Gayle De Maria

4th Symposium
on Continuous Flow Reactor Technology for Industrial Applications

GAYLE DE MARIA
Chimica Oggi – Chemistry Today / TKS Publisher

Chimica Oggi - Chemistry Today, together with its partner Corning SAS, organized the 4th symposium on "Continuous Flow Reactor Technology for Industrial Applications" on 26-27 September 2012 at Lisbon, Portugal, reaching an international recognized role in the flow chemistry networking. More space was given to case studies, vendor communications, downstream processing and discussions related to the technical and economic future of flow chemistry. Three contemporary workshops were arranged in order to give an overview of the current / future situation and help attendees understand what a company really needs to start working with continuous.
Below a summary of the lectures, vendor communications and workshops.

LECTURES

David Ager - *DSM Innovative Synthesis*

Keep it coming: sustainable advantages?

The use of flow reactions continues to grow in the life science arena. In addition to improved safety through better control of exothermic reactions and the minimization of hazardous material inventory, there can be other advantages. Removal of a product from the reaction medium can improve stoichiometry, for example. The capability to run reactions at higher temperatures can improve reaction rates so that large excesses of a reagent are not required. With improved heating and cooling capabilities, energy usage can be reduced in a flow system when compared to batch. All of these factors can provide sustainable advantages to a flow process, in addition to mitigating potential hazards. The petrochemical industry has a very low E-factor and uses flow methods, while the pharmaceutical industry is the opposite and produces large amounts of waste for every Kg of drug produced. The use of flow chemistry to help minimise these often forgotten side issues of waste, energy usage, etc., can contribute to the implementation of the principles of sustainable and green chemistry. In turn, this reduces the cost of a process.

Sigurd Buchholz - *Bayer Technology Services GmbH*

Implementation of flow chemistry: from research to production

Process intensification and flow chemistry are opportunities to open novel pathways in process design and engineering. These step changes can significantly improve efficiency and safety in chemical and pharmaceutical synthesis and reduce capital expenditure. Continuous processes can yield value chemicals at higher efficiency and lower manufacturing costs or even allow the access to new or tricky molecules. A number of highly innovative approaches and protocols are currently being developed in both industry and academia. The presentation highlighted selected examples from current development activities at the Bayer Group. The examples covered innovative route selection, introduction of special technologies, micro structured equipment design as well as scale-up and modularized approaches. The examples illustrated the methodology of intensified continuous process and product development demonstrating how novel routes can be identified and what the benefits and hurdles from a process and manufacturing point of view can be. The presentation illustrated how scale up effort and time to market can be reduced when moving from "lab chemistry" to pilot and production scale. As reduction of manufacturing costs is becoming increasingly important for the production of even high-value chemicals such as API it was discussed how routes and technologies can be assessed at a very early stage of development and what the impact of novel processing conditions and continuous manufacturing can be.

Yi Jiang - *Corning Reactor Technologies, Corning SAS*

Continuous flow reactor technologies in Asia

This presentation highlighted some progresses of recent technology and application made in continuous flow reactors in Asia, and how these progresses have been motivated by regional business challenges and governmental initiatives. In the last few years Asia pacific has been packed with a significant number of CRO/CMO who have been competing with quality, cost, and service reputation etc. On the top of that, increased governmental initiatives have pushed for safer, cleaner, and more efficient production environments, especially in China. Continuous flow reactor technologies have been one of technologies started attracting great deal of attentions in Pharma, fine and specialty chemicals areas. This presentation summarized how module-based and solution-based flow reactor technology have been applied for effective flow-chemistry process development, for "green" upgrading of conventional batch productions, and for large-scale manufacturing of chemicals. Yi discussed why flow reactor technology could quickly meet the R&D and production demands in such competitive and dynamic ecosystem in Asia.
Yi shared what are the challenges that people today are

facing from the mind-set changes to plant integration engineering, and to manufacturing operations.

Wessel.F. Hengeveld - *Flowid*
Client example: switch from batch to continuous flow of an exothermic reaction
For the production of a raw material for the food and flavour industry a pilot set-up has been developed that can produce up to a two kilos of crude product per day. To increase the capacity and enhance safety of production the manufacturer wants to switch from batch production to continuous flow. The reaction is characterized as extremely sensitive with respect to handling of reagents, reaction conditions and reagents ratio. The reactants have extreme properties, making dosing of the reactants challenging. The main reactant is extremely volatile, flammable and reactive and the other is very viscous. The reagents are poorly miscible. In addition, particularly low amounts of catalyst needed require extremely low flow. Due to several side reactions, product yield is very sensitive to process parameters as temperature, reactant ratio, and residence time. Flowid succeeded in developing a pilot set-up that can control the process parameters and thus the reaction outcome, to achieve more reproducible and safer production comparing to the current batch mode. After a thorough investigation of the reaction parameters a set up with two temperature zones was designed. It was found that to minimize side-product formation, the two-phase mixture at the start of the reaction needs to be cooled thoroughly. And since one of the operational constraints is the maximization of the product yield, a subsequent high temperature zone is applied to increase conversion within reactor residence time. The final goal is to produce 100-200 tons of product per year. Final optimization and subsequent scale up of the system to a larger throughput is now on-going.

Peter McDonell - *Genzyme UK*
Opportunities and challenges in the introduction of continuous manufacturing of an API at multi hundred ton scale
Other industries have adopted continuous manufacturing strategies that have transformed their business, making opportunities that would be impossible using batch processing. Why is it that adoption has been low in the pharmaceutical industry? Reasons for this were presented, together with ideas for extending adoption through both primary and secondary manufacturing. Obstacles that are often raised are high installed batch capacity and the need to utilize overcapacity, resistance of regulators to change, risk associated with adopting new control strategies, inability to deal with solids adequately and filing strategy being unknown. Arguments to counter each of these objections were presented, together with tactics to deal with them within reluctant companies. Principles for dealing with process excursions were also presented, showing that the transition from batch to continuous manufacturing actually reduces risk. Progress towards real time and parametric release was discussed.

Laurent Pichon - *Mepi*
What future for the flow chemistry markets in Europe?
While the interest for intensified continuous processes is growing among the traditionally batch minded chemical sectors, the implementation of FC industrial processes within the Pharmaceutical, Agrochemical, Fine and Specialty Chemicals fields, hasn't proved to be as fast as all FC actors were expecting few years back. MEPI, the innovative technology platform based in Toulouse, France, is attempting to understand the reasons why this economic situation is currently such. The Flow Chemistry (FC) markets in Europe, have been analysed through now 4 years of existence and many experiences to be shared. In addition, a survey of the European FC markets was produced by MEPI on economic and strategic issues. The results were described and analysed in the presentation.
The slowing down and accelerating market growth factors were discussed to promote the percolation of the FC solutions and implement associated strategies for clients, equipment makers, and technology providers.

Tony Warr - *Dr Reddys Laboratories*
The continuous cash flow diagram
Using a mixture of production examples Tony explored whether flow technology conquers all, or whether batch is best... or more sensibly use the best technology for the right reason. "Does continuous really pay" is a question regularly asked when alternative process technologies are discussed, commented Tony. Whilst the obvious answer is yes and no, the opposing question "does batch pay" seems rarely addressed either. One often hears commercial, safety, strategic, space, energy and even 'for the hell of it' given as reasons to try continuous processing – clearly each process is an individual case. Each must be assessed to understand whether true benefits exist or whether a more conventional batch or mixed approach is merited.

Joseph M. Lambert Jr. - *Parr Instrument Company*
Catalysis 101 – The science and engineering of three-phase catalysis
Various types of catalysis were named and categorized by the reagents involved. Enzymatic catalysis, phase transfer catalysis, homogeneous catalysis, and heterogeneous catalysis are a few of the more well-known branches of study. This presentation focused on heterogeneous catalysis and, in particular, on three-phase catalysis in which gas and liquid reagents react with each other on a solid catalyst. Emphasis was placed on evaluation of reaction rate data and how it is affected by bulk diffusion in liquid, pore diffusion, adsorption, desorption, and chemical reaction. Summaries were provided of various analytical techniques commonly used as well as an overview of ideal reactors (CSTR and PFR) and how they relate to one another. Examples of well know real reactors were given, such as ebulating bed, fluid bed, trickle-flow and multi-tube reactors.

Christopher Hwang - *Genzyme*

Integrated continuous production of recombinant therapeutics proteins

Over the last few decades, the biotechnology industry has delivered many effective treatments to numerous patients with unmet medical needs. As the industry continues to develop new therapies, there is increasing competition due to the arrival of New Molecular Entities (NME) and/or Biosimilars for same disease indications. Consequently, there is a greater need for companies to develop innovative manufacturing platforms that focuses not only on manufacturability and time to market but also on efficiency and cost effectiveness. To meet these challenges, Genzyme is currently developing a novel continuous manufacturing platform that integrates upstream and downstream processes that can be universally applied to all protein therapeutics. Specifically, high density perfusion cell culture has been integrated with a novel continuous multi-column periodic counter-current chromatography system (PCC) for the continuous capture of candidate protein therapeutics. This platform has been evaluated using a relatively unstable molecule (enzyme) and a relatively stable molecule (MAb). Significantly higher process output, higher resin capacity utilization, and lower buffer usage are predicted when compared to current at-scale processes. Moreover, steady state with respect to in-process indicators, in-process controls and critical product attributes (CQA's) was achieved. The impact of this new manufacturing platform on process simplification, facility design, technology transfer and operational and capital cost efficiencies was also discussed.

Charlotte Wiles - *Chemtrix*

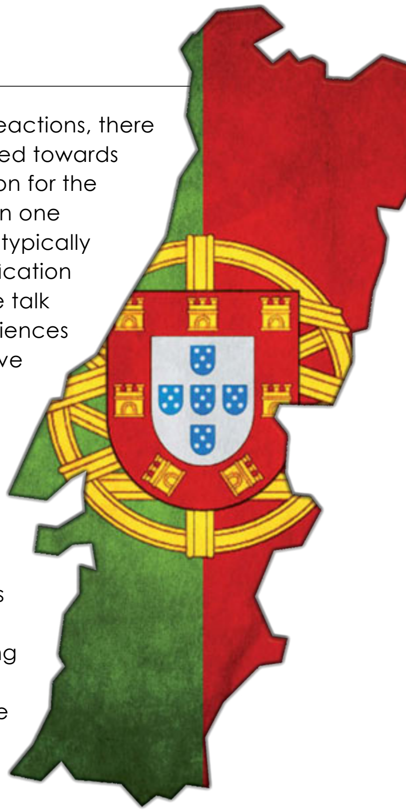
Application of continuous flow processing to the research, development and production of personal care products

Along with the pharmaceutical and fine chemical sectors, it is a target of the consumer goods industry to reduce their environmental burden, and costs, by minimising the transportation/storage of its products through the employment of satellite production facilities at the point of use. To achieve this, small footprint, highly efficient and reliable installations are required to enable pilot-scale production facilities to be distributed and maintained around the globe. With successful application in pharmaceutical and fine chemical production, continuous flow reactors have the potential to facilitate the attainment of this goal; whilst it is acknowledged that further developments are required to overcome challenges associated with the manipulation and production of highly viscous and wax like materials-common in this sector. A commercial surfactant was selected as a case study, whereby the goal of the on-going investigation is to attain greater process understanding and higher surfactant activity, to afford increased production rates and lower side product formation when compared to the current batch process. With success criteria for a continuous process based on a reduction of throughput time, increased product activity, reduced oxidant over-dosing, chelant concentration and higher product quality, it was the aim of this research program to combine in-line analytics and dynamic modelling to deliver an intensified, flexible process suitable for the production of materials that possess a complex phase behaviour.

Paul Hellier - *Institut de Recherche Pierre Fabre*

Pilot scale demonstration of a continuous process including product precipitation and filtration

Rapid progress has been made in recent years in exploring the use of continuous processing in process research and development. Whilst the major part of this activity has been focused on continuous chemical reactions, there is growing attention being addressed towards other unit operations. The motivation for the interest is readily appreciated when one considers that a chemical process typically involves more separation and purification operations than reaction steps. The talk related some of Pierre Fabre experiences in this area as part of a collaborative R&D project, INPAC, carried out with the Laboratoire de Génie Chimique of the University of Toulouse and Boostec Industries. A key objective was to investigate innovative technologies resulting in the pilot demonstration of a fully continuous process integrating chemical synthesis with product isolation using continuous precipitation, filtration, washing and drying operations. The synthetic reaction was performed in a silicon carbide reactor manufactured by Boostec Industries (now part of the Merson group). Optimisation was carried out using on-line analysis with Raman spectroscopy. This part of the project was implemented on the MEPI (Maison Européenne des Procédés Innovants) pilot platform in Toulouse. The fully continuous process was then demonstrated at the Pierre Fabre pilot facility. Acid mediated reactive precipitation of the product took place in a continuous stirred tank with the feed streams being introduced via an impinging jet mixer. The product was then isolated using a continuous vacuum belt dryer, with subsequent impurity removal via washing and finally hot air drying. The pilot trial was followed up with a complementary study to investigate further conditions for continuous precipitation. This was performed by Microinnova Gmbh.



Alastair Florence - *Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC)*

Continuous crystallisation and control of pharmaceutical solids

There is considerable interest in developing continuous crystallisation processes as an alternative to traditional batch methods. The Continuous Oscillatory Baffled Crystalliser (COBC) offers a range of potential benefits compared to traditional stirred tank crystallisation techniques including effective control of mixing and heat transfer, ease of scale-up and reduced costs. The formation of co-crystals, involving the intentional incorporation of a neutral molecular species within the crystal lattice of a compound, has attracted significant attention as a potential approach to manipulating the physical properties of pharmaceutical and other molecular solids. To date, there has been much focus on the small scale discovery of these interesting materials but relatively few studies on the scale-up of the processes for their manufacture. Alastair presented the discovery and scale-up of a novel co-crystal form of a nutraceutical compound using continuous crystallisation in a COBC. This model system is used to demonstrate co-crystal formation and performance enhancement, the application of solid-state characterization for phase purity and structure determination and scale-up of the process from 10mL vial to COBC. Over 1 kg of co-crystals was produced continuously in a COBC with excellent purity and particle size distribution. The presentation presented the characterisation, scale-up approach and final COBC process.

The practical challenges associated with the incorporation of process analytical technologies (PAT) for crystallisation processes within a COBC were also discussed.

Lahbib Abahmane - *ESK Ceramics GmbH & Co. KG*
EKasic® modular flow reactor systems for chemical production under severe conditions
Often mentioned drivers for the development of flow chemistry are cost savers, improvement of the scale-up and access to a wider range of reaction conditions. Flow chemistry enhances the process safety, reducing the risk of cross contamination. Microreactor technology has certainly opened up new avenues for synthetic organic chemistry and the chemical manufacturing industry. However, the majority of synthetic transformations performed in microreactors have involved mostly moderate reaction conditions in order to conduct highly exothermic reactions safely. More recently, following the concepts of "Process Intensification" and "Novel Process Windows", flow chemistry executed in harsh regimes conditions have become increasingly popular. Handling of hazardous chemical reaction in safer and controlled manner demands numerous reactor materials; they have to withstand extremely rigorous specifications, in which new physical and chemical properties have been added to the already known ones. For instance, increased corrosion resistance and better thermal conductivity are necessary. Those required special material properties, such as high thermal conductivity and corrosion resistance makes ceramics one of the most operational materials for the chemical equipment. It can be used for applications that cannot be realized by metal or polymer systems. The material silicon carbide (SiC) and especially the option to join it by diffusion welding are new in the field of ceramic chemical equipment. Welded SiC ceramic offers several advantages over conventional materials. The presentation focused on the material properties, the kind of reactor modules, the operation range and some hazardous application examples.

Ian Grayson - *Evonik*
Choosing the right reactor for each reaction
Surveys of reactions suitable for batch-continuous transfer have shown that most industrially applicable reactions are neither extremely exothermic nor extremely fast. The specialised reactors that have been designed for continuous processes with high mass and heat transfer have therefore limited applicability for the reactions found in most fine chemical and industrial processes. A selection of different reactors developed and used at Evonik was presented, which are suitable for a range of processes which are not very rapid or exothermic, but where the transfer to continuous operation gives an improvement in quality, throughput, and/or safety. These include loop, tube, and oscillatory flow reactors, which have been operated at pilot or full production scale. Some of these continuous processes also address the continuous work-up and isolation of the product, as experience has shown that these process steps often remain a bottleneck when a reaction stage is operated as a continuous process.

Dilwyn John Roberts - *Eli Lilly*
The continuous flow barbier reaction: a greener alternative to the grignard reaction?
A key pharmaceutical intermediate for production of Edivoxetine.HCl was prepared in > 99% ee via a continuous Barbier reaction, which improves process greenness relative to a traditional Grignard batch process. The Barbier flow process was run optimally by Eli Lilly and Company in a continuous stirred tank reactor (CSTR) where residence times, solvent composition and operations temperature were optimized to produce 0.4 kilograms of intermediate 1. Key benefits to the continuous approach included greater than 30% reduced process mass intensity and magnesium usage relative to a traditional batch process. In addition, the flow process imparts significant process safety benefits for Barbier processes including >100 x less excess magnesium to quench, >100x less diisobutylaluminum hydride to initiate, and in this system, maximum long-term scale is expected to be 22 litres which replaces 2000 litres batch reactors.

VENDOR COMMUNICATIONS

Andrew Fallows - *Motor Technology / Fuji Techno Industries Corp.*
Pump that makes sense
Reactors are the core of this technology for industrial applications but they are not the only devices needed for productive operations. To maximize yield and product quality, it is essential to have non-pulsating flow of liquid at high accuracy and repeatability. Only non-pulsating flow can realize perfect mixing ratio of various chemicals. Fuji Techno's triplex plunger metering pump offers non-pulsating flow at high accuracy and repeatability (< +/- 0.1%). Andrew explained operating principles, performance of the pump and successful feeding of organic lithium in details.

Robert Ashe - *AM Technology*
Flow reactors for multiphase systems
Much of the work on flow chemistry in recent years has focussed on micro reactors. These deliver good plug flow under (laminar) parallel flow conditions and primarily rely on molecular diffusion for mixing (although some micro reactors also employ static mixing). Whilst micro reactors can deliver excellent performance, they are constrained by low throughput capacity and poor handling characteristics for multiphase mixtures. In larger tubes, mixing and plug flow are dependent on bending and folding of the fluid as it passes through the channel which can be achieved by static mixing elements or turbulent flow. The performance of such systems however is sensitive to axial velocity of fluid in the channel. This results in a variety of practical problems such as high pressure drop, long channels, sub optimal mixing, a tendency to block and inflexibility. An alternative solution is the dynamic flow reactor where mixing is achieved by mechanical stirrers. If the mechanical mixing is restricted to radial plane, then good plug flow is also achieved by default. The advantages of such systems are low pressure drop, flexibility, high capacity and good handling characteristics for two phase fluids. Historically, dynamically mixed flow reactors have proved difficult to build as rotating stirrers are not suited to tubular channels (flow reactors need to be long channels for good heat transfer and good plug flow). The problems relate to mechanical seals, shaft stability, centrifugal separation and the difficulty of designing baffles. AM Technology have developed a new dynamic flow reactor which uses free moving agitators rather than rotating stirrers. This design is self-baffling and overcomes the problems of shaft stability, mechanical seals and centrifugal separation. Coflore reactors are now in common use and have proved ideal for high throughputs and multi-phase mixtures.

Dominique Roberge - *Lonza*
Lonza "Factory of Tomorrow" with flow processes and microreactors
The key concept behind the utilization of flow is to achieve extreme process intensification. The intensification process enables inherently safer conditions that lead to the

development of new processes, so-called "Flash Chemistry," that could otherwise never be performed under batch conditions. In a microreactor it is possible to perform highly energetic reactions, work with unstable intermediates, employ more reactive reagents, and use more active catalysts that enable new, out-of-the-box chemistry. In addition, the workspaces can be designed for high temperature and high pressures reactions; a new domain for a typical organic chemist. A microreactor will be at the heart of flow processes to control the "Flash Reaction" but will be implemented in parallel with other flow unit operations such as liquid-liquid extraction, distillation and crystallization.
The outcome will lead to highly intensified mini-plant approaches that will be the basis of the "Factory of the Future." The ultimate results of the initiative are more sustainable, greener, and economical processes for producing a wide range of pharmaceuticals.

Anders Ernblad - *Alfa Laval*

Case study - Economical evaluation between continuous processing in Alfa Laval ART® Plate Reactors and batch production

Chemical industries, especially the specialty chemical and pharmaceutical industries, traditionally use the conventional batch reactor technology. Stricter environmental regulations and product competiveness however pressure these industries to create more efficient production plants. Process intensifying batch reactors to plug flow reactors of the milli- and micro scale has shown promise in this regard. In this presentation a case study, focusing on the analysis of the financial effects when choosing to go for a process intensification solution utilizing a continuous flow reactor compared to a traditional batch reactor was presented. The case study is based on input from a customer in the specialty chemicals industry currently operating both a traditional batch reactor and an Alfa Laval ART® Plate Reactor for similar processes in production scale. Results show that the investment in the process intensification with Alfa Laval reactor technology was returned after 2 years. The Alfa Laval plate reactor technology also showed to be significantly economically superior to batch operated technology regarding new product development, in addition to being a more attractive choice when it comes to scale up from product development to full scale process plant.

Craig Johnston – CMAC
The workshop attendees constituted a broad international group with varying levels of experience in justifying continuous processes. It was structured through an initial survey then discussion.
The survey contained 18 questions; with 5 potential responses from strong agree to strongly disagree. Highlights are listed below

Agreement / Strong Agreement
Continuous manufacturing allows the use of smaller production facilities with lower capital and operational costs, with a reduced overall plant footprint.
Continuous manufacturing has potential to reduce labour and inventory costs significantly. Continuous process is capable of reducing overall cycle time of the process.
Continuous manufacturing minimises waste, energy consumption and raw material use.
Financial justification for investment in continuous processing due to excess existing batch capacity.
Lack of experience and fear of unknown are delaying the implementation of continuous manufacturing.
Continuous technology is still more challenging in crystallisation, isolation, filtration and drying system. Solid formation in general can block the reaction channels and is difficult to overcome.

Disagreement
General perception that continuous processing is only suitable for large volume.
Solvent can be recycled more effectively in continuous process compared to batch process.

Mixed views
Common perception that existing regulatory system is rigid and unfavourable to the introduction of continuous process.
Implementing continuous processing requires a change in processes that have already been validated.

Key Points from Workshop Discussion

Simulation of costs	Sensitivity analysis
Understanding Finance difficult, decision makers	Bx culture + organisation
Existing (change route) or New Products	Risks, speed, time to market
Cost of Goods / Quality	Platform rather than single use
Consortia share work	Narrow margins better view of costs
Capex for CMO difficult	

WORKSHOPS

The participants were divided into three groups and each group had a topic to discuss. Each group had a facilitator who managed the exchange of opinions and draw the conclusions.

1. **Economics** – *Reasons, results, aims to convince your company's management to invest on continuous manufacturing*

The above was presented back to wider conference. This also included some relevant materials from CMAC (continuous manufacturing and crystallisation) supply chain academics based at Universities of Cambridge and Strathclyde.

2. **Barriers to continuous** – *What does a company need to start working with continuous? A process of interest, a problem to solve, the suitable staff, the right contacts*

with suppliers, peripherals, time, contract research organizations etc. What is the cause that stops the process, after having proved its potential benefits?
Jean-Marie Bassett – TNO

A lively discussion developed amongst the 30 participants in the workshop, held on day 2 of the Symposium. Having a good international mix, with representatives coming from pharmaceuticals, life sciences, fine chemicals, reactor and equipment suppliers and academia, ensured that a diverse range of opinions could be aired. Key subjects were identified for further debate: culture, communication and collaboration. The brief synopsis given below provides a flavour of how the workshop progressed. In elaborating the cultural barriers, the discussion centred on the early education of scientists and the development of an awareness of the impact of engineering in achieving breakthrough improvements in chemicals production. Here, an understanding of how a chemical reaction progresses needs to be coupled with ideas for innovative engineering and technology to make optimum use raw materials, energy and available production space. Assessments of safety issues, previously left to ad-hoc solutions, can now be addressed in a more dedicated way, using flow chemistry, leading to the performance of tightly controlled hazardous chemistry for higher efficiency. In the past a more cumbersome (and less efficient) approach was adopted to minimize risks. The workshop identified the need for more internationally recognised champions of flow chemistry technologies. With improved communication between academia and industry, the workshop could see real benefits in the adoption of flow chemistry ideas, adapted to practical applications developed by technology providers. At the same time, equipment providers emphasised their need for clearer communication of enquiries from their customers, requesting greater freedom to choose the appropriate flow-technology to achieve results, even if that meant considering chemistries deemed too hazardous for classic batch processing. A better awareness, through more advertising, symposia, articles etc. of available technology toolboxes can ensure that flow chemistry receives more attention at all levels in industry : R&D, production and management. The key to cultural change and communication improvement can lie, in the view of the workshop, in a better collaboration between chemists and chemical engineers. The results, for which different success criteria could be deployed, would be expressed in a better familiarity and understanding of risks, improved costs and enhanced production and product quality.

3. **Where is flow chemistry leading?** *What are the processes that in the future will have to be in continuous (hydrogenation where continuous will become an "industry standard" or hazardous reactions or others)? Do you expect plants to become completely in continuous or will there always be a mix of batch – continuous?*
Yi Jiang – Corning

This workshop concluded with several interesting topics which will probably be the focus of continuous flow chemistry (CF) in the next few years:

1. **Set right expectations:** FC is not the technology for all reactions. A mix of Batch and CF in the future.
2. **Demonstrate economic advantages:** the economic benefits of CF were recognized, by the majority of people, to be case dependent due to a variety of chemistries and process characteristics. Chemists, process engineers, and CF equipment suppliers demonstrated that working together to speed up implementation at plant scale does matter
3. **System Integration:** the integration of flow chemistry and upstream/downstream separation steps becomes critical to drive in order to obtain maximum benefits from continuous flow manufacturing. Successful multistep synthesis production for general applications take significant time to develop, but it is definitely positive for Pharma
4. **Decentralized business models** may be developed through CF technologies to reduce transportation logistics cost, and to better manage local demand.
5. **CF** can also be **new tools** for new chemistry route discovery, high-throughput screening, and exploration of expanded boundary conditions where Batch is limited.
6. **Scale-up direction:** numbering-up and higher flow, two main streams, depend on the application and customer needs, which are driven by cost analysis results. The flow throughput of unit reactor continue increasing in the last few years: 0.5t/y today, 1+ t/y future. Some application may push for super flow and allow certain downgrade of performance. The range of flow (Min –Max) is also important to drive for more flexibility.
7. **Geographical moves:** different opinions were expressed by the team. Opinion 1: keep this technology at home due to IP/competitiveness consideration; Opinion 2: adoption rate in Asia may be higher than in western world due to high demand of production investment.

In depth discussions came along with the workshops and were managed by the chairman Gilda Gasparini of AMTechnology and moderator Professor Christophe Gourdon of the University of Toulouse. Great interest was expressed concerning economic data and potential barriers to invest on continuous.
The networking and exchange of opinions continued during the Lisbon tram tour and dinner in a typical Portuguese restaurant tasting characteristic Portuguese food and wine.
Exhibitors noted that attendees were more prepared from a technical point of view and were more keen on embracing this technology compared to the previous years.
During his closing speech Yi Jiang, Global Business Director for Corning Reactor Technologies, Corning SAS, commented: "*This is once again a great symposium after three successful ones. We have seen increased application demonstrations of continuous flow reactor technologies presented with attractive benefits. The dialogues and debates in three designed workshop were honest and helpful. We have seen lots of new faces among participants which made a good mix for opinion and experience sharing. It has been our pleasure partnering with Tekno Scienze for this great symposium series*".
The event ended with a farewell cocktail (rigorously with Porto wine) accompanied by a fado singer performance who delighted the entire audience. Tekno Scienze staff is already working on the next symposium therefore I would like to invite those who are interested in our next event to stay tuned and watch out for announcements.

ACKNOWLEDGEMENTS

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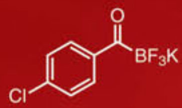

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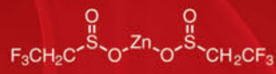

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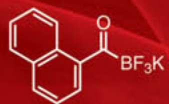

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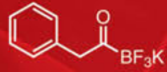

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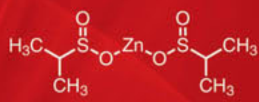

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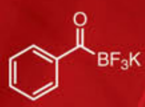

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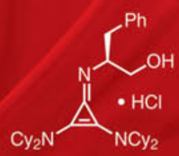

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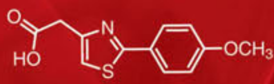

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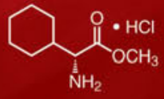

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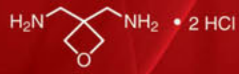

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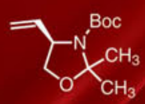

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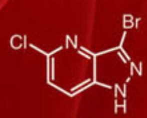

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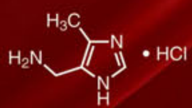

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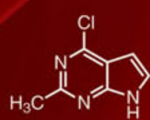

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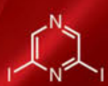

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