Flowing from the Alps

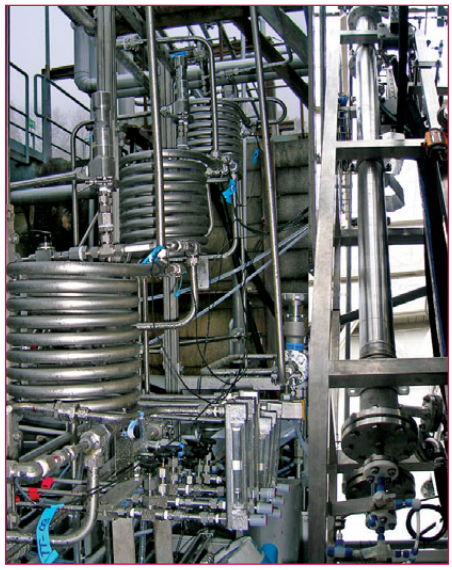
How far will flow chemistry take over in the synthesis of APIs and pharmaceutical intermediates? We asked some of the major players from **Switzerland**

Flow chemistry, typically using microreactors, or continuous processing - the terms are often used interchangeably though of course they are not the same thing - is, we are told, the way of the future in fine chemicals. And Switzerland is still, despite the ever increasing competition from China and India, the heartland of the fine chemicals industry.

So, as they look to ways to maintain their technological edge, many of the major Swiss fine chemicals companies have led or followed their customers in investigating synthesis in flow, to varying degrees and for different specific reactions and customer applications. Many have developed their own equipment, alone or alongside more specialised suppliers. Naturally their perspectives on the future opportunities for flow vary too.

The advantages of flow over traditional batch and semi-batch processing are known well enough. To generalise, because the term 'flow chemistry', however we define it, covers many bases, these include: much shorter reaction times; less batch variability; a significant improvement in intensification, thanks to excellent heat and mass transfer; improved safety in some reactions with rapid kinetics for hazardous materials; a greatly reduced physical footprint, solvent and material consumption and often lower cost too. And 'numbering-up' by simply adding more microreactors is much more straightforward than scale-up.

However, batch is not without its advantages. It is flexible and versatile, able to handle all common unit operations except product isolation in a single vessel. It is also the incumbent technology and incumbents can be hard to shift, even when something that seems intrinsically superior comes along. Moreover, the dynamics of pharmaceutical manufacturing, where a sub-optimal process technology can be locked in early on as the patent clock ticks, do not easily lend themselves to change.



'Conti-rack' (left) and time residence unit (right) at Dottikon ES's site

Of all the Swiss firms that have investigated continuous flow, **Lonza** has perhaps come the furthest, with the 'Factory of Tomorrow' concept at its main site in Visp. In co-operation with Ehrfeld Mikrotechnik of Germany, Lonza has developed a plate reactor technology that is now available on the market in the form of the FlowPlate* microreactor in four models that cover the range for laboratory- to commercial-scale manufacturing.

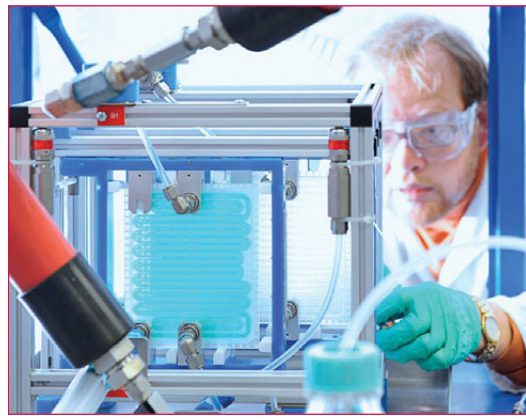
The FlowPlate is designed specifically for modularity and versatility, with individual Hastelloy plates sandwiched between highly thermally conductive aluminium plates for the passage of thermal fluids. Thus, the thermal fluid layer is not directly bonded onto the reactor plates and plates appropriate for many kinds of application, including gas-liquid and multi-injection, can be developed.

Dr Dominique Roberge, head of business development, for microreactors and continuous flow, has published and presented extensively on the use of the FlowPlate in real world reactions. Most recently (*SCM*, November 2012, pages 17-19), he showed how the FlowPlate, used alongside a specially developed ultrasonic device, outperformed a static mixer and a glass microreactor in a lithium-hydrogen (Li-H) exchange reaction with an adiabatic temperature rise of >75°C.

Since then, Lonza has also implemented other technologies beyond Li-H, though mostly for the early phases. In 2012, it completed a project transfer into production based on the 'Factory of Tomorrow', in which highly intensified laboratory equipment is used at production scale. A process operated at high (250°C) temperature and pressure (80 bar) showed a clear cut in capex when compared to batch. The company is seeing both pharma - including GMP - and non-pharma projects coming through using FlowPlate at various scales and Roberge expects to see some come to fruition this year.

Dottikon Exclusive Synthesis (ES) has over 40 years of experience with continuous flow processing, which has its origin in large-scale (up to 2,000 kg/hour throughput) nitrations of aromatic compounds, combined with continuous extraction, separation and distillation.

Today, for pharmaceutical applications, the company uses microreactors at laboratory-scale and - mainly - flow reactors for multi-purpose applications at kilo to multi-tonne scale. This, it says, requires a combination of considerable knowledge and know-how of process chemistry and engineering, from conceptual to basic design and qualification, as well as as process analytical technology to establish a complete flow set-up



Continuous flow technology laboratory at Siegfried

Dottikon ES's key technologies are hazardous, high pressure and low temperature chemistry. Günter Weingärtner, head safety and technology, has spoken at various past events, including the RSC Symposium during Chemspec Europe 2012 in Barcelona, about the company's work on carrying out these types of chemistries in flow on in-house designed 'conti-racks' and tubular flow reactors at its single site in Dottikon.

'Conti-racks' are modular frameworks that have been adapted to various reactions. They have been used, for example, in an oxidation rearrangement process whose starting materials were concentrated strong acid and 50% H_2O_2 mixed in static mixers and susbsequently run through coiled and specially engineered residence time reactors.

"In principle, each continuous set-up is a dedicated mini-plant. The general incentives for modularity are flexibility, reduced lead times and reduced equipment and set-up costs," says Weingärtner. "The conti-rack is only part of the equipment - we also have cooling units, pumping stations, control units, feeding tanks and so on that can be combined in many different ways."

Some continuous reactions, he adds, can be challenging to control, so Dottikon ES mixes and matches batch and continuous. For instance, it may start the penultimate reaction batch-wise but do the final reaction continuously. The quench is often done first batch-wise, then continuously in an extraction column for better control. Highly exothermic reactions like nitrations may need to be done in a continuous adiabatic way from the outset.

"As an alternative to scaling up or numbering up, you can do something in between, like increasing volumes or prolonging residence

times. Broadly, you need to think about which steps are best to do in batch or continuous before making a decision to invest."

Dr Beat Weber, head of process research and evaluation at **Siegfried**, is another familiar face on the conference circuit. At Chemspec Europe 2011 in Geneva, for instance, he presented the company's work on oxycodone, a market compound that is used as an intermediate in an API for a controlled drug derived from a poppy straw alkaloid.

Oxycodone is one of several compounds for which Siegfried has evaluated batch and continuous alternatives and it currently carries out the reaction in flow, with the isolation performed batch-wise. A second compound is now in early stage development.

"Our interest in using continuous flow for this was triggered by the specific characteristics of the molecule, which needs immediate downstream processing, including isolation and drying, because it cannot be stored for very long," Weber says.

At its site in Zofingen, Siegfried has a mixture of equipment, from static mixers it made in-house to glassware from Corning and reactors from Alfa Laval, put together in mobile, modular units. To date, it has used this at laboratory scale to run quite a few reactions, including double deprotonation of an organometallic, pinacolato-dichloromethylborane formation, the nitration of an aromatic system, the α-alkylation of a carboxylic acid, various nitrations, oxidation with H_2O_2 and the ammonolysis of an ester.

At present, the company is examining flow chemistry generally to see how it can apply this technique to chemical development. Weber believes that the best opportunities might be in organometallic reactions, especially with Grignards or mixed metals such as Li-Mg species, where it affords the advantage of carrying out rapid reactions at high temperature without such intensive process control.

Buchs in eastern Switzerland is one of many sites within **Sigma-Aldrich**. It produces mainly APIs and advanced intermediates, excipients and reagents for research, analytic and drug manufacturing customers, though the largest part of its work is for internal needs.

Senior scientist Dr Gregor Wille headed a flow chemistry project that began in Buchs back in 2006 by looking at small-scale applications of up to about 1 kg, mainly for research products but now also for multi-client products. Since last year, the team there has been focused on large-scale applications and is examining the portfolio to see which products could be transferred to flow. Another company site in Sheboygan, Michigan, has got further still and is now building its own large-scale capabilities.

"What we are doing is optimising API synthesis with new equipment," says Wille. "For instance, we have pulsation-free syringe pumps from Cetoni and in-house designed flow reactors reactors. Bringing in new equipment enabled us to revive a project dealing with lithiated intermediates handled in batch that had been on the shelf."

One of the site's notable past projects was on azide synthesis in flow, which it can now do at kilo scale. It has completed a cGMP campaign for a Swiss-based customer on flow equipment at medium scale. This was quite an odorous product, Wille remarks, so flow was an enabling technology that made it feasible. It is also focusing on online work-up procedures like phase separation and space diffusion infiltration.

"In the early years of flow chemistry to 2005, the focus was on perfect microreactor design but peripheral equipment like pumps is just as important as a nice reaction cell that enables you to produce challenging targets to high specifications," says Wille. "The work we do on optimising our equipment is a very significant part of our job."

The key challenge, in his view, is demonstrating the products and processes on a commercial scale and showing the practical reasons for adopting flow chemistry. Often it is about safety or facilitating work-up, possibly making it possible to use aggressive reagents that cannot be used at kilo scale in batch.

Carbogen Amcis, a CMO which is active at three Swiss sites and across all the phases of pharmaceutical development, has supported some of its customers with flow chemistry. Most usually, says senior scientific adviser Volker Wolfart, this is in the early phases, where biotechs are looking to produce results as quickly as possible in order to get further investor backing. However, some are also interested in it in the later phases too.

"I expect in the long term that there could be a validated continuous process to Phase III," he says. "Currently it is only really an option to Phase II, unless you count SMB chromatography, which is continuous but is physics rather than chemistry. Over 95% of Phase I compounds die there, so there would probably have to be 30 to 50 flow reactions in Phase I to yield one later phase compound, but it will happen eventually."

Continuing the story...

The Swiss site of **CABB** at Pratteln, near Basel, formerly known as SF-Chem, is somewhat different to its compatriots in that it has used continuous processing at large scale for many years. It does not use flow chemistry in the strict sense of the reaction taking place in microreactors and/or using microwaves, although CABB's former KemFine site in Finland does.

"Flow is of interest to us, however," says Dr Jörg Schrikel, new business development manager. "We were already looking at microreactor technology and one chemist here is dedicated to following developments in the field but we have not yet had any projects it could fit into. Essentially we are following what is happening elsewhere."

Dedicated continuous plant for the Wolff-Kishner reaction at CABB's Pratteln site

The continuous processes CABB carries out typically start at 20 tonnes scale, going up to multi-thousands of tonnes. They take place in dedicated multi-purpose plants that have been running continuously for many years.

The firm has a huge bank of knowledge about continuous chlorination, which, along with sulfonation chemistry, is one of the two core technologies at Pratteln. It also has the knowledge and equipment for continuous distillation, extraction or separation, enabling it to create complete processes as a sequence of continuous standard unit operations with no batch bottlenecks.

"It all comes down to the efficiency of doing the chemistry at large scale. We can scale down if needed, but the projects we get are usually at the high volume end," says Schrickel, who will be presenting on the subject at the RSC Symposium at Chemspec Europe 2013 in Munich on 4-5 June.

Indeed, chlorinations with cyanochloride create SO_2 and HCl as off gases, which elsewhere have to be treated with caustic soda in multiple scrubbers, generating a lot of waste water in the process. By running the process continuously in combination with the on-site *verbund* and recycling system, CABB can efficiently separate out these gases, reusing the SO_2 as a feedstock and selling the HCl as hydrochloric acid on the open market.

"This is one reason why we can still compete from a Swiss base. We have been doing it for 50 to 60 years. It was really Green Chemistry before the concept ever existed. None of our customers could do this in such a green and sustainable way," says Schrickel.

This knowledge of continuous processes has also been introduced into other fields. Recently, CABB built a dedicated continuous plant for the Wolff-Kishner reaction, the selective reduction of a ketone or an aldehyde to the corresponding aliphatic compound. This cannot be done safely in batch on a large-scale as it could potentially release large amounts of nitrogen at one time, but when done continuously, the volumes are too small for this to happen.

"We aren't actively looking for reactions to convert from batch to continuous, but where we see it could make sense or when new projects come along, we have the continuous capability ready," Schrickel says.

The company has a commercially available H-Cube from ThalesNano of Hungary, which it can modify in terms of, say, temperature, pressure and flow rate according to specific project needs. It has also drawn on the expertise of IO3S, a sister firm in the Dishman Group, in ozonolysis and has developed proprietary reaction units in flow chemistry, something Wolfart believes to be unique.

Carbogen Amcis most often uses flow for very reactive intermediates and labile products. Wolfart also believes that the applicability of the technique to hazardous products could help to reverse the drift of these to Asia

Markus Blocher, CEO of Dottikon ES, is the most emphatic of all those interviewed about the limitations of flow chemistry in pharmaceutical campaign production, particularly due to the limited accuracy of demand forecasting during clinical development. In fact, he estimates that in 98% of cases batch is still and will probably remain the economically favourable option.

"There has been a lot of hype about microreactors but, while they are often fine in the lab, at larger scale it becomes more complex," he says. "Numbering up at the scale needed for commercial production can cause quality inconsistencies due to the clogging of single channels, for example. Moreover, it isn't just about the flow reactor, you also need an equivalent number of pumps, connectors and other kinds of equipment, which drives up costs," he adds.

Wolfart likewise cautions that numbering up is not necessarily easier than scaling up. "You need to do more than just a quick calculation and decision of where to put the equipment. It will just be a different challenge and you will need to validate it and ensure complete control of the process," he says.

While most are reluctant to put a firm percentage figure down, Wille broadly agrees with Blocher. For Sigma-Aldrich's business concept, flow chemistry will be less than 5% of the total, he says, unless work-up in flow is greatly improved, in which case 10-20% might be possible. Certainly, though, flow cannot cover the whole market and will never make sense for slow reactions.

"The chances to convert a well-established batch process to flow chemistry will be rare. You have to have a good reason and there usually isn't one," Wille says. "The major bottleneck is that the possible cost advantage is diminished if you need to work up batch-wise after running the campaign in flow mode."

"Flow chemistry is more complex than batch and that makes implementation a higher risk, especially if you are a new player," agrees Roberge of Lonza. "The key question is 'Will there be widespread adoption if it is held up by complexity?' My guess is that there will be more development but the need to master complexity means that flow chemistry won't be mastered by everyone. For a real revolution to take place, a broader understanding will be needed."

The reason for this complexity comes down to the fact that more equipment is required for flow chemistry than batch, where everything is done in series; there must be, for example, temperature and pressure sensors, a pump, process control and an algorithm at each position. The failure of one does not mean the failure of all, but they can influence each other.

Carbogen Amcis carries out ozonolysis in flow at its early phase process R&D labs in Neuland

"You need technicians to be able to fix pumps quickly, for example. There are different control systems, each with different cables - all kinds of things that chemists generally don't need to think about. It will take time to build up the critical mass of experience needed and that requires the companies involved to have a critical mass themselves," Roberge says.

"From what we see in the field," adds Wolfart, "flow chemistry is not like batch chemistry, where you can work in isolation at the early stages. You need to have the engineer by your side from the start to get the equipment and the control right. You also have to build the plant, so there is more interaction between process chemists and development engineers."

Weber of Siegfried says that he sees continuous flow as an additional tool in the toolbox that will have niche applications. "I don't believe batch will vanish because the chemical industry is quite conservative," he says. "To change a compound's manufacturing process requires a lot of documentation. Many of our products are multi-client and we don't want to change all the files for the sake of a marginal process improvement. This is a big hurdle for continuous processing to overcome."

Customers' attitudes vary, according to Blocher: some pharma companies are developing continuous flow approaches, then looking for partners to do the scale-up for them because they do not want to produce the equipment themselves. Some of them try to force projects into flow, while others work in different ways. It is important to note, he adds, that it is not always necessary to develop special equipment; adapting the existing plant can suffice.

Most processes that CMOs receive, Weber says, have been developed for batch and customers generally want CMOs to do what they did as quickly as possible and with as little change as necessary. Moreover, the trend is increasingly towards giving away less early on for IP reasons, so fewer processes are finding their way to CMOs. The opportunities may arise more when compounds go generic.

Most customers, Wille notes, are open to the idea that flow could benefit their reactions; certainly they are very receptive to the idea of shorter development times in early phases, where flow can help. Much depends on how near to registration the product is, as it gets harder to change a process later on. "Flow is a technique to make a product; you can't sell it for its own sake, the product must benefit."

Nonetheless, all would broadly agree with Wolfart's words. "Flow chemistry won't be a passing fashion, it will stay and wait for its chance. One day, a continuous process will go to the FDA for validation. It will have to be for the right drug, which will go all the way to market and where there is a clear advantage for flow over batch. Then we'll see."

* - FlowPlate is a trade mark of Lonza

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