Gayle
De Maria

Successful 1st Symposium on Continuous Flow Reactor Technology for Industrial Applications

GAYLE DE MARIA
Chimica Oggi/Chemistry Today
gayle@teknoscienze.com

Chimica Oggi/Chemistry Today organized a first symposium on "Continuous Flow Reactor Technology for Industrial Applications" on October 12th, one day before CPhI, in Madrid. In coordination with the symposium sponsor, Corning SAS, *Chimica Oggi/Chemistry Today* brought together seventeen speakers from industry and academia to discuss the most recent applications and experiences from the world of continuous flow chemistry. In a packed, full-day agenda, the presentations were organized in sessions, including: - Continuous Flow Reactors in Industrial Production - Best Practices for Continuous Flow Reactors - Pumps, Control Systems and On-Line Analysis, spaced out by two panel discussions on future applications for continuous processing and practical experiences from the industry (1).
The aim of the symposium was to highlight the breakthrough technology of continuous flow reactors in the area of industrial chemical synthesis, enabling fewer reagents, less discarded materials, high throughput, more efficiency, increased safety and reduced environmental impact. Conventional synthesis normally occurring in "batch" reactors, where reagents are mixed and react in bulky vessels, often generate by-products that are wasted, and in the case of dangerous processes or highly toxic reagents, may represent a safety issue. Flow reactors continuously and efficiently stream chemicals together in a highly controlled manner. Given the high level of optimization, significant savings can be realized by bringing together fewer reagents to obtain the same amount of final product achieved by batch.
Let's enter into details of the lectures and fulfill our curiosity through brief interviews.

Barry R. Johnson, Alfa Laval Reactor Technology
Speech: *Plate Reactor for flow chemistry in multi-purpose plants*
One of the hurdles for flow chemistry is that the traditional batch equipment is a limited but flexible reactor system. This means that the bulk of the pharmaceutical, fine and specialty chemical plants are based on multipurpose batch reactors. Flow reactors can be considered to work together with the traditional batch reactors, where the batch reactor can be feed prep/product tanks. The Alfa Laval ART Plate Reactor is a continuous flow reactor with excellent mixing and heat transfer characteristics. It is based on a plate and frame concept, enable to use the number and type of plates required for each specific process. The result is a multi-purpose tool that is easily adjusted to different processes. Due to the plate concept with ports throughout the length of the channel it is possible to add different reactants or measure and take samples.

How do you clean the unit when it is used for multiple product campaigns?
"The Alfa Laval Plate Reactor units can be fully opened to provide access to the process channel. This means the user can develop a Cleaning in Place (CIP) and verify the method by visual inspection of the reactor surfaces, or the user can disassemble the reactor and clean all the parts individually. Parts will fit into a laboratory dishwasher or an industrial autoclave unit".

Dominique Roberge, Lonza Ltd
Speech: *Economical Impact of Microreactor Technology*
Microreactor technology is currently redefining the way many small molecules are manufactured. This presentation focused on the economical outcomes of using microreactor technology in an industrial context as well as the additional advantages, such as reduction in labour costs, quick change-over (high flexibility) in system setup, and fast kg-ton scale productions. The analysis was based on several years of manufacturing experience using a wide range of leading and proprietary technologies.

Table 1. Overview of assumptions and economical gain for the three scenarios in commercial production[a].

	batch	continuous batch	process synthesis design
campaign size (tons)	5	5	5
batch assets	six 6-m³ reactors	five 6-m³ reactors	two 6-m³ reactors
MR CAPEX[b]	0 Mio $	less than 1 Mio $	more than 1 Mio $
operators	3.5	2.8	2.0
throughput[c] (kg/min)	1.7	2.1	2.1
bottleneck	coupling	distillation	distillation
gain in yield (%)	0	+5	+5
economical gain (%)	**0**	**+10**	**+16**

[a] Cost distribution: starting materials (intermediate, solvent, and reagents) 76%, energy 2%, manugacturing 16%, and change-over 6%. [b]Depreciation over 5 years with 80% plant utilization. [c]Overall throughput at coupling reaction including product and solvent. Source: Vol. 12, N 5, 2008 / Organic Preocess Research & Development.

Are there already esteems of the global economical impact of flow reactors in an average production?
"A typical expected economical gain is between 10-20% depending on the yield increase and throughput achieved with the new continuous process. Please have a look at table 1 which gives an overview of assumptions and economical gain for batch, continuous batch and process synthesis design production".

Bernt-Dietmar Schober, DSM Pharma Chemicals
Speech: *Continuous processes in small-scaled reactors under cGMP conditions*
To meet quality requirements of their products, the pharmaceutical industry has historically almost exclusively used batch processes even where continuous processes are superior in terms of chemical selectivity, safety and process control. Margins were high and volumes were frequently small. Therefore the drivers to increase the economy and the ecological footprint of processes have been small compared to the drivers to produce high quality material reliably. The key element of pharmaceutical batch synthesis has been the "in-spec batch produced by a well- understood process in a qualified plant". The U.S. FDA's Process Analytical Technology (PAT) initiative now strongly encourages producers of active pharmaceutical intermediates and ingredients to consider continuous processes more seriously, encouraging their use whenever possible. Apart from their potential to apply "quality by design" principles, these processes offer possibilities for continuous improvement over the life cycle of a pharmaceutical. Their superior selectivity allows reducing waste drastically. As a technology-driven company, DSM has already developed continuous processes based on microreactor technology to improve selectivity and throughput of fine chemicals synthesis involving hazardous materials and to increase yields of various processes considerably.

Is it easier to obtain cGMP conditions using flow chemistry reactors?
"Continuous flow reactors address especially one aspect of "GMP conditions", i.e. stability of reaction parameters. These are not necessarily easier to obtain, but can be easier kept constant over a longer production period. Once they are established, you can run a continuous reaction over days or weeks, while in a batch process you have to establish the exact reaction conditions again and again".

Gregor Wille, Sigma-Aldrich
Speech: *Industrial application of micro- and macrostructured devices in small scale synthesis*
Today Sigma-Aldrich is manufacturing approx. 40 commercially available products in microstructured continuous flow systems. In its Centre of Excellence (located in Buchs, Switzerland) the company has set up a variety of glass and metal mixing systems for experimental and small scale manufacturing purposes. The major issue is on handling critical processes under improved safety standards and assuring constant product quality. Subsequent converting of in-situ generated instable intermediates into the final product using 2- or 3-stage systems became a standard operation in the past. This enables productivity rate ranging from 1 to 200 kg/d. It was found that microstructures optimised for certain reactions may mismatch with multipurpose demands. That's why microstructured instruments used at Sigma-Aldrich usually represent a compromise between tailored channel design for maximum conversion and maximised throughput performance.

When are micro-macro structured reactors best used?
"Narrow structures are mainly preferred. However, when it comes to a point that higher flow rates (required for higher productivity) result in a significant loss of pressure drop switching to wider channels is indicated. Solid or slurry formation may also exclude fine structures. We found universally applicable mixing structures in the range of 0.5 – 2 mm to be a good compromise for 100 g to multi-kg manufacturing. Most of the prominent benefits of flow chemistry (enhanced safety, instant interception of instable intermediates) were earned from continuous conduct and very good – but not essentially perfect –heat and mass transfer. Particularly mixing sensitive reactions may require fine-tined microstructures, rather those requiring efficient heat exchange".

Sergio Pissavini, Corning SAS
Speech: *Corning Advanced Flow Reactor: one modular tool from Feasibility to Industrial production*
Continuous process chemistry in small channels presents several advantages over traditional batch processes as yield and selectivity improvement, reduction of solvent usage, better mixing and mastering of exothermic reactions. These advantages have relevant impact on downstream units reducing the required capacity or avoiding it with important reduction in the total cost of manufacturing. Corning technology based on glass fluidic modules offer the combination of wide corrosion resistance material together with the flexibility of a library of basic fluidic modules which can be assembled in numerous configurations to fit specific chemistry needs. The "engineered" reactor can be then equipped with PAT tools for on line control and measurements.
Corning has developed different generation of fluidic modules which allow the transition from process development phase to pilot phase and to industrial production in a simple and risk free scale up methodology by the combination of fluidic module design capabilities and the numbering up of reactors. This approach allows a greater degree of simplification for the final industrial plant lay-out providing solutions from the few hundreds of kilogram up to the tens of thousands of ton per year.

What range of flexibility can be achieved by flow reactors?
"The flexibility range of micro-reactors depends on the different technology and construction materials in terms of flow-rate range, the operating window for temperature and pressure, and the range of chemical corrosion resistance. Corning equipment operates from -70°C up to 250°C, up to 20 Bar reaction pressure, sustaining a strong acid and strong base environment. Corning's flow rate capability ranges from 5 gr/minute up to 3'200 gr/min allowing total throughput capacity of 10s of thousands of tons of product by utilizing "scale-out" of module volume and "scale-up" by simple numbering up. Numbering up is a critical path; it is not necessary to imagine thousands of flow reactor in parallel with the associated complicated process control. We expect the needed range is no more than 10s of flow reactor in parallel. Configurations range from a fully passive distribution to fully active schemes depending on the specific reaction".

Jonathan Madec, PCAS
Speech: *"Development and Scale Up of a Diastereoselective Ritter Reaction: From a Semi-Batch to a Continuous Flow Process"*
The Ritter reaction is widely used for the laboratory and commercial production of N-substituted amides. This chemical reaction successfully transforms a nitrile into an N-alkyl amide from olefins, alcohols (primary, secondary, tertiary and benzyl alcohols) or alkyl halides by using various alkylating reagents as strong acid (2). Optically enriched b-methyl secondary alcohol (e.e. = 97% - d.e. = 99%), prepared from corresponding racemic ketone via reduction and enzymatic resolution, was submitted to a diastereoselective intermolecular Ritter reaction using various reaction conditions and, in particular, Continuous Flow Process to produce expected N-substituted amide. This enriched trans-substituted intermediate provides access to the synthesis of an optically pure Active Pharmaceutical Ingredient. To succeed in isolating the Ritter reaction product, PCAS, in collaboration with Corning, has used its continuous micro-reactor processing technology which is very compact and scalable, optimizing the cost of manufacturing and overall quality of isolated intermediate.

What are the main differences between having Ritter reaction totally in batch rather than having it in flow reactors?
"The main differences between performing Ritter reaction totally in semi-batch rather than in flow continuous process are a better control and understanding of the process (exothermicity + heat transfer performance), a higher reproducibility (conversion + chemical purity) and an enhanced production capacity and productivity".

Frans Muller, AstraZeneca
Speech: *Small scale continuous manufacture*
Continuous manufacture is of course not new to industry, and in fact many of the large companies benefited from successful implementation of the early continuous processes like the Solvay process, or the Haber Bosch process. In the fine chemical industries, where a wide range of products are manufactured in standard units using batch technology, continuous processing is not wide spread due to its inherent inflexibility to cope with process upsets and the fact that manufacturing processes are developed in small scale batch equipment. The development of a continuous process in a 100mL CSTR can very quickly require 1 to 3L of reagents per experiment, whereas conventional batch development will use only 0.05-0.25L. In early development starting materials are rare (=expensive) and systems are frequently heterogeneous and this makes batch development an attractive proposition for the chemist … With advent of "micro" reactors the material requirements of continuous process development have gone down to the order of mL and hazard issues are removed. This has opened up the interest of the academic community and it was quickly demonstrated that many transformations can be done continuous. The industrial challenge is now to a) develop new continuous processes and b) manufacturing equipment that allows the scale of these processes from gr to 10s of kg and beyond. Although it takes chemists a while to get accustomed to "thinking continuous" once established they observe that up to 70% of chemistry could be done continuously, but economically only in 10-15% of transformations can it be economically justified. The presentation concluded with an introduction of the new European "Flexible Fast & Future Factory" (F^3 Factory) project.

Would you define the F^3 factory project as a nursery of novel and emerging scientific idea?
"The F^3 factory consortium's vision is that the EU's chemical industry's competitive position would be strongly enhanced if it could operate modular continuous plant (F^3 factory plant) which combines world scale continuous plant efficiency, consistency and scalability with the versatility of batch operation. Our project will deliver such a radically new production mode based on: (i) a) Plug–and–play modular chemical production technology, capable of widespread implementation throughout the chemical industry. (ii) applying process intensification concepts and innovative decision tools. So the F^3 factory concept is a radically different engineering approach that will facilitate the implementation of continuous processes. Once the new platform is in place, it will greatly enhance the use of equipment based on novel and emerging scientific ideas. Rapid implementation of innovative equipment is achieved by providing a standard interface with conventional process equipment. Notwithstanding that the case studies in the consortium will foster science and innovation, the real output of the F^3 factory project is to provide the design principles and standards, a blue print, for "nurseries" in which future innovations can flourish".

Ryan L. Hartman, Massachusetts Institute of Technology
Speech: *Silicon-based Microchemical Systems for Continuous-flow Synthesis*
Microchemical systems have evolved rapidly over the last decade with extensive chemistry applications. Such systems enable discovery and development of synthetic routes while simultaneously providing increased understanding of underlying pathways and kinetics. Silicon-based microchemical systems offer advantages over classical batch-wise procedures, such as enhanced heat and mass transfer characteristics, safer synthesis of dangerous compounds, isolation of air and moisture sensitive chemistry, and reduction of hazardous waste. Optimized reaction conditions and rapid experimentation also add value to the technology by shortening product development life cycles. These advantages have prompted application of microsystems to study synthetic chemistry. Chemical synthesis typically involves different unit operations, presenting challenges in terms of the choice of methods and materials of fabrication, mixing, handling of multiple phases, synthesis procedure, and separation. Traditional batch synthetic transformations utilize separations to purify, switch solvents, and isolate products during work-up. Separations are, therefore, central in carrying out synthetic chemistry, and examples include liquid-liquid extraction, filtration, evaporation, and distillation. Strategies for separation by liquid-liquid extraction and distillation were highlighted. Integration of multiple reaction steps and separation schemes give rise to continuous-flow synthesis of more complex synthetic routes. Moreover, optimization strategies and integration of analytics presents new opportunities for automation of industrially relevant pathways. Finally, major challenges and outlook related to these topics were discussed.

What are the strengths and weaknesses of silicon based systems with respect to the other ones?
"The selection of construction materials depends on the chemistry to be performed, operating conditions required for a system, and ease of fabrication. Mechanical micromachining,

stamping, and LIGA techniques can be used to create metal microchannels. Metal devices are able to withstand high temperature and pressure, but most metals face problems with strong acids. Ceramic microstructures have advantages of being chemically inert and stable at very high temperatures. Microfabrication of ceramics is, however, complicated by the need to match shrinkage with thermal expansion during firing. Polymer-based devices, such as those based upon poly(dimethylsiloxane) (PDMS) and SU-8, take advantage of rapid prototyping and fabrication, but at the cost of dissolving in or swelling by common organic solvents. Recently, fluoropolymer integrated devices have also shown utility due to chemically inert properties. However, the bond strength between glass and fluoropolymers or other polymers is weak, which limits operation at elevated pressures. Alternatively, fluoropolymer capillaries may be used but also have temperature limitations. Glassware is the tool of choice for most synthetic chemists, and multilayered glass microreactors have been created. However, the isotropic etching used to realize most channels in glass could limit the feature density on chip. Silicon-based microsystems are readily fabricated using photolithography, wet etching, and deep reactive ion etching (DRIE) techniques. Capping of three-dimensional silicon structures by anodic bonding to Pyrex creates transparent reaction channels capable of operating at high temperatures and pressures. Moreover, oxidation of silicon surfaces enables glassware-like compatibility and the IR transparency offers potential for the integration of analytics. The high heat transfer coefficient of silicon also enables precise control over reaction temperature. Cost and device failure with strong bases can, however, be potential limitations".

Steve Donegan, CPI (Centre for Process Innovation Ltd)
Speech: *Continuous Flow Reactors and the Whole Process Design*
A range of clear benefits can be derived from the application of continuous flow reactors for chemo and bioprocessing compared to more traditional batch processes using stirred tank reactors. The transition from batch processes to continuous processing places a range of challenges for the whole process design project. The challenges can derive from a range of sources and whilst engineering solutions may be provided via catalogue ready equipment. Process chemistry or biology may fit better and provide optimum efficiencies or economics with some modification to the development or traditional process. The conventional CSTR can in some ways to a process be very forgiving, simplistically the unit material is charged, stirred and heated and the product is produced, the real experience is not quite this with the CSTR's requiring years of tweaks and adjustments to compensate the technologies flaws. The flow reactor solution is in a way bespoke to a reaction or process and in many cases to continue the analogy tailored. There is a higher imperative to know kinetics, mechanisms, calorimetry, the effects of materials addition as the flow reactors strive to plug flow there is no opportunity for adjustment as the process proceeds. In a properly optimised process design molecules all undergo the same experience but that experience needs to be the correct one.

Dirk Kirschneck, Microinnova Engineering Gmbh
Speech: *Intensified continuous API and intermediate synthesis: from potential evaluation to production scale realization*
Process performance in the synthesis of API and its intermediates can be reached through new technologies and methods. Significant development time reduction, operating cost reduction by yield improvement, energy savings and a fundamental improvement of plant safety are some of the main results of process intensification concepts. The activities can be divided into 4 phases: 1. evaluation, 2. verification, 3. development and 4. realization. A risk based approach according to ICH Q9 is used during the whole project. First of all the identification of reaction performance potential of existing chemical plants needs to be analyzed ending with the formulation of a target for the verification (basic feasibility). The evaluation starts with a process capability check, followed by the generation of a cost flow analysis and ends with a technology evaluation and comparison. In the second phase the intensification potential of

the reaction needs to be verified. Typically a continuous plant setup is developed and modified according to the needs of the chemical process. An operating procedure will be generated and optimized. Finally, a rough parameter scan of a few key parameters will deliver a relevant overview for the verification. Once the potential is proven the process development needs to be done, where the basic feasibility delivers a good basis for the work (phase 3). The reaction process will be optimized. A knowledge based approach according to ICH Q8 will be used for the development by applying methods like the critical parameter concept and cause effect chains. Engineering data necessary for the scale up will be generated in this part of the work. Finally in the fourth phase the observed performance needs to be realized. The specific knowledge in process intensification equipment needs to be combined with process experience and competence. A plant design concept needs to be generated. The best possible equipment solution needs to be selected and calculated under considerations regarding the common standards like ATEX or cGMP. A deep knowledge of process intensification technologies is absolutely necessary for the optimal equipment selection and plant construction.

What are the pivotal points when shifting from batch to flow?
"The challenging of shifting from batch to flow is in typical multi-purpose applications, keeping the flexibility of batch and combining it with the process efficiency of flow processing. A modular plant concept fulfils these needs, where the flexibility is achieved by first module selection and overall reactor configuration based on the needs of the chemical process".

Sergio Pissavini, Corning SAS
Speech: *Flow reactor technology versus traditional batch technology: a capex comparison*
Flow reactor technology is well understood as capable of delivering several technical advantages in terms of yield improvement, better selectivity, solvent reduction, and better safety and process control. These technical advantages need to be evidently transformed into economics, reducing the total investment and production cost, in order to become real. Corning's presentation covered capital investment analysis and operational cost difference by directly comparing a two process lay-out (flow reactor and batch) for two important reaction classes: nitration and hydrogenation. The comparison was not limited to the reaction section but it also estimated the downstream impact on other operating units (size and operation cost) when a process switches from batch to a Flow Reactor process.

Hans-Rudolf Marti, Siegfried AG
Speech: *MRT in a Custom Manufacturing Organisation, set up and Examples*
Siegfried's main business is in custom manufacturing of APIs for the pharmaceutical industry. The company selected MRT as an additional new technology platform to offer to customers. The presentation described the setting up of the MRT unit and showed example reactions that have been performed recently.

What are the reasons which took Siegfried to embrace MRT technology?
"Siegfried as a CMO is always looking to expand its technological toolbox. MRT or continuous flow reactors as they are called now were the logical answer to meet increasing demands in the field of sensitive or short living intermediates. The technology allows to perform – and scale-up – reactions having a very narrow margin between the desired conversion and (exothermic) decomposition. These are reactions that are difficult to nearly impossible to scale the "classical" way. Using microreactors for this type of chemistry cuts investment costs substantially. In addition even for the development of standard reactions MRT can be very useful as it allows to screen reaction parameters within a few days versus weeks of batch labwork".

Laurent Pichon, SNPE
Speech: *MEPI, an innovative facility for piloting and industrial demonstration of green process engineering*
Economical, energy savings, and environmental challenges are pushing a technological breakthrough in process engineering aiming at productivity, product quality, process safety, and reliability improvements. This explains the current growth of interest in innovative technologies and methods known as Process Intensification (PI). Until now a few innovations have been successfully scaled up, most probably due to the lack of experience and retrofitting in front of a technology change that always brings the question of technical and financial risk. There is now more than ever a clear need of industrial demonstrations of successful PI experiments in full respect of confidentiality. In light of this, a piloting and demonstrating facility has been created in Toulouse to speed up the implementation of PI technologies in the Industry in the frame of Green Process Engineering. MEPI is a dedicated tool to achieve these targets by promoting a unique technical plate form involving university, equipment providers and industrial end users partners on an SNPE industrial site in Toulouse.

What is the advantage for MEPI to be located on a SEVESO site?
"Being located on a Seveso site is stretching the chemical possibilities of MEPI for testing and demonstrating the intensification of synthesis brought by our clients. This will also promote the short cutting program we propose by using more reactive intermediates in full health, environment and safety conditions, in order to reduce the number of steps in the synthesis of a molecule".

Bertrand Buisson, Sanofi-Aventis
Speech: *Catalytic slurry hydrogenation with continuous flow reactor technology*
Heterogeneous catalytic hydrogenation is a well known reaction inside pharmaceutical chemistry. This reaction is often operated into large specific reactors on a batch mode. Due to heat and mass transfer limitations, the productivity is quite low, hydrogenation is often several hours at moderate temperature and pressure. Even though the hydrodynamic is quite complex, the continuous flow reactor sounds as a good idea to switch to an intensified process with high productivity. Beginning of 2008, Sanofi Aventis decided to go through a development study in closed collaboration with Corning and the Centre for Process Innovation. The basis of the study was the industrial batch hydrogenation and the challenge was to reach the same quality and the same yield – at a minimum – within one year. They first went through a feasibility study then an optimization study. We learned quite a lot on the chemistry and the technology and they finally achieved conversion and selectivity within a residence time of few minutes only. Unfortunately, due to outside reasons, we did not go to the industrial scale.

Paul Watts, Chemtrix
Speech: *Fine chemical synthesis in continuous flow reactors*
Current production technology is based on the scale-up of successful lab-scale reactions in order to achieve mass production. This approach is however fundamentally flawed as at each stage of the scale-up, modifications made to the reactor vessel result in changes to the surface-to-volume ratio, which in turn have a profound effect on thermal and mass-transport properties of the reaction. Using an approach referred to a scale-out, a reaction is first optimised within the laboratory using a single micro reactor, and in order to increase production volume, the number of reactors employed is simply increased. This approach is therefore cost effective, time-saving and flexible, enabling changes in production volume to be made

with ease. With these factors in mind, demonstrate watt's group the use of miniaturised flow reactors for the synthesis of an array of organic compounds of pharmaceutical interest.

What are the differences faced during scale-up?
"The challenge for scale up is how to optimise the process conditions effectively. In the case of multi tonne production if a few kilograms (or even more) of starting material is used this is not a problem, however if the goal is to prepare gram to kilo quantities one wants to optimise the process using small amount of materials, otherwise more is wasted in the optimisation process than is trying to be produced. This is particularly important in pharmaceutical processes where starting materials can sometimes be very expensive. Consequently one goal is to develop micro reactors with very small reactor volumes, which means that processes can be optimised using small quantities of reagent; another advantage that follows is that the optimisation process then becomes faster. Once optimised, the process can then be scaled through pure parallelisation of the micro reactors or by moving to 'meso' reactors containing mixers which enable equal efficiency to be realised".

Harry Morikawa, Fuji Techno Industries Corporation
Speech: *Check That Pulse*
Continuous Flow Reactor Technology is the core in this emerging field but it is not the only technology needed for a productive operation. 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. Triplex plunger metering pump offers non-pulsating flow at high accuracy and repeatability (< +/- 0.1%). The presentation described operating principles, performance and applications of the pump.

Concerning the continuous flow reactor application, what issues or shortcomings pumps have?
"It is not suitable to use a gear pump for pumping a low viscous liquid (no more than 10 cp) or discharge pressure over bar. Consistency of flow rate of a gear pump very much depends on the parameters of liquid and pressures. Flow rate fluctuations take place with the viscosity change of liquid, just like a centrifugal. As to a diaphragm pump, pulsation takes place in the discharge side. Besides that, Diaphragms tend to be expanded and contracted. This reduces the accuracy of pumping. Also, a diaphragm is not durable and a diaphragm's fatigue leads to a hole or crack. Pumps, other than a diaphragm pump, have a chance of leakage. Our pump is no exception. Under the normal circumstance, our pump does not leak liquid but, since we use plungers and seals, there is still a possibility of leakage. Therefore, our pump has a drain hole for collection of liquid".

Herman Bottenberg, Zeton
Speech: *Process intensification - How to implement continuous flow reactor technology at pilot and small scale production*
Facing strong competition from low labour cost countries, many companies in the subject industries (pharma and fine chemicals) are urgently looking for ways to reduce such costs as well as to win the constant battle of being first-to-market with new products and processes. One of the better solutions, is to change from batch to continuous processing thereby ensuring constant quality, high production efficiency and reduced labour costs. Nowadays new mixing, reaction and separation technologies provide opportunities for designing the process to fit with the chemistry rather than fitting the chemistry to the batch process. Implementation however, requires a new set of tools and engineering and construction capabilities. Especially because the throughput, the construction size, the instrumentation and the control strategies deviate from the traditional large vessel batch operation. When looking at continuous processing many similarities can be found in continuous processing in Oil & Gas, petrochemicals and bulk chemicals industries. By taking examples from these industries, significant improvements can be achieved in simple though smart solutions. The deviation of pharma and fine chemicals industry from these industries are the scales (fine chemical/pharma is much smaller) and the quality control and cGMP requirements are much more important. However, when taking the perspective from a pilot plant manufacturer capable of engineering and building of laboratory scale continuous pilot plants and batch wise operated pharma kilo-labs, it is possible to identify solutions for transforming batch processes into continuous operated process plants for fine chemical and pharmaceutical industry.

Is it always possible from an economic point of view to transfer batch processes into continuous for the Pharma and Fine chemicals industry?
"Changing from batch to continuous processing often requires a complete change in the processing and hardware requirements. Therefore, depending on the business situation and the current business model, companies may need to decide between existing not fully occupied batch facilities or investing in new hardware. On the short term this could mean that the change to continuous processing is not economically feasible. However, looking at the whole picture, including labour, quality control, processing efficiency, product quality and development time, I am confident that, when the chemistry fits with continuous processing, the change to continuous is an economical feasible option!"

Brian J. Marquardt, University of Washington
Speech: *Benefits of On-line Sensors for Advanced Flow Reactor Analysis, Optimization and Control*
Process Analytical Technology (PAT) has been used by various industries for gathering data to develop and monitor processes. It has proven a valuable tool to optimize productivity and quality

for decades, and recent advances in analytical sensors and sampling technology have continued to improve measurement capabilities. New technology for micro-machining, along with new material developments, have allowed for advances in the miniaturization of instrumentation and in operational devices such as continuous flow reaction equipment and analytical tools. Many micro-analytical developments have been focused on the need for measurement tools to support the growing use of micro-systems. These systems have been used predominantly for high throughput experimentation, a widely used technology for new material discovery. This approach to working with a large number of reactions and achieving fast results has been recently broadened to include process development, process optimization, and product development activities. Recently a program was initiated to develop and optimize new chemistries using advanced flow reactors, analytical measurement tools and NeSSI (New Sampling and Sensor Initiative) sampling components. The program is a collaboration between the Food and Drug Administration (FDA), Corning, Kaiser Optical Systems, Parker and CPAC (Center for Process Analytical Chemistry) to demonstrate the value of the advanced flow platform in conjunction with micro-analytical tools and modular sampling systems components to improve process understanding and control.

What efforts have been necessary in order to adapt measurement systems to the concept of flow processing?
"Primarily, development has occurred in the area of effective sampling systems for continuous process monitoring. These systems include flow paths and connections that are on the same approximate scale and easily adaptable to commercial flow reactors and process systems. These sampling systems, generally termed NeSSI (New Sampling Sensor Initiative), provide a modular, flexible platform for flow control components and process analyzers that are easily adapted to continuous flow monitoring applications. The development of these sampling system components has been an ongoing effort by Parker, Swagelok and Circor for the last 8 years. Historically, the development has been focused on the design and manufacture of valves, gauges, filters, etc. for flow control and sample management. However, more recently advancements have been directed towards the development of measurement interfaces, sensors and analyzers for deployment on these sample systems".

Rich discussion took place after each session, especially during the two panel discussions which utilized a post-it exercise. Both panels were held by Rob Bryant, a fine chemicals consultant. Participants were invited to write down their ideas on the topic "continuous flow reactor chemistry for industrial applications" and their expectations about the "take-home message" they wished to get from the symposium. What can be drawn from the sometimes provocative questions of the audience and the respective answers of the speakers is that continuous reactor technology works but collaboration between chemists and engineers is key. Cost issues and production logistics play a crucial role too, and quantifying the economical impact of flow reactors is critical. The event drew accolades from attendees: "I found the symposium to be valuable, informative, and a great opportunity to engage with leaders in this exciting new field. I look forward to attending next year's event", said Martin Jönsson, Sales and Marketing Manager, Alfa Laval during the event's closing reception. Closing the Symposium Gary Calabrese, Senior Vice President, Corning Incorporated, stated "We were very pleased by the sold out response and very engaged participation from more than 140 attendees representing 75 organizations and 20 countries at this first annual symposium. Based on this very strong reaction, **we look forward to working with Teknoscienze (*Chimica Oggi/Chemistry Today* Publisher) in planning next year's program". Therefore see you in Paris next year (3-4 October) at the 2nd *Symposium on Continuous Flow Reactor for Industrial Applications* with thanks to all participants' comments and suggestions. We believe the symposium will prove to be another success.**

REFERENCES

1. For further information on the Symposium please visit: http:// chemistry-today.teknoscienze.com/lp/madrid_symposium.html

INFORMEX

2010

MOSCONE CONVENTION CENTER – SOUTH HALL
February 16 – 19, 2010 – San Francisco, CA

ITALIAN CHEMISTRY GROWS ACROSS THE YEARS

Italian Pavilion
Booths numbers:
from **502** to **514**
and from **601** to **613**

APIs
Active Pharmaceutical Ingredients

Reliability
Italian manufacturers guarantee consistent quality and global market knowledge.

High technological know-how and culture

Experience on the qualified USA market

Passing severe FDA inspections

Regulatory compliance

Italian manufacturers have upgraded their quality standards according to the GMP standards.

Ministero dello Sviluppo Economico

ITALIA
Italian Trade Commission

italtrade.com
The Made in Italy Official Portal