

# **Continuous Flow Technology 2012**

**19 – 21 March 2012**

**King's Manor, York**

## **Abstracts**

### **New Tools for Molecule Makers**

**Professor Steven Ley**  
**University of Cambridge, UK:**  
**<http://leygroup.ch.cam.ac.uk/>**

#### **Abstract**

The search for new ways to assemble molecules continues to be an important driver for organic synthesis. The biological activity and exquisite structural diversity of many natural products stimulates invention by challenging today's synthetic methodology. However, preparing such materials from small and commercially available building blocks inevitably involves more than one synthetic step. For most modern drugs and other complex molecules, it is not uncommon for syntheses to require at least 10 steps, and sometimes many more.

In order to make molecules more efficiently and economically, our group has developed and used solid-supported reagents in a multi-step fashion without the use of conventional work-up procedures. Now we have extended these concepts to make use of advanced scavenging agents and catch-and-release techniques, and combined these with the use of continuous flow processing to create even greater opportunities for organic synthesis.

## Continuous Flow Chemistry in High Temperature/Pressure Process Windows

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### Abstract

The popularity of dedicated microwave reactors in many academic and industrial laboratories has produced a plethora of synthetic protocols (>5000) that are based on this enabling technology. In the majority of examples, transformations that require several hours when performed using conventional heating under reflux conditions reach completion in a few minutes or even seconds in sealed vessel, autoclave-type, microwave reactors. However, one severe drawback of batch microwave chemistry is the difficulty in scaling this technology to a production scale level, mainly because of the restricted penetration depth of microwaves into absorbing materials, i.e. solvents or reaction mixtures.

This lecture demonstrates that this limitation can be overcome by translating batch microwave chemistry to scalable continuous flow processes. For this purpose, *conventionally heated* micro- or mesofluidic flow devices fitted with a back pressure regulator are employed, in which the high temperatures and pressures attainable in a sealed vessel microwave chemistry batch experiment can be mimicked.

In an extension of this concept, production scale high temperature/pressure flow chemistry can be realized by using tubular flow reactors heated by microwave irradiation. The advantages of direct in-core microwave heating for continuous flow applications are most prominent for larger tubular reactors with  $\geq 10$  mm i.d. where the rapid volumetric heating to a high-temperature/pressure regime allows processing benefits not easily duplicated by conductive heating principles. In order for these flow reactors to be implemented into large scale chemical manufacturing processes, the use of powerful magnetrons operating in an optimized frequency range and the fabrication of microwave transparent and durable reactor components that can withstand high temperatures and pressure is required.

By using several model transformations the good scalability of various synthetic organic transformations to industrial scale will be demonstrated. Particular emphasis will be placed on the energy efficiency of the microwave-driven processes.

# Continuous Production and Use of Hazardous Chemicals in Flow Reactors

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## Abstract

A multitude of hazardous chemicals are presently transported on large scale over long distances. Doing it in a safe way is undoubtedly possible, but requires considerable efforts related to loading, unloading, cleaning and storage. Legislation will impose further restrictions on transport of hazardous chemicals.

Laboratory scale processes frequently make use of hazardous materials that are not available on plant scale, so process scale-up requires to change the chemistry: longer synthetic routes or "safe" equivalents of hazardous materials with low atom efficiency are chosen.

Production of such chemicals *on site on demand* in continuously operated small-structured reactors avoids transport and storage. Moreover, it allows using chemicals that presently or in the near future cannot be transported at all for reasons of product safety or stability.

DSM has developed a number of methods of *in situ* production and use of hazardous chemicals as starting materials for pharmaceuticals, agrochemicals and other fine chemicals.

The lecture contains a comparison between lab-scale batch processes and their large scale equivalents in continuous flow mode. It gives examples how to translate laboratory recipes into production methods and devices. Furthermore it gives examples of applications of in-house generation and use of hazardous materials.

## **Flow Chemistry at Low Temperature**

**Günter Weingärtner**  
**Dottikon Exclusive Synthesis AG, Switzerland**

### **Abstract**

The presentation will focus on low temperature chemistry and the applications of flow chemistry under such cryogenic conditions. In many publications it could be demonstrated that cryogenic conditions can be avoided by using micro reactors to intensify the reactions conditions up to normal temperature ranges.

In our presentation we discuss CSTR (continuous stirred tank reactors) as useful and simple tools for the production of reactive intermediates under cryogenic conditions from lab up to production scale. Chemistry at low temperature often involves salt intermediates (lithiated compounds) that can lead to clogging of conventional flow type equipment like micro reactors or static mixers. A CSTR approach can be a good alternative for preparation of such insoluble intermediates although there is an essential disadvantage of incomplete conversion in a CSTR. However, if cheap or easy available starting materials can be used or they can be recovered by simple processes, a CSTR is a good alternative, especially to deal with solubility or certain selectivity issues at low temperature.

We will present different case studies from recent development projects.

Building blocks like boronic acids for modern coupling reactions with transition metals can be produced in a continuous way. Controlled conditions are often required to prepare (highly) substituted boronic acids with high conversion and good selectivity.

Functionalising of heterocyclic compounds can be obtained by the choice of a specific base system and the right temperature range. With this example it can be demonstrated how the batch process is developed and then transferred into a continuous process.

The last case studies will focus on special selectivity issues. A chlorination reaction has to be done under low temperature to prevent isomerisation of E/Z isomers during the reactions. The batch and the continuous processes are compared.

I would be happy to get the chance to talk about some recent development and present some different case studies.

## **Flow Reactors - Some Unusual Operational Aspects**

**Allen Wright**  
**LyraChem Ltd and University of Newcastle, UK**

### **Abstract**

Continuous reactors have some advantages over batch reactors. Heat and mass transfer is intensified, capital and operating costs are lower and plant footprint is reduced.

This presentation will explore and illustrate through case studies some technical aspects of design and operation of flow reactors which are not normally considered, in particular controllability and thermal safety, and use of continuous operation for reactive distillation processes.

Continuous reactors have a lower inventory than batch reactors, and are considered inherently safer. In some cases however,  $TMR @ MTSR$  may approach zero rendering the continuous reactor unsafe with respect to its potential for thermal runaway.

A flow reactor with no apparent distillation facility can be operated such that it effectively acts as a reactive distillation system. This has important implications to industrial scale condensation reactions.

## **Scale-up and Product Slate “Tuning” of Carbonylation and Hydrogenation Reactions with a Bench-Scale Flow Reactor**

**Jasbir Singh  
HEL Group (UK), UK**

### **Abstract**

The potential benefits of operating in flow mode are now being appreciated in the fine chemical and pharmaceutical industries. Of particular interest are high pressure reactions, especially in heterogeneous catalysis where the benefits are greatest especially compared to batch operation. This presentation will discuss the key design features and operating criteria for a small scale flow reactor, as distinct from a catalyst cartridges used for reaction screening. It will discuss aspects of catalyst loading which is important for both reproducibility and also optimising catalyst costs. It will describe how the reactor can be successfully used over a wide flow range thus allowing the equipment to be used as a research tool first and then later to produce enough material for trials. Using the same design criteria, it is relatively simple later to move on to production scale. These points will be demonstrated by reference to a bench-scale flow reactor running a several high pressure hydrogenations and even a carbonylation. The benefits of a flow reactor where all parameters can be individually monitored and controlled become apparent when tuning of the product slate becomes simple and repeatable.

## Industrial Designs, Scale-up, and Use of Microreactors

Dominique M Roberge  
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### Abstract

Microreactor Technology enables processes to be run in a continuous manner using a minimal quantity of reagent. Thus, it permits the rapid and scalable development of continuous processes in the fine chemical and pharmaceutical industries. Under such circumstances, advantages are associated to the continuous way of operation and to the micro structure as well such as the good thermal control. It is important to differentiate from where the advantage is coming from because it will significantly influence the scale up strategy for larger productions.

In the fine chemical industry, productions are made in multi-purpose plants of high flexibility. The integration of a continuous system in such an environment is feasible given appropriate modules are employed with (i) good chemical resistance (i.e. glass, Hastelloy, Teflon), with (ii) excellent material stability over a large range of temperatures, and with (iii) ease of connection avoiding dead volume. In addition the various modules need to take into account the physico-chemical properties of the reaction such as the reaction kinetics ( $\Rightarrow$  residence time) and the reaction phases (solid – liquid – gas). This approach leads systematically to a toolbox concept.

A detailed analysis at Lonza [1] showed that ca. 50% of the reactions studied could fit into a microreactor based on their kinetic. However, by taking into account the reaction phases, this number shrinks to ca. 20% of potential candidates because a solid phase is present in more than 60% of the cases. In addition, the reactions were classified into 3 classes namely Type A (mixing controlled reactions), Type B (rapid but kinetically controlled reactions), and Type C reactions (batch reactions with thermal hazard).

The 3 types of reaction define of course 3 types of reactor modules required to operate in a flexible manner various pharmaceutical reactions. The poster will analyze the industrial designs of reactors, review their use, and address in details the scale-up concept. The Lonza MicroReactors have already produced several tons of material. Thus, manufacturing examples will be presented based on Lonza experience showing the applicability of continuous processes and microreactors in an industrial environment.

### References:

1. D.M. Roberge, L. Ducry, N. Bieler, P. Cretton, and B. Zimmermann, "Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries?", *Chem. Eng. Technol.*, **28** (3), pp.318-323, 2005.

# **The Application of Micro Reactors for the Rapid Optimisation of Chemical Processes**

**Paul Watts**

**Chemtrix BV, UK**

## **Abstract**

Current production technology is based on the scale-up of successful laboratory reactions in order to achieve large-scale 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 the thermal and mass-transport properties of the reaction. As a result of these variations, it is often necessary to re-optimize the process at each stage of the scale-up process; consequently, the route from bench to production is both costly and time consuming. It is therefore postulated that through the application of micro reaction technology, the transfer of reactions from the laboratory to production will be both rapid and cost effective. Using an approach referred to as scale-out or numbering up, a reaction is first optimized within the laboratory using a single micro reactor and in order to increase production volume, the number of reactors employed is simply increased. As a reaction only needs to be optimized once (with all subsequent reactors being controlled using the same operating conditions), this approach is both cost effective and time saving.

With this in mind, the last five years have seen interest in the miniaturisation of chemical processes grow; however, in order to facilitate transfer of the technology from its current position as a research tool to widespread industrial application, a core understanding of the challenges associated with the transfer of reactions from the macro to the micro domain is required. The work described herein therefore aims, to tackle this problem by investigating the application of micro reactors to a range of commonly employed synthetic reactions. Using the synthesis of compounds of pharmaceutical interest, we were able to demonstrate advantages such as rapid optimization, enhanced conversions, reduced reaction times, reduced by-product formation and increased diastereoselectivity, as a result of employing micro reaction technology. The use of solid supported reagents adds even greater diversity to the range of reactions that may be achieved within such systems.

# Enabling and Optimizing Chemical Reactions in Real Time

Jon Goode  
Mettler Toledo AutoChem Inc, USA

## Abstract

Flow chemistry is one of the hottest topics in organic chemistry today. In the chemical development and processing environment, improvements in product quality, yield, synthetic route, safety and overall time efficiency have become key factors in driving chemists and engineers to seek alternative chemical development methods. Reaction control is key to ensure only desired product is produced, as opposed to other substituents such as toxic and/or highly reactive intermediates that can be challenging to control and therefore pose significant personnel safety risks. Continuous flow reactors have the ability to:

- Better control chemistry
- Use higher temperatures and pressures to access new chemistries and compounds
- Reduce reaction times from hours to minutes
- Increase selectivity and yields while reducing purification needs and waste at the same time
- Screen many different sets of conditions in one reaction, all with minimal amounts of expensive or quantity limited materials
- Scale-up from milligrams to kilos with minimal optimization

The combination of flow reactor technology and *in situ* analysis takes flow chemistry to another level. The formation of products, by-products and reactive intermediates are all followed, and this information used to make 'on the fly' adjustments and educated decisions, leading to optimized operating conditions of the whole system. Offline analysis is no longer required and optimum results are achieved in minutes, saving valuable time and resources. The use of Fourier Transform Infrared (FTIR) spectroscopy with an integrated, micro flow cell provides an ideal inline measurement device to monitor and provide reaction feedback on control parameters for immediate understanding and optimization of the process.

This paper will focus on

- An overview of FTIR *in situ* analysis in industry
- Chemistry examples showing the rapid optimization of reactions using the combination of flow technology and *in situ* analysis
- The potential for *in situ* FTIR technology to be used as a PAT tool in API production
- Ideas for the future of flow chemistry and *in situ* analysis

## **Multi-stage CSTRs: Scaling up Flow Reactors**

**Gilda Gasparini**  
**AM Technology, UK**

### **Abstract**

The Coflore reactor is designed as a series of CSTRs, using dynamic mixing and stage segregation to achieve mixing and plug flow behaviour instead of relying on flow rate and geometry. These differences make scale up in the Coflore reactor much simpler than conventional statically mixed reactors (CTRs, OBRs). It is not necessary to evaluate dispersion numbers and mixing/velocity characteristics for different fluid velocities and tube sizes. This saves time and eliminates guesswork. Moreover, when scaling up a flow process, the key design data (kinetics and heat of reaction) can be obtained using a small reaction calorimeter. In the second phase, the flow reaction should be optimised with a low throughput bench scale flow reactor (ACR). The way this information is used to design the full scale reactor will be presented. The first example is a second order reaction: the challenge is to control the initial fast stage and drive the reaction to completion efficiently over the slower phase. The second example refers to a class of reactions traditionally considered not suitable for flow reactors: biocatalytic oxidase. This is a multi-phase reaction (G/L/S) with a reaction time in batch of over 24 hours. Results of the optimization from batch to continuous at the lab scale have already shown a reduction in reaction rate from 24 to 3 hours and the following production scale up study results will be shown and discussed.

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## **Recent Advances in Flow Chemistry Technology**

**Mike Hawes**  
**Syrris, UK**

### **Abstract**

In the last 10 years flow chemistry has evolved from obscurity to the most rapidly developing synthetic chemistry process. Chemists are now able to perform a wider range of faster, cleaner, safer chemistry. This presentation looks at how flow chemistry has developed over the last decade but specifically looks at the recent advances, including examples

# **A Flexible Approach to Continuous Chemistry at Scale**

**Paul Sharratt**

**Institute of Chemical and Engineering Sciences (ICES), Singapore**

## **Abstract**

Flow chemistry can bring substantial benefits in terms of reduced cost, accessing difficult chemistries, reduced hazard, process efficiency and many other areas, but is not a panacea. Problems exist in dealing with solids, difficult rheologies, slow reactions and other issues. ICES Singapore has been developing the capability to deploy flow chemistry at scale in a flexible way, and have developed a facility and approach that can deliver a range of chemistries at a nominal scale of 20L/hr. Our approach has been to take on chemistries of interest to us or research partners and where there would potentially be business benefit, rather than looking for chemistries that inherently and obviously run well in flow.

The facility uses a range of “plug and play” skids that can be configured so as to deliver different processing for different reactions. We are able to run “hybrid” batch-continuous processes, which allow us a pragmatic way around some of the issues that would disable purely continuous implementations of chemistry. We have demonstrated a range of continuous reactions [some in combination with batch work-up], and we are currently strengthening our ability to carry out continuous separations such as crystallization and distillation.

This paper will share some of our learning around the development and implementation of flow chemistry, covering issues such as team skills, development activities, control, PAT and equipment design. It will be illustrated with our experience in reactions including simple ionic reactions, peroxide oxidation and Reformatsky

# **Continuous Crystallisation Collaboration and Conundrums**

**Alastair Florence and Craig Johnston  
Strathclyde University, UK**

**Abstract Awaited**

# Flow Chemistry and Microreactors Turn Process Performance into Money

Dirk Kirschneck

Microinnova Engineering GmbH, Germany

## Abstract

Flow chemistry in combination with process intensification tools as microreactors offers a lot of new possibilities in development and production. Microinnova has worked out plant systems which fit in this new approach of development and production and meet perfectly the demand of efficiency and flexibility: For development and small scale production the flow miniplant. With the manufacturing-systems plant redesign, dedicated plant, unit operation and modular multipurpose the entire spectrum of manufacturing strategies are covered.

## INTRODUCTION

A batch reactor provides a flexible and relatively easy solution without looking too much at process performance and space-time-yield especially for small and medium volume products. Therefore there is a significant change to develop and implement flow processes. High performance flow processes based on the best possible operating costs will generate a significant business advantage.

## Methods & Technologies

The fundamental aim of the flow approach is to give the chemical reaction what it needs. To fulfill these needs, the critical parameters need to be established out. These parameters are different for every chemical reaction. They might be classical ones like temperatures or concentrations or others that are quite new to the classical chemist, such as mass transfer at the beginning, dispersing during residence time or heat transfer for very exothermic or endothermic reactions. Another might be uniformity achieved by perfect plug flow with an impact on back mixing, concentration spots and so on. Residence time and residence time distribution can be relevant to the process as well. The drivers for can be divided into three groups: better processing, new process windows and new synthesis routes. Furthermore this involves a significant change in process development methodology. Development times are reduced and lower volumes of raw materials are needed.

## Systems and Plants

A wide range of laboratory systems are available on the market. The new generation systems are easier to use and address the needs of the medicinal chemist (chips systems in  $\mu\text{l}/\text{minute}$  range) and the synthesis chemist (benchtop systems run typically in ml to hundreds of ml/hour range). Microinnova's flow miniplants address the needs of the process chemist. In contrast with classic batch technology development, where the lab and pilot plant and phases are strictly separated, some of the lab and pilot phases of a process development can even be operated on one and the same plant only with small modifications. Furthermore, these flow mini-plants are also applicable for small scale manufacturing. There are two typical classes of flow rates for the flow miniplants. The S-(small) Class operates with a range of 1-10 litres/hour, focusing mainly on development. It has typically a lower level of automation and is run by an operator. The M-(middle) Class operates at 10-100 litres/hour total flow, focuses on manufacturing and is typically designed with full automation. However, both can be designed for either manual or for automated operation.

Microinnova follows two approaches to design flexibility into miniplants and manufacturing plants, 'on-module flexibility' and 'inter-module flexibility'. 'On-module flexibility' means that it is possible to quickly exchange certain plant parts and parameters, such as the reactor, heat exchangers,

residence time, etc., to change the process by the planning of so called 'engineered spaces' on the module.

### **Manufacturing Systems**

Microinnova Engineering has developed three different new systems on full manufacturing scale and a classic fourth one for a continuous dedicated plant, which is typically for large scale processes. The possible drivers for customers to implement one of these manufacturing systems are multiple, most often to improve yield but also to achieve better process control, save energy or increase safety.

The **plant redesign** option integrates microreactors or other micro-structured components into existing production plants at suitable points. This is based on the approach to achieve best results while still keeping the interventions as limited as possible. The starting point is one single process step or similar processes in existing chemical and pharmaceutical plants.

**Unit operation** achieves a chemical process step in a plant with all related aggregates and measuring devices in the form of a skid construction. In this way, individual reaction steps in a continuous process can be carried out without changing the other process steps.

The **modular multi-purpose** plant combines the flexibility of batch technology with the process performance of continuous process management. The variably combinable and replaceable modules, such as the feed, reactor module and residence time module, make it possible to create temporary chemical plants for a wide range of different purposes, adjusted to the respective product.

# Networked Flow Systems for Evolvable Reactionware

Lee Cronin  
Glasgow University, UK

## Abstract Awaited

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## The Rapid Optimization of Hazardous Chemistries Using In-line FTIR Analysis and Flow Reactor Technology

Richard Jones,  
ThalesNano Inc, Hungary

### Abstract

Flow chemistry is an important area of research in organic chemistry today. The number of scientific articles published on this topic every year is rapidly increasing and 20 out of the top 20 Pharmaceutical companies are continuing to invest significantly in flow technology.

Why is there so much excitement? Flow reactors can enable you to do things in compound synthesis that weren't possible before.

- Use higher temperatures and pressures to access new chemistries and compounds.
- Reduce your reaction times from hours to minutes.
- Increase selectivity and yields while reducing purification needs and waste at the same time.
- Screen many different sets of conditions in one reaction, all with minimal amounts of potentially expensive or quantity limited materials.
- Scale up from milligrams to kilos with minimal optimization.

The combination of flow reactor technology and in-situ analysis takes flow chemistry to another level. The formation of products, by-products and reactive intermediates can all be followed, and this information used to make 'on the fly' adjustments and educated decisions, which lead to optimized operating conditions of the whole system. Analysis would no longer have to be done offline and optimum results could be achieved in minutes, saving valuable time and resources.

The presentation will feature the following:

- An overview of flow chemistry and how it can be utilized to perform hazardous reactions in a safe and controlled manner.
- An outline of how easily FTIR flow cells can be linked to ThalesNano's H-Cube®, X-Cube™, and O-Cube™ flow reactors.

The presentation of chemistry examples where the combined systems are utilized to perform difficult and selective optimizations using instant FTIR analytical feedback. Applications include hydrogenation, carbonylation, and ozonolysis.

## **Achieving Production Scale Flow Chemistry**

**Barry Johnson**  
**Alfa Laval, UK**

### **Abstract**

Alfa Laval has embarked upon a demonstration programme for Plate Reactors at large scale in order to contribute to the case for continuous process plants in the Fine and Pharmaceutical Industry. Reactions which utilize reagents and chemistries common in the industry are chosen to address the issues of operating with real materials. The study is aimed primarily at developing scale up guidelines, but will also, inevitably, give lessons on process startup and shutdown, economics and equipment (both reactor and ancillaries) performance.

In this presentation we will present our experience from 2 reactions, a TEMPO catalysed oxidation and an organometallic synthesis / reduction . These reactions introduce different and common processing challenges including immiscible phases, competing byproduct reactions, sensitive reagents and highly energetic materials. In addition a customer implementation at large scale will be introduced and the learning's and benefits from that highlighted.

Studies are performed at a number of different reactor sizes and thruputs culminating with operation in a ART® Plate Reactor PR49 at the 50 to 100 L / hr range. At each scale the reaction yield is assessed with regard to the reactor operation and performance. Adaption's to the operating scenario and to the reactor for operation at the next larger scale are determined and implemented.

# Continuous Processing – A New Paradigm in the Manufacturing of Active Pharmaceutical Ingredients?

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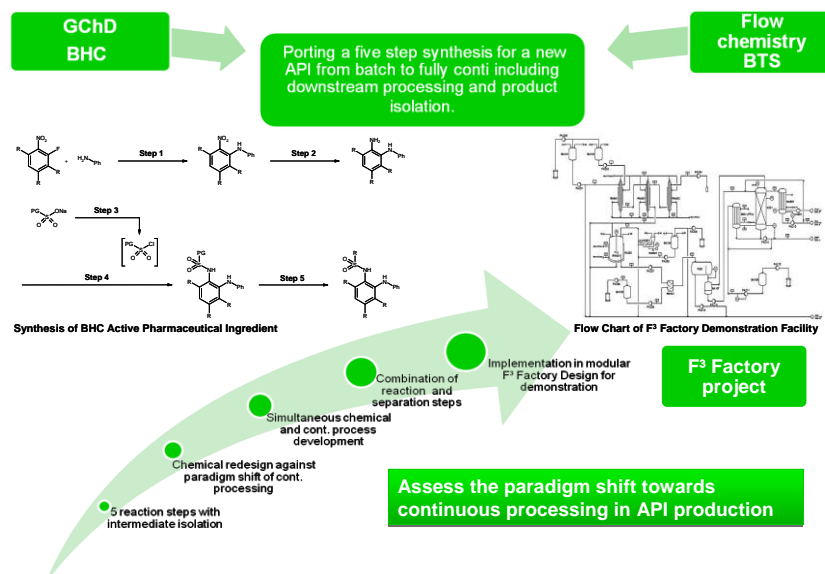
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## Abstract

Continuous processing provides a promising path forward for the pharmaceutical industry to reduce the cost of manufacturing of APIs, to further improve its capability to respond flexibly to fast changing demands and to achieve an even more consistent product quality. Continuous processing is an integrated approach that combines chemistry, process technology, and quality controls. Currently, most major pharmaceutical companies are engaged in several initiatives to prove the benefits of these innovative processing methods.

BHC Global Chemical Development and Bayer Technology Services are working together to develop and apply a continuous manufacturing concept for the multi-step synthesis of the new MEK inhibitor BAY 86-9766, an active pharmaceutical ingredient. The demonstration and combination of processing steps is part of the F<sup>3</sup> Factory initiative by the EU [1].

The presentation will give an overview on the project frame and will show the results of this collaboration.



## REFERENCES

[1] The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 228867.

# Leaving the Tap Open: Examples of Continuous Processing in Pharma R&D

**Anna Stenemyr  
AstraZeneca, Sweden**

## **Abstract**

The use of continuous processing in the pharmaceutical industry is still in its infancy, but is subject to much interest in academia and the wider pharma business including equipment manufacturers and contract manufacturing companies. Numerous application of continuous technology to reactions as well as subsequent unit operations, such as extractions and crystallisations have been demonstrated on various scales. Also, many related areas such as in-line analytical technology, QA/release and regulatory compliance are developed in parallel to meet the needs of continuous GMP manufacture. Some often mentioned drivers for this development are cost savings, process safety, improved scale up and access to a wider range of reaction conditions. The presentation will focus on the application of continuous processing in chemical process development and illustrate some of the aspects mentioned above through specific examples.

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