of implementing a new technology such as flow chemistry into production is through partnering. By engaging an experienced research partner, with a proven track record for transferring flow processes from development into production, the process of adoption and translation can be significantly simplified. Indeed, there are now several research laboratories across the globe, including CSIRO, that offer such services.

**What role can modelling play in flow process development?**
With the advent of additive manufacturing for flow reactor design, and the myriad of possibilities it brings to address new otherwise inaccessible reactor geometries, the design question becomes more and more important. As one of the key guiding tools for flow reactor geometry, CFD (Computational Fluid Dynamics) plays an increasingly important role in the reactor design process.

**Does one size fit all or should we consider integration of technologies / techniques?**
"One size fits all" is unlikely to be effective; a "fit for purpose" design approach is more likely to succeed. The driving philosophy should always be about fitting the engineering around the needs of the chemistry, not the other way around.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
The high value, low volume sectors, such as pharmaceuticals, fine chemicals, and specialty polymers have been the fast adopters. While the reasons for uptake of flow processing are manifold, and application specific, increased process efficiency and safety will always be key considerations.

**How important is collaboration?**
Collaboration will be very important! Flow chemistry will see closer collaboration by chemists, chemical engineers, material scientists, modelers, and statisticians, to name a few!

**What challenges remain?**
Solids handling remains a limitation of flow chemistry; Indeed, this has been a challenge from day one! Another challenge is equilibrium driven co-product separations; for example, simple dehydration reactions are often challenging to perform. Finally, field implementation challenges relating to equipment reliability and performance are now emerging. As more industrial processes find their way to the "factory" more attention will be directed towards implementation issues.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
Yes. As new reactor designs emerge the utilization of photoredox processes will increase. The combination of glass flow reactors with immobilized heterogeneous catalysts will provide new access to this important reaction class chemistry.

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**Tony Warr,** *Head of Process Technology*
Dr. Reddy's Laboratories

**Why change from batch to flow?**
Dr Reddy's strives to make safely produced medicine more affordable for the patient. This means that we look to change from batch to flow to create a step change. Better means on commercial, safety or throughput grounds. Targeting greater quality, reduction in impurities, consistency of production and cost all merit a process change. As a batch process should be safe in the first place then safety is often more of an enabler of something new, than a cause of change. To be clear, using flow as an enabling technology i.e. new chemistry/regime, is not a change from flow to batch but an adoption of a new process.

**Approaches for minimizing risk when implementing a new technology / technique?**
Use people with genuine experience at scales from lab through to plant implementation, or, give your people time to deeply understand the factors influencing the process, equipment and control of the new technology. Successful (and fast) implementation requires the full interaction of flow experienced engineers and chemists from day one. Your engineers must have some knowledge of control as development of good control is essential for success.

**What role can modelling play in flow process development?**
Anywhere from none to inspirational. Good technical people can assimilate process information better than we give them credit. However what a process model can do is support a hypothesis which is good for your documentation, or, pose new hypotheses when the process appears to be misbehaving. There again, if we are talking about engineering models for equipment, scale-up and safety then these can be a necessity.

**Does one size fit all or should we consider integration of technologies / techniques?**
No. Technologies and techniques always need integrating.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Bulk chemicals and petrochemicals due to their volume, process intensity, cost optimization and consistency/automation of running. After this, more advanced intermediate manufacturers including pharmaceutical key starting materials (KSMs). Some pharmaceutical KSMs have been made in flow for innovators for several decades. Pharma APIs and drug products have been very late to the technology due to their inherent (and necessary) conservative nature. Typically bulk manufacturing is run by engineers on old chemistry whilst pharmaceuticals are driven by scientists running new chemistry on old engineering. We must work towards using the best equipment on the best chemistry bringing all skills together.

**How important is collaboration?**
If you are a pioneer, there are few to collaborate with.

We are now in an environment where there are a good number of collaborators both in the academic field and in small companies to help bring products to market. However this must always be done with the right team under the right confidentiality conditions. Currently there are many people experienced at the small scale and few who have genuine hands-on experience at implementing full scale solutions. As in anything success is driven by finding the right people.

**What challenges remain?**

a. People underestimate the importance of process control and monitoring in implementing real plants.
b. I still see few good solutions for isolation/filtration and drying of small volume products.
c. Doing flow should be done for a rational reason not a whim.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**

Yes and it is already used very successfully at large scale. Regarding some of the recent academic pushes into visible light, then we just need to put together the process inventors with the equipment suppliers as new controlled chemistries emerge.

**In which markets will flow processing have the greatest impact?**

No answer: Hard to say… where there are the best applications...?

**Can developing countries exploit flow processing to start new industries?**

Certainly and they are doing! Flow processing can be expensive but does not need to be so. When you have minimal installed assets, then investment in the right equipment for the right process is easier. Where it becomes trickier is that developing countries almost always need to import the experience at the moment. However in the longer run, creating their own in-house knowledge will end up putting them in a good position. As ever, anyone with a technical advantage needs to run hard to keep ahead or they will be caught in due course!

**Jochen Becker,** *Global Project Manager*
Evonik Nutrition & Care GmbH
Health Care

**Why change from batch to flow?**

Compared to batch manufacture, continuous processing enables an improved control of process parameters and access to a larger process design space. This is associated with more options for improved quality, higher safety, improved sustainability, and better efficiency. In addition, several synthetic transformations with hazardous or energetic reagents are safer to operate in flow mode. The support from regulatory agencies, such as the recent FDA draft guidance on quality considerations for continuous manufacturing, is additionally encouraging the utilization of flow processes for pharmaceutical manufacturing to shorten the drug supply chain.

**Approaches for minimizing risk when implementing a new technology / technique?**

A thorough risk analysis is an excellent tool to identify possible risks early on and thus to reduce or even eliminate them at early stages of development. A risk minimization strategy requires an early involvement of all stakeholders, especially the involvement of customers. At Evonik, this is performed in a standardized approach, involving an interdisciplinary team with external partners and internal experts in chemistry, engineering, regulatory, quality control, manufacturing, and process safety.

**What role can modelling play in flow process development?**

Modelling plays a crucial role in flow process development, especially for the reactor design and for the definition of process controls. Process modelling is typically done with commercially available software packages, such as AspenPlus or gPROMS. These process simulators are useful tools to gain a better understanding of process dynamics, a requirement also set by the FDA for pharmaceutical flow processes. For high quality of these simulations, it is vital to feed the software with sound data, mainly concerning the physical properties of both pure substances and mixtures thereof. The physical properties have to be either experimentally determined or can be calculated with state-of-the-art methods, e.g. modified UNIFAC and others. If the modelling is done properly, very often the process start up matches exactly the *in silico* model.

**Does one size fit all, or should we consider integration of technologies / techniques?**

The target should be to identify the technical solution that fits best to the specific requirements of a process and product. Hence, at start of a project all technologies and tools should be evaluated and a flexible modular set up considered for the process design. For obtaining an elegant and economic process set up creativity and a good understanding of the available technologies are crucial to make the right decision. For continuous processes on the pharmaceutical manufacturing scale it is often preferred to run some parts in batch mode and others in continuous mode, for which nowadays several reactor types are available for rapid development and scale-up. In some cases, the requirements of the chemical transformation may even trigger the invention of a new reactor design or type.

**Which sectors have seen the fastest uptake of flow chemistry & why?**

Flow chemistry has been extensively applied for more than a century in industrial chemistry. To date, the high-volume commodity chemicals sector has applied flow chemistry more than fine chemical and pharmaceutical companies. Evonik is producing more than 2/3 of its products by volume via continuous processes already. In the pharmaceutical industry, the interest in flow chemistry has been increasing substantially in the last decade. A significant future growth can be expected driven by intended improvements of the supply chain, sustainability, and the quality of pharmaceutical products.

**How important is collaboration?**

Collaboration is key! Developing a flow process requires a broad range of competencies. This is in particular true for pharmaceutical production, where regulatory requirements need to be considered besides technical competencies. In the Custom Manufacturing field, a very close collaboration of the drug originator and the CMO is required to align product and regulatory requirements with process design elements and process controls. In a QbD (Quality by Design) approach chemical process development needs to be closely linked to reactor engineering. The latter is typically provided by equipment and reactor suppliers.

**Torfinn Haaland**, *Research Coordinator*
GE Healthcare

**Why change from batch to flow?**
There are many different drivers. Flow chemistry can allow reaction conditions that is not possible in batch. That can be due to better mixing, better temperature control and allowance of rapid temperature changes. Dealing with hazard chemicals, flow often would be preferred from an EHS perspective. If you develop a chemical process for a new product or need higher production capacity in an existing process, flow might be attractive if the investment is lower and/or the productivity is higher compared to batch.

**Approaches for minimizing risk when implementing a new technology / technique?**
It is important to understand the chemistry in high detail when considering a new technology. This should be adapted to the chemistry and not the other way around. It is also necessary to evaluate the whole process (upstream, downstream and side stream handling) when considering a new technology for a process step. People from production and technical department should be involved even in the R&D phase to ensure that a new technology is implementable on industrial scale and to minimize risk in the industrial implementation phase.

**How important is collaboration?**
This is crucial. Normally a company does not have all the different competences and capabilities required to do the necessary R&D work and to implement a new technology on industrial scale. Universities and research institutions are often heavily involved in the R&D phase. Then it is important to collaborate very closely in order to ensure that external partners understand the goals the company has for the work. You are normally faced with several challenges in such a work, and close collaboration will make it significantly easier to solve these in a fast and proper way. It would also be easier to change strategy faster when beneficial. Building of competence inside the company by collaboration with external partners is also essential, and this would be advantageous both in future projects and in existing production.

**What challenges remain?**
There is still a lack of chemistry students that are well-educated in flow chemistry. Therefore, many chemists will still have barriers to work with flow chemistry in laboratory, and their mindset could also represent a barrier.
The regulatory aspect is often another challenge both in the case of developing a flow process for a new product and transforming an existing batch process to flow.

**Can developing countries exploit flow processing to start new industries?**
I think yes. It is normally significantly harder to implement flow processing in established industries, in particular in pharmaceutical industry which often have batch processes where the equipment is partly or fully paid off. Hence equipment for flow processing must replace the existing batch equipment. This normally requires considerably higher productivity compared to starting from scratch.

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**Flavien Susanne**, *R&D Drug Substance Continuous Processing Lead - GSK*

**What role can modelling play in flow process development?**
In the past decade, Pharmaceutical companies have adjusted their business models to react to the generic competition. This led to the emergence of continuous manufacturing processes for Active Pharmaceutical Ingredients. Flow chemistry is desirable because it enables a diversity of reactions, facilitating the synthetic route to a molecule that may in turn produce a simpler and more effective manufacturing process. In addition, telescoping multiple unit operations together in a continuous supply chain leads to benefits including reduction of inventories and lower labour and overhead overall cost.
Up to recently, the development and the control of processes in the pharmaceutical industry have been dominated by experimentation. The definition of the optimum process and the control strategy has been supported by Design of Experiments (DoE) feeding into statistical models.
Such approaches are extremely cost and time ineffective due to its high consumption of material, numerous experiments and high labour requirement.
Implementing continuous processing in the Pharmaceutical industry is not trivial. It often requires solving high complexity problems such as chemical transformations including intricate pathways from the starting materials to the product and a high number and diversity of impurities to be controlled to precise level. Therefore, the current process development methodology and the statistical models applied are not always the most suitable solutions to provide answers to complex and non-linear problems.
With the growth of continuous processing, a new workflow positioning process modelling at the centre has emerged. Kinetic and thermodynamic process models of the unit operations developed by software companies are now able to predict performance of the process and equipment. Understanding the intricate mechanisms taking place between the chemistry and the technology is key to the design. These models are used for the process development and process optimisation activities, enabling a faster and more efficient work. Additional sensitivity analysis of the critical quality attributes against the process parameters can be performed.
This allows to Pharmaceutical companies to understand how a parameter or combinations of parameters influence process responses and ultimately critical quality attributes. The yield and quality of the process can be displayed using standard contour plot and multi factorial design spaces to support a QbD filing as recommended by the regulatory authorities.
With the understanding of the process performance as a function of the process parameter dynamics, models can be used to support the design of flow equipment. Requirement on the transfer phenomena such as heat transfer coefficient, macro mixing time and residence time distribution can be specified by the model and captured onto a data sheet or User Requirement Specification (URS) as supporting documents for design and construction of the reactors.
In some pioneer pharmaceutical companies, process modelling is now well embedded as part of the process development workflow. Further initiatives have investigated transferring process simulation into manufacturing for real-time monitoring of quality and yield and for more advance control strategy supported by Model Predictive Control where linear and none linear models can trigger feedback and feed forward actions to enable tight and efficient process control.

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**Silvia Werner**, *Project manager*
Heraeus Pharmaceutical Ingredients

**Why change from batch to flow?**
Flow chemistry is becoming more and more popular and bears several advantages compared to the batch approach. And its use in sustainable and forward-thinking chemical manufacturing industries has, hence, significantly increased. Although there are already several chemical processes, which include this alternative established batch processes in existing plants will not be converted into continuous flow processes. On the other hand, for novel syntheses in the fine chemical industry as well as in the pharmaceutical industry, the situation is changing. Responsible for this turnaround are several advantages of the flow approach over the batch mode:

- better heat transfer rates
- higher efficiency
- minimizing reaction times
- reducing amount of reagents

Besides those ecological aspects, however, there are also safety-related advantages: While the use of toxic reagents and the production of highly potent APIs may cause limitations during batch reactions, the handling of those compounds is facilitated within a continuous flow approach. Considering the numerous benefits, also the US FDA supported continuous flow synthesis.

However, in order to use it for a novel process, the continuous flow has to be implemented already in the development phases also with regard to the technical application.

**Does one size fit all or should we consider integration of technologies / techniques?**
For multi-step syntheses, especially in API manufacturing, a combination of the batch and the flow modes will be established in the future. The method of choice depends on the individual reaction kinetics.
Nonetheless a paradigm shift in process engineering from batch to continuous flow processes, which are based on micro- and millireactors, is not easily accepted by production managers - although it may offer great opportunities.

**How important is collaboration?**
International and interdisciplinary networking and a close collaboration with partners are essential to successful development and scale-up in this expanding field.
The industrial development and engineering teams necessary for quality and regulatory departments to acquire deeper knowledge in this field. For manufacturing APIs the FDA and/or the local authority has to be involved, too.

**What challenges remain?**
Besides several benefits from the continuous flow synthesis, there are still some certain challenges and limiting factors remaining, which restrict its extensive usage in industrial applications today. The diameters of the channels, used in continuous flow applications, are on micro- or millimeter scales. Therefore, any appearance of a solid compound during or before a reaction may cause problems and clog up the tubes.

Company name: **Heraeus Deutschland GmbH & Co. KG**
Year of foundation: **1851**
Number of employees: **13 000**
Headquarter country: **Germany**
Website: **www.heraeus-pharma.com**

**Offered services**
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- Photochemical synthesis

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Heraeus

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Another limitation is connected to the simple incorporation of purification procedures. Therefore, complex multistep syntheses often still consist of both batch and flow systems. One of the most important challenge is, hence, the work-up of the reaction solution and the purification of the target compound.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
The versatility of photochemical flow processes has rapidly been expanding in the past decade because of the fact that continuous photochemical processes make scale-up of these reactions possible in an efficient way.

The commercial availability of efficient light sources, in particular powerful LEDs, has increased the interest in new synthetic photochemical reactions. Besides granting a better control of heating and mixing for continuous photo-flow reactions, those processes are safer to operate on scale-up, especially if LEDs are used instead of Hg lamps. Moreover, compared with batch photoreactions, flow approaches offer a higher surface/volume ratio, homogeneous irradiation and more efficient light penetration.
In a whole, this opens the possibility of shorter reaction times, better reproducibility, higher yields and selectivity, and easier scale-up of reactions.

**Rui Loureiro,** *Director, R&D Process Chemistry Development* - Hovione

**Why change from batch to flow?**
The change from batch to flow must be carefully thought through as there has to be a significant driver to allow for this decision process. We at Hovione have established a methodology that evaluates parameters like safety, product demand, type of chemistries and other factors that allow us to take a decision if a process should be transferred from batch to flow.

**Approaches for minimizing risk when implementing a new technology / technique?**
When implementing a new technology, we should not rely solely on it to ensure we deliver our products. We should have alternative ways to still make the required product otherwise the risk and the pressure on the team to deliver is extremely high. Nevertheless, if this is not at all possible then you need to assemble a team with the right knowledge and ensure that the project manager leads the team to success. Additionally, it is very important to have on the team people that have implemented other new technologies in our company as they can anticipate challenges that are identical when implementing new technologies, especially in environments that are GMP compliance.

**What role can modelling play in flow process development?**
In our view, modelling plays a pivotal role in any process development and as such the same is applied for flow processes. The investment done in having a dedicated team member to generate a model is easily recovered since without spending product we can predict the conditions that should be used and therefore reduce the overall number of experiments. This in turn results in a cheaper and faster development. The data obtained from modelling also allows for a better planning at scale since we can predict with some degree of accuracy the time to complete the process.

**Does one size fit all or should we consider integration of technologies / techniques?**
We do not think that one size fits all because the issue that needs to be solved may be different between different projects. Thus, what is right for one process, may not be exactly the same for the other. For example, one process may need very efficient mixing and another may need high temperature and the solutions are different. In order to decide which is the best technology to use we should consider all the data that we have available and as we are entering the world of digitalization, use this technology to help us decide which other ones we should also be prepared to integrate. It is necessary to measure the gains of moving a batch process into flow chemistry and only if there is a clear advantage (e.g. safety, efficiency, quality, environmental impact, cost reduction) we move the process into flow chemistry.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
The flow chemistry uptake has been slow and we feel that the pharmaceutical industry is now making a concerted effort to introduce and scale-up this technology. The reasons for the slow uptake are related with the necessity of finding solutions to meet some unmet needs from the past and to improve the sustainability and efficacy of the chemical processes. One of the areas that have seen some applicability of flow chemistry is our Generics area, since it is an area that benefits very much from slight increases in productivity.

**How important is collaboration?**
Collaboration is essential because it is through the sharing of knowledge and challenges that we can come to a new solution and make science advance. The skills set required to implement a certain technology/technique do not reside only on one type of person and therefore if there is no collaboration the implementation is but intended not to achieve its targets on the required timelines.

**What challenges remain?**
In terms of flow chemistry there are several challenges still to overcome as we need to make sure we can make chemistry and isolate the products with the required quality. One of these, maybe the largest one, is the cleaning validation of flow chemistry reactors. The authorities investing in getting a good knowledge about continuous manufacturing and flow chemistry and its challenges need to be understood in order to establish the necessary standards.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
We believe that photo-redox chemistry never really took off because when making this type of reactions in a large vessel it is almost impossible to ensure that all the product is exposed to the same quantity of light and for the same amount of time. Although it is possible to recirculate a batch content and expose a small part to light it is not enough to ensure equal exposure. The use of flow chemistry through tubes with short cross sections that can easily be exposed to light is the necessary step to make this type of chemistries a reality in API synthesis at large scale.

**Steve Pollington,** *Research Leader*
Johnson Matthey

**Why change from batch to flow?**
Continuous production in various industries is favoured over "batch" processes for reasons such as EHS, quality, cost, footprint etc. Indeed, Flow chemistry is already employed in various sectors of the chemical industry (i.e. petrochemical) so not new and indeed some sectors of the chemical industry have employed continuous for decades. However, these processes are usually designed for one product(s) and defined volumes. The chemical sectors (e.g. fine chemicals, pharmaceutical) which produce multiple products at different volumes/scales utilizing the same assets inevitability chose batch. Processes that can retain the flexibility but utilise flow for the same reason as above would therefore be advantageous. This has led to technologies being advocated (e.g. electrochemistry, photochemistry etc.) that may allow flow processes to leverage chemistries impractical in batch in the future. This may allow for advantaged routes in flow versus batch for these systems.

**Approaches for minimizing risk when implementing a new technology / technique?**
The key word in the question is "new". Approaches taken would include an open mind, is this really the "Right" technology/ technique for the process transformation that I wish to perform? Do I really understand the process transformation i.e. the chemistry. Ensuring that a full and robust understanding of the chemistry and involving the right team (chemists, process engineers, chemical engineers, EHS, regulatory affairs etc.) at an early stage of the concept is desirable for minimizing risk. 90% of the scale-up work should actually be done in the laboratory to provide a solid, robust basis for implementation.

**What role can modelling play in flow process development?**
I think that modeling has a huge role in helping to understand the process transformation. If you really understand the chemistry then modelling and targeted experimentation/ validation will be crucial in flow process development and speed up understanding and therefore implementation. Industry sector that employ continuous (flow) operation use modelling to accelerate their development programmes. Flow process development has more variables to play with which can add time to early development stages. Modelling therefore has an important role to play for fine chemicals/ pharmaceuticals to compete with the speed of development in traditional batch approaches. However, modelling can play a similar role in batch as to continuous manufacturing.

**Does one size fit all or should we consider integration of technologies / techniques?**
Understanding the chemistry and the process will define the selection of technologies/techniques. There will be transformations that will be very fast, fast, slow and very slow, be exothermic, endothermic, changes in volume, evolve gas etc. so I don't think a one size fits all approach would work. The challenge will be to utilize the same space (footprint) for a variety of chemical processes. This suggests modular systems and integration of techniques and measurement techniques probably employed on a campaign basis.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
The sectors of the chemical industry that have seen fastest uptake and indeed used flow chemistry for decades are primarily ones that produce one product on a large scale e.g. petrochemical industry. Other sectors that are starting to advocate the use of flow include the pharmaceutical, fine and specialty chemicals. The reasons focus on EHS, cost saving and regulatory compliance in the near term.

**How important is collaboration?**
Collaboration is very important. Flow approaches require a multi-disciplinary team (chemists, process engineers, chemical engineers, EHS, regulatory affairs, possibly even computational or data scientists) but collaboration between regulators, equipment vendors, manufacturing organizations and molecule owners (e.g. virtual pharma) is also important to realize the full potential of flow chemistry.

**What challenges remain?**
There are "few examples" of Flow in commercial/production. This is more evident in China than Europe. The pace may accelerate if examples from Europe are publicized. The reactor technology for all type(s) of chemistry in flow may be currently available, but the associated auxiliary equipment (e.g. pumps) could be one of the factors that hampers implementation for different chemistries. The asset would need to be flexible to different chemistries that utilizes the same space/equipment would be a prime requite and are we there yet? Another problem is that upstream/downstream processes may still be batch operation which may change the bottleneck from the chemical reaction process to another aspect of the production.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
I have been aware that photo-redox chemistry has been shown as a technique for activation of organic substrates. However, the same problems exist that were apparent with advocation of photochemistry in terms of scale where over-irradiation of the reaction mixture can occur when reaction times are substantially increased as in the case of large reaction vessels. Therefore, there are advantages in employing flow chemistry for this technique where narrow channels in microreactors can ensure a more uniform irradiation of the organic material. Exploitation of photo-redox chemistry with flow has also been demonstrated for API synthesis.

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**Pierre Giuliano,** *Managing Director*
La Mesta - Yriel Group

**Why change from batch to flow?**
The question if and why to change a batch reaction to a continuous flow process have been discussed several times. Flow reactor cannot be used for all the chemical reactions and we believe that standard batch processes will remain the most adapted solution for many operations in Fine Chemicals field. For continuous transfer, the synthesis needs to be fast or "intensifiable", playing on temperature / pressure / mass transfer. The reagent / reactant needs to be transferable, taking into account that you will need to maintain a stable flow in the reaction chamber.
However, once you have defined the reactions that can be a good candidate for a Continuous transfer, advantages are substantial.

- **Safety is one of the more important reasons.**
  Continuous processes are much safer: the miniaturization of the reaction chamber (ranging from few microliters to liters) allows to heat & chill easily, and you can afford high pressure or extreme temperatures (this is a large range capacity that will allow process intensification). Moreover, flow miniaturized reactors can be used for handling and keep under control some hazardous gases (Phosgene, Carbon Monoxid, Ammonia…) or gases generated during the reaction ($CO_2$ in case of decarboxylation)
- **Productivity and cost**
  It is possible to increase the reaction productivity moving from batch to flow, due to the much better control of the reaction parameters and to get a better mass and heat exchanges. Our best example is the transfer in continuous of a reaction involving a $6m^3$ reactor + workup used during 25 weeks for a yearly campaign, to 10 weeks in a 1 liter flow reactor. If you add the fact that intensification allows to reduce the solvent volumes and improve the ratio reagents/reactants, the impact on cost is highly positive
- **Carbon Footprint**
  This argument, which is the result of the 2 advantages detailed above, is more and more considered as valuable by customers. Beyond the immediate savings when you use less solvents, your effluent charge per kilo of product is improved as well as the carbon footprint.

**Approaches for minimizing risk when implementing a new technology / technique?**
New technologies implementation represents an opportunity for Fine Chemicals companies, but also a risk in case of unsuccessful investments.
Whatever the reasons which drives your choice (safety, cost, carbon footprint), flow chemistry implementation requires a collaboration between Chemists and Engineers.
While the Chemists usually used to make fit their process to the existing equipment, in Continuous Flow they must integrate in their development teams some engineering skills with a common target : address some new problems which they do not face in batch (reaction chamber feeding, flow stability, process control, in line control systems…) and find together some technical solutions.
In that sense, continuous development projects require deeper involvement of the high level management since they need to organize the synergy of two categories of people that do not collaborate "naturally".

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Customers requiring GMP, see in the flow chemistry a way to achieve stable, reproductive and robust processes, and government agencies (like FDA) are supporting these technologies. This advantage of the process control convinced them easily over the last 10 years.
But Flavor & Fragrances or Cosmetics industries are also very interested by intensified processes when they allow to perform some sensitive chemistries, generating less impurities, using less solvent and, at the end, showing a substantial carbon footprint advantage. Customers are giving more and more importance to this argument that will probably drive their choices in the future.

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**Rajiv Khatau,** *Managing Director*
LODAAT LCC

**Why change from batch to flow?**
There are several reasons for changing from batch to flow. The primary one is that efficiencies are created and an ultimately a decrease in capital spending. At LODAAT Pharma, both our botanical extract and pharma customers demand quality testing with JIT delivery methods. Excessive lead times can diminish delivery and quality lead times.
For example, when testing an assay chromatograph for a botanical extract, each batch may take 26 minutes with traditional HPLC batch methods. Flow, however, can reduce this testing time period to 5 minutes. Thus, our production process creates 5X time more efficiency for quality testing. Imagine a molecular fingerprint being tested 5 times more than a traditional method—there is now a smaller variance and we create a "Near Natural" ingredient and a premium product. Our customers, major brands, can now confidently advertise a quality product without hesitation.
On the pharma side when registering a drug and the development of a dossier flow allows for better control of reaction parameters including temperature control. This yields a more efficient time line for dossier development and faster registration- an important criterion when several competitors are looking to be first to market with a generic drug or with new drug discovery. Additionally, flow processing can also help with other efficiencies including less inventory, and more space for productions and warehousing. This also decreases fixed costs and labor thereby increasing overall ROI. If consumers are demanding a "fresher product" this efficiency is ideal.

**Approaches for minimizing risk when implementing a new technology / technique?**
Flow technology processes many batches without interruption. The technology calls for larger machinery.
The biggest risk is that Flow technologies are still an emerging technology and due to the large size of the vessels, training and implementation need to be carefully addressed. Experimenting and taking a measured approach to Flow processes is probably the best method to move forward.

**What role can modelling play in flow process development?**
Process modelling can definitely play a positive role in flow process development. Several tools exist including flowsheet modelling including those for solid based pharmaceutical processes, and continuous feeding and blending processes. We have also found that flowsheet simulation results can be compared with experimental findings- helping with overall implementation of process development.

**Does one size fit all or should we consider integration of technologies / techniques?**
We believe that an integration of technologies and techniques is the best method. I believe part of the reason that a One Size Fits All (OSFA) is not as effective is that the types of products, and molecules just doesn't support an overall one-size fits all process. That being said, if you are specialize in just one molecule of product group, then efficiencies with OSFA may be more effective. Again, modelling and experimentation with techniques may be the best way to move forward.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
At LODAAT Pharma, we have found that our customers which include Big Pharma, Agrochemical, Flavor companies, Fragrance firms and nutraceutical firms all can benefit from flow chemistry.

The large Branded CPG firms and their CMOs ultimately want a consistent quality product with efficient lead times. Ultimately, the most important net result is providing a product, whether it is an ingredient, or genericized dossier that helps build a Brand and can get to market registration in a timely manner.

**How important is collaboration?**
Collaboration is always an important part of the process. Learning and sharing techniques with both equipment vendors, outside labs, vendors, and all parts of the supply chain is critical. Lets also not forget open communication with customers and regulatory.

**What challenges remain?**
The primary challenges are the learning curve and the exploitation of these new processes. But this is just a matter of time, before flow chemistry becomes the norm.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
There is definitely a benefit of flow chemistry to Phot-redox chemistry. Specifically, photo-redox chemistry has many uses including those of water splitting, carbon dioxide reduction. But the area of most relevance is the development of solar cell material. This application could potentially change the way material production is processed and used. By recognizing that organic dyes can convert visible light into chemical energy- even in mild conditions- molecules can be a strong oxidant and simultaneously a reductant. Process flow chemistry can help in this process.

**Amanda Evans,** *Scientist*
Los Alamos National Laboratory

**Why change from batch to flow?**
Flow chemistry approaches to synthesis have provided chemists with innovative platforms for probing molecular reactivity and, in most cases, flow approaches can afford improved safety, better scalability, increased yields with shorter reaction times, optimum reaction temperature control, and enhanced reproducibility over traditional batch methodologies. However, a complete change from batch to flow for all chemical processes is NOT recommended – there are some processes that should be performed in batch because a flow approach will not provide a significant advantage. This caveat should certainly not be used as an excuse to avoid experimenting with flow paradigms for a given reaction, particularly if the process involves tight temperature/safety controls or can definitely be improved by adopting a flow-based approach. A scientist must be willing to explore all possible parameters for a reaction or set of reactions and make a processing choice based on optimal outcome and observed data, without bias.

**Approaches for minimizing risk when implementing a new technology / technique?**
Discovery equals risk. However, risk can be mitigated by improved training, thoughtful design of experiment, and accurate protocol/data reporting by the scientific community. Too many scientists are focused on presenting pretty results and forget their responsibility to their community to report both protocols and data accurately. This results in inaccurate data sets that bias future experiments – and more importantly greatly increases risks to all other scientists who want to implement reported results towards establishing new technology. Inaccurate data reporting and repression of negative results is not just bad science, it is a safety hazard and prevents discovery. Flow approaches can significantly minimize operator exposure and provide enhanced temperature control, thereby reducing overall risk. Reproducible protocols and data sets and standards for reporting on results for new flow techniques are therefore very important to establish and maintain.

**What role can modelling play in flow process development?**
The issue with using modeling approaches for flow-based processes is that many flow-based experimental processes are under kinetic control and far from equilibrium; whereas most computational approaches rely on thermodynamic assumptions. Yes, in an ideal world it would be wonderful to have a data-driven feedback loop that could involve modeling to drive reaction choice. We are not there yet – but I have no doubt that we can develop these capabilities and use computation to drive reaction discovery and molecular design.

**Does one size fit all or should we consider integration of technologies / techniques?**
One size has never fit all – and integration of technologies is absolutely essential. Discovery will rely on standardization of known processes – one cannot ascend a mountain if there are no solid rocks to climb on top of. However, integration of technologies and data sets will also require secure storage and selective transmission/communication. Who will set these standards? Industry? Government? Academia? Each of these parties is biased towards their own interests. This is an ongoing discussion within the scientific community and is actually a much bigger question that should also concern the general public.

**How important is collaboration?**
Collaboration is essential. The traditional silos of academia will not survive the integration of technologies – ego equals bias and greatly hinders true scientific discovery. Discussions across disciplines will continue to be vital – chemists can learn a great deal about alternative characterization techniques from fellow disciplines (e.g. physics, biology, geology). Learning to communicate ideas without getting lost in jargon, not being afraid to ask questions (or make mistakes) to improve understanding, remaining curious about the world around us, and openly speaking with others about the bigger queries that tug at our hearts and minds – these are the characteristics of a true scientist and require a collaborative if courageous mindset.

**What challenges remain?**
How to report, process and prioritize data. How to improve and integrate online monitoring technologies. How to shift bias (funding, research, etc) away from the known and the safe and towards the useful and adventurous. How to disseminate information on new flow-based protocols and paradigms to move recalcitrant scientists from traditional batch processes that are generally less effective and less safe than flow systems that accomplish the same chemistry. Additionally, scientists need to be encouraged to think more laterally and broadly – for the benefit of society. There are bigger problems to address than the next iteration of a coupling reaction.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
Absolutely – photo-redox approaches are a form of processing that are always going to be more efficient in flow.

**Dirk Kirschneck**, *Managing Director*
Microinnova

**Why change from batch to flow?**
We see different reasons to switch to flow. One important reason is shortening time-to-market/a reduction of tech-transfer times. Other reasons to take the step in the direction of flow chemistry are safety or an increase in quality.

**Approaches for minimizing risk when implementing a new technology / technique?**
At Microinnova, we have developed a specific procedure in order to minimize development risks. We execute a first theoretical evaluation, then go into a very short lab phase to learn about the system and then we enter into a risk assessment, together with a first sketch or block diagram of the plant, so that we always have the plant in mind. This way, we can examine where we see a feasible realization or identify hurdles to find the best way to realize the plant. The importance of having a clear vision of the final plant is substantial. This is covered by our process design phase very well.

**What role can modelling play in flow process development?**
We work on strategies to reduce the experimental effort in the lab as well as on technology selection methods. In the project "Synthesis Control" we work under the leadership of RCPE, together with other partners on methods for the design of control strategies for the synthesis of APIs. Simulation tools are essential in this project.

**Does one size fit all or should we consider integration of technologies / techniques?**
The concept that one technology fits all is a nice idea, but what we have seen is that a broad spectrum of various technologies is key. Therefore, the approach we follow is trying to characterize the chemical reaction and then work out chemical technologies depending on the critical process parameters we found. We select a certain technology for a specific application.

This process depends on factors such as the viscosity of the material, solids being present, which scale the final plant is supposed to be an optimization of mass and/or heat transfer. For the integration of technologies we see a modular approach as the most useful way to attain flexibility, as well as minimizing tech-transfer time, sometimes by magnitudes.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
The uptake of flow chemistry is broadening to other branches, such as coating, formulation and polymers. This can be observed in formulation where mass transfer is an important factor. By means of flow chemistry, formulations can be executed on the minute scale, whereas with batch systems the process typically takes hours. If sub-streams are separated in flow systems, opportunities to optimize a formulation towards a certain application increase dramatically. We know people who are convinced their businesses will fail if they were to not turn to continuous formulation within the next 10 to 15 years.

**How important is collaboration?**
In my opinion, collaborations are crucial. It is crucial to get the latest knowledge from universities and research organizations about the latest approaches and new findings. Cooperation is necessary for specific components and realizations, because the standard engineering departments are limited in their knowledge of these highly specialized areas.

**What challenges remain?**
There are still a number of challenges remaining, since continuous manufacturing is not a standard technology right now. All of us in the field are continuously learning. We make good progress with handling solids, but there are still a few open issues with them as well. Standardized methodology for bringing the development into plants is still under discussion. Most organizations have developed their own approaches, which are not publically available.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
We see very interesting new options opening up for executing chemistry, for example we work on photo chemistry together with the CC Flow Team with Oliver Kappe.

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**Steven T. Perry**, *Senior Product Manager*
Parr Instrument Company

**Why change from batch to flow?**
Researchers and manufacturers opt for continuous flow reactors over batch reactors for two main reasons: to decrease cost per unit product, and to incorporate desirable technical features enabled by continuous processing. Potential technical improvements include improved yield via better control of reactant mixing and mass transport or tighter control of reactor temperature profile/history, automation and real-time analysis of changes in reaction conditions, easier long term catalyst testing, and potential for integration of separation and recycle for low conversion processes. For example, small continuous flow reactors may be ideal for testing long term catalyst activity, catalyst poisoning, and catalyst activation/regeneration. Flow reactors also include designs not available in batch reactors, such as fluidized bed, trickle bed, or multi-step reactors with rapid changes in temperature or catalyst composition.

**Approaches for minimizing risk when implementing a new technology / technique?**
When considering implementing a new technique, clearly define your objective and scope. Be thoroughly familiar with literature examples and don't hesitate to contact authors or equipment manufacturers with questions. Specifically seek out information on specific challenges the new technique may present, such as startup and shutdown, equipment limitations, solids handling, safety implications, corrosion, catalyst activation/regeneration, and associated costs. Model important aspects of the process.

**What role can modelling play in flow process development?**
Given proper assumptions, a process simulation can help you optimize the economics of a process, evaluate the impact of varying operating conditions and assumptions, and alert you to issues such as pump cavitation, liquid condensation, and buildup of inert gases in a system. Dynamic process simulation can also be used to model how equipment will behave during startup and shutdown. Computational fluid dynamics analysis can be used to help properly design reactor dimensions to achieve the desired reactor performance, but will require some knowledge of catalyst kinetic activity.

**Does one size fit all or should we consider integration of technologies / techniques?**
No one technique will be optimal for every chemical process- heat of reaction, rate of reaction, production scale, and ultimately economics will dictate what technologies should be considered.

**What challenges remain?**
Two important challenges in flow chemistry, especially when medium to high pressure is involved, are the steady feeding of solid reactant materials and the need for ever higher temperature capability, approaching or even exceeding 1000 °C.

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**Ryan Seongho Oh**, *Vice President, Head of R&D*
SK biotek

**Why change from batch to flow?**
There are many advantages to continuous processing when compared to traditional batch processing. In my opinion, continuous processing offers three distinct advantages in the pharmaceutical industry:
**Efficient Scale-up and Increased Flexibility:** Highly exothermic reactions can produce material at lower yields. This can be a function of insufficient control of local and overall heat generation. However, continuous process provides a solution for this by superior heat transfer capacity. In addition, batch processes requiring cryogenic conditions can be routinely carried out in a continuous manner with higher temperature, allowing easier scale-up of low temperature batch reactions.
**Improved Safety:** Continuous processes are more suitable for extreme reactions conditions. Having a small hold-up of reactants within a closed system, reduces the risks and improves process safety when compared to traditional batch processing.
**Environmentally Friendly:** The application of flow chemistry makes the process more environmentally friendly and economical. In addition, continuous process is the perfect way to produce large volume of product. Especially for fast kinetic reactions, such as organometallic reactions, flow chemistry is advantageous over a conventional batch reaction by in-situ control of highly unstable intermediate with a subsequent in-situ quenching. This leads to improvement of product quality and reaction yield.

**Approaches for minimizing risk when implementing a new technology/ technique?**
At SK biotek, we apply a phased approach when implementing new technologies. Initially, an in-depth literature review on the technology will be performed along with a feasibility study. Factors we consider during the early stages are safety, cost, throughput and reaction complexity. These items determine the potential to utilize continuous flow process for a particular step. If appropriate, we develop the continuous flow process as a matter of priority.

**What role can modelling play in flow process development?**
As a process development tool, modelling of continuous flow process development is not well established yet, however, it has become more popular in recent times.

**Does one size fit all or should we considering integration of technologies/ techniques?**
Ultimately, we need to consider an integrated approach, which is currently not always easy. In my opinion, one of the ideal solutions would be a "plug and play" type integration. This would involve minimum change of key parts and provide flexibility to cover a range of new chemistries. Our commercial production facilities can cover a variety of projects with appropriate modification. In addition, we try to constantly expand our technology capabilities to efficiently cope with a rapidly changing technological environment.
We are continuously trying to improve processes with the aim of integrating novel technologies.

**Which sectors have seen the fastest uptake of flow chemistry & why?**
Organometallic reactions such as lithiation and coupling reactions have grown the fastest in this area.

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Scale-up is facilitated by avoiding cryogenic conditions in batch process and performing continuous process at higher temperature conditions.
Generally, organometallic reactions produce reactive and unstable intermediates, which cause critical issues during scale-up and impact on product quality. Applying flow chemistry has the potential to easily resolve these issues.
Each year, SK biotek produce over 20 tons of advanced intermediates through organometallic reactions in continuous mode. Our continuous reaction system is a fully validated cGMP facility (Process validation (2009), Japanese PMDA (2013) & US FDA (2014) approved) and capable of handling various types of organometallic reactions. The construction of our new plant in Sejong increased the production capacity to over 60 tons per year.

**How important is collaboration?**
Flow chemistry has a short history compared to batch process development. The industry is continuing to build knowledge, expertise and understanding with the aim to establish flow chemistry as a viable synthetic strategy for commercial activities. This effort requires extensive collaboration between chemists and engineers to overcome challenges such as thermodynamics, new equipment design, and scale-up of new chemistries. The integration of GMP systems is a critical area of focus ensuring our flow chemistry is designed to satisfy GMP requirements.

**What challenges remain?**
In recent years, many new reactions have been developed for continuous processing. The main challenge for flow process is to develop commercial processes from proof of concept. It is necessary to investigate, design and install multi-purpose continuous production facilities that can be used for various reactions and projects, while minimizing downtime on the plant. Flow chemistry is not a new concept, however, limited knowledge is available when compared to traditional batch processing.

**Matthew M. Bio**, *President & CEO*
Snapdragon Chemistry

**Why change from batch to flow?**
There are a number of reasons to transition a process from batch to flow. There may be technical, safety, supply chain and/or financial reasons to switch from batch to flow. Flow systems can provide greater control over product quality as a result of the ability to tightly control parameters such as mixing, temperature and reaction time. Photochemical and electrochemical processes are significantly more efficient in flow systems due to the physics of photon and electron transport. The rapid and well controlled mixing in flow can deliver significantly improved mass transport, particularly with gas / liquid reactions. Tubular reactors offer low-cost, safe access to high pressure conditions in flow can somewhat decouple the reaction temperature from solvent selection. Highly efficient heat exchange characteristics of most flow reactor types means that cryogenic batch reactions can often be run at much higher temperatures significantly reducing the energy costs.

The opportunity to closely couple a series of flow reactions in time allow for the generation and use of unstable intermediates that are not practically employed in batch with the result that chemists may be able to design more efficient manufacturing routes to target molecules.

Flow system output is a function of time instead of reactor volume. The output can be adjusted to accommodate demand thus providing on-demand production and reducing inventories. This allows production to respond to market demand

**Approaches for minimizing risk when implementing a new technology / technique?**
As with any chemical manufacturing process, the key to minimizing risk is to reduce the uncertainty in the process. Spending the time in the lab to develop a deep process understanding will go a long way to de-risking any new technology. I find flow less risky than batch since in a flow process, only the small amount of that valuable material that is in the reactor at risk and the reaction performance can analyzed nearly continuously if desired.

**Does one size fit all or should we consider integration of technologies / techniques?**
Flow chemistry is but one tool among many available to the process development scientist. A wholistic approach to process development will invariably lead to an integration of technologies.

**How important is collaboration?**
Flow chemistry, well executed, required expertise in a broad range of disciplines including chemical engineering, mechanical engineering, electronics, automation, analytical science, chemistry and even physics. We collaborate with experts from a variety of fields to deliver manufacturing solutions to clients. We work closely with experts in industrial controls, automation, spectroscopy, pumping technologies, heat exchange, static mixer and others to design continuous processes and reactor systems. It is also important to learn from other industries where continuous processes have long been used.

**What challenges remain?**
Off-the-shelf lab-scale equipment appropriate for flow process development are not really commercially available. In our lab we have developed a set of laboratory flow systems that allow us to efficiently design and develop scalable flow reaction. These lab-systems are designed as accurate scale-down models of our production scale reactors.

New and more sensitive analytical technologies for flow development would be most welcome, especially purpose-build HPLC / UPLC for at-line analysis. The design of multiplex, small footprint IR and Raman spectrometers would greatly enhance the utility of these analytical technologies.

**Could flow chemistry enable exploitation of photo-redox chemistry for material production?**
Snapdragon has developed a flow photoreactor capable of kilo/hour production in some cases. We have scaled a variety of photoreactions, including photoredox, for manufacture. I see no barrier to scaling photoredox flow chemistry to 10 kilo / hour or higher production rates.

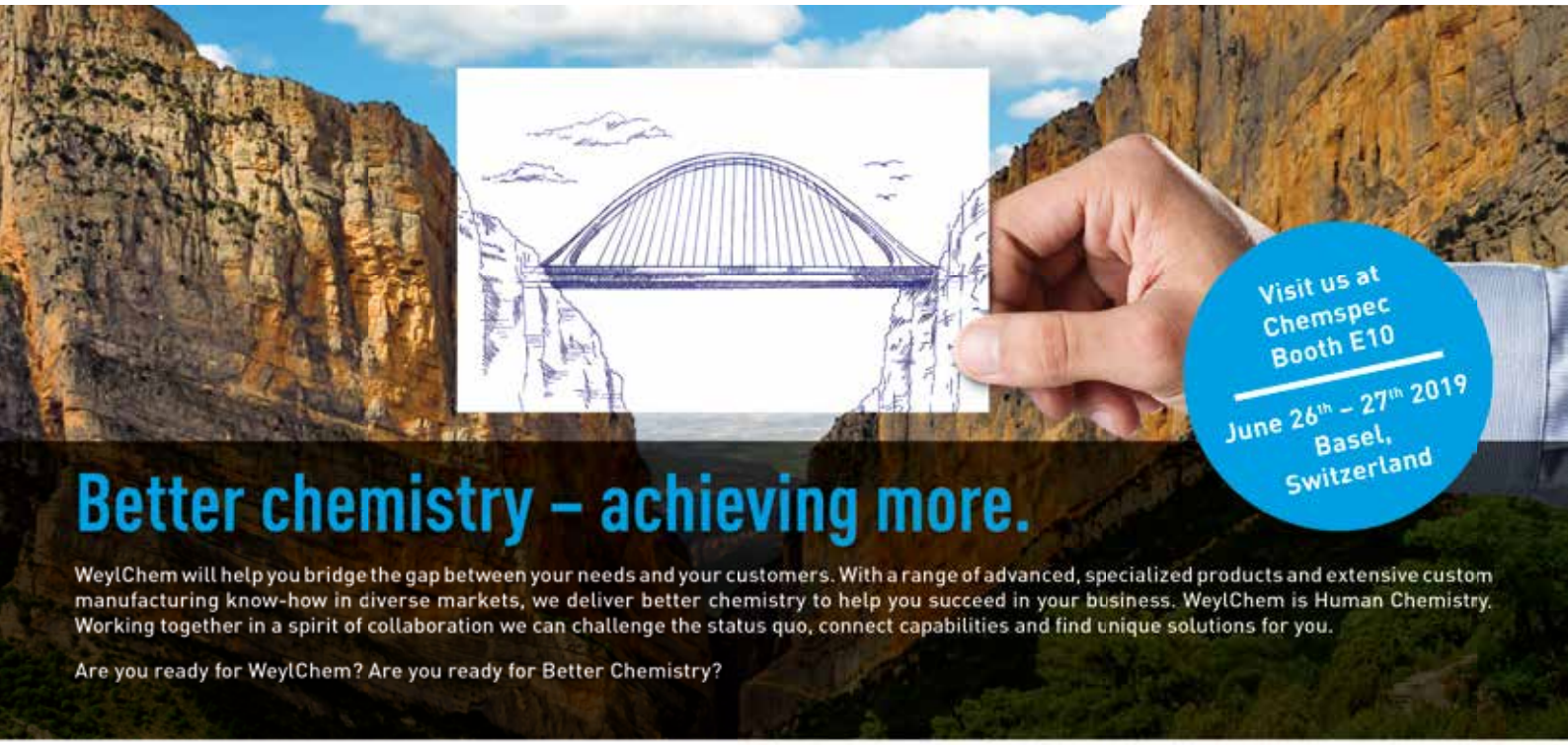
**Frank Gupton**, *Department Chair*
Virginia Commonwealth University

**Why change from batch to flow?**
The decision to use batch or flow in commercial operations often is driven by the availability of existing batch manufacturing capacity. In many cases, hybrid systems that utilize both batch and continuous unit operations are frequently used in scenarios where continuous processes are adventitious but also benefit from existing batch capacity. Some of the usual reasons why organizations will elect to use continuous processing instead of batch are related to risk mitigations and safety issues. By minimizing the instantaneous reaction volume, one can carry out highly energetic reactions that normally could not be carried out safely in a large batch operation. However, there are additional advantages to continuous operations that can be more subtle. Cleaning between batch operation represents one of the major cost drivers in pharmaceutical active ingredient manufacturing. This is particularly important in the manufacturing of highly potent compounds that require short campaign derations. These processes can be run in more dedicated equipment and in a manner that minimizes exposure to personnel.

**Which sectors have seen the fastest uptake of flow chemistry and why?**
Highly energetic reactions seem to be most frequently carried out in flow for obvious reasons. These include hydrogenation reactions and nitration reactions. These types of reactions can benefit from flow not only from an operational perspective but also from a capital investment standpoint. In addition, highly potent compounds are good candidates for continuous operations, since containment is a major issue in the production of these materials.

**How important is collaboration?**
Collaboration is essential to the successful implementation of a continuous process. Much of the development work for continuous manufacturing project requires interdisciplinary skillsets that include process chemistry, process engineering, reactor design, kinetics, in-line analytical support, process control, and feedback. All of these skill sets are required to successfully address the technical needs of a continuous process.

**What challenges remain?**
To date, most of the emphasis on continuous processing has focused on the chemistry component of the process. In order to successfully achieve the benefits of continuous processing, all unit operations must be holistically considered. There are significant gaps between the chemistry and downstream unit operations that include liquid/liquid separations, liquid/solid separations, filtration, and drying. Until all of these specific unit operations can be carried out continuously, the full benefit of continuous reduction will be limited.

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