Demonstrating a new paradigm in sustainable manufacturing

Dr Sigurd Buchholz, Bayer Technology Services GmbH (Project Co-ordinator).

As the F³ Factory project enters its final year, preparations for demonstrating this new flexible, modular manufacturing concept across a number of chemical processes are well advanced.

Focused on seven industrial demonstrator projects spanning pharmaceutical intermediates, specialty polymers and large scale chemical intermediates, the 26 partners in the project have united in an almost unprecedented collaborative spirit to develop and validate sustainable future processes, process equipment and a versatile modular development and manufacturing platform for the EU chemical industry.

During the first 36 months of the project, the academic and industrial partners have worked in parallel across seven industrial sub-projects and nine strongly interlinked work packages, to define novel system solutions that has potential for leveraging great benefits for all sectors of the chemical industry.**

**Notable successes to date:**

- development of new process automation and control concepts for modular processes – from early trials to manufacturing execution systems
- construction of a modular manufacturing platform capable of serving a wide variety of chemical product classes and production rates present within the EU (INVITE).
- The formal opening of the INVITE Research Center (a 50:50 partnership between Bayer Technology Services and TU Dortmund), in October 2011, is a clear example of the partnerships and collaborations that have been forged successfully within this important €30 million public/private initiative.
- The impressive facility at the Chempark site in Leverkusen, Germany - is open to all European stakeholders who wish to participate in the development and implementation of container based processes.
- In addition to the F³ Factory industrial demonstration projects, the INVITE facility will provide a lasting legacy to ensure that flexible, modular, continuous manufacturing concepts will be further implemented across the European chemical industry to create a new paradigm in sustainable manufacturing.
- While the common backbone plant and design guidelines developed within the F³ Factory project are key milestones towards widespread industrial implementation, a number of challenges still need to be faced in relation to the equipment portfolio and validated applicability across the full chemical product portfolio. Finally, the transferability of the F³ Factory concept to other process industries will be ensured to fully leverage this innovative approach.
- A critical success factor for this will be how we can combine the excellent research and deep understanding of the near molecular process level with clear development targets and application specifics, as well as with equipment suppliers and process owners.

The success of the F³ Factory project and unique collaborative work model of the partners - both inside and outside the consortium – will be a lasting testimony to how complex system solutions for sustainable processes can be developed, validated and implemented.

As coordinator of this European Framework 7 project, I am confident that the knowledge and successes developed within the project will help spread the concept of flexible, modular production across the European chemical industry and – in turn – across the wider European process industries.**

**EU stakeholders meet at INVITE**

Over 50 stakeholders from European industrial and academic organisations visited the newly opened INVITE Research Center facility as part of the 2nd annual F³ Factory Interest Group Meeting.

The event showcased key developments in the project and, in particular, the new backbone facility that will be used to demonstrate the F³ Factory modular production concepts.
F³ Factory set to prove efficiency gains for modular, flexible API manufacture

The Bayer Technology Services (BTS) demonstration project, to transfer a multi-step synthetic batch process for pharma intermediates to a fully continuous manufacturing process including downstream processing, will move into its final demonstration phase - in a modular, flexible infrastructure - at the end of 2012.

Transfer of the chemical synthesis to an intensified fully continuous process has led to a significant reduction of processing steps, reaction time and solvents involved. The process sequence was also operated for several days at bench scale and has confirmed the assumed benefits of the F³ Factory approach in terms of impact on footprint, resource consumption, continuous monitoring and process operability. As the first industrial case study to be demonstrated in the INVITE backbone facility, the Bayer project has led the way in establishing standards for Process Equipment Assemblies (PEAs), the Process Equipment Container (PEC) and its integration with the backbone infrastructure services at INVITE. This has been facilitated in a key series of productive collaborations with both industrial and academic partners across the F³ Factory project. For maximum flexibility, it is envisaged that the standardised and scalable equipment for development and production, will enable a fast and robust transfer from research to production - according to the development timeline - with minimal effort.

Modular PEAs will provide the respective production capacity along the full product life-cycle. In addition, standardised chemical and physical processing PEA units will enable faster implementation of new manufacturing strategies in the highly regulated environment of pharmaceutical production.

By the end of 2012, Bayer aims to demonstrate synthesis steps 1 and 2 in the PEC, producing high quality pharmaceutical intermediate. This will ease the pathway for introduction of new technologies, production concepts and process equipment solutions for the pharmaceutical manufacturing sector.

And, in spin-off benefits, it will also progressively enable the F³ Factory partners to secure faster development, design and engineering of future processes.

Modular production at medium scale to validate new bio-based process

Development and validation of the F³ Factory concept at the medium scale plant level (20-30 kilo-tonnes/per annum) is a key focus of the Arkema sub-project.

As well as seeking to address a range of process intensification and modularisation challenges, Arkema is looking to validate a new bio-based production process for acrylic acid using glycerol – a green by-product of bio-diesel and the oleochemicals industries. Acrylic acid is an industrial chemical manufactured in highly optimised, large scale plants - typically producing 100's kilo-tonnes per annum. Over 25% of production for the €6-€8 billion global acrylic acid market comes from Europe and is manufactured using propylene as a key raw material.

Collaboration key to success

Collaborative activity with project partners - TU Dortmund, Process Design Centre and CNRS - has been a key success in the Arkema project developments to date and has resulted in a number of published papers. The F³ Factory concept of installing identical, modularised, medium scale plants may be suited to meet incremental market growth for new products. Improved environmental performance and adjusted carbon footprint may also be achieved as a result of higher energy efficiency and optimisation of plant location.

Within this project, Arkema has developed two types of innovative, intensified reaction technologies for gas phase reactions that use bio-based feedstock. Additionally, a scheme for the purification of bio-based acrylic acid using an innovative combination of purification technologies with reduced equipment has been validated. Cooperation with CNRS to achieve a high purity product was made public in a presentation of results by Marie Le Page - voted the best presentation from a young researcher at the F³ Factory General Assembly meeting in March, 2012.

A number of patents have been filed to reflect the innovative developments in this project and further patents are pending. A pilot plant for validation of this case study, at a scale of several kg/h, has been constructed at Arkema and validation studies are underway.
Standardisation rules provide solid foundation for modularised production

A key aspect of the horizontal activities within the F³ Factory project has been the development of design guidelines and standardisation rules to foster the modularity approach and flexibility requirements for Process Equipment Assemblies (PEAs) and Process Equipment Containers (PECs).

The design principles have focused on a combination of apparatus and the functionality required within a PEA, as well as the connectivity and distribution of utilities and disposal of waste streams.

A key development has been the design of a PEC grid. This necessitates the design of individual PEAs within a discrete footprint and fosters the standardisation and interchangeability of modules. It also optimises interior space within a PEC for process equipment whilst maintaining high levels of flexibility.

By far, the greatest challenge has been the development of standardisation rules for the interface connections between the backbone facility (INVITE) and PEAs, PECs and the PEAs installed inside them, as well as between individual PEAs within a PEC - for the transfer of process streams.

Using innovative concepts, a docking station was developed to allow the safe and efficient hook up of PECs to the infrastructure services that will be provided by the INVITE backbone facility.

Through the effective collaboration of project partners, a solid foundation has now been established for the design and standardisation of PEAs and PECs that will underpin future development of truly modular and flexible processes.

As the F³ Factory industrial case studies progress through demonstration, the design guidelines for standardisation will be refined and extended to leverage the knowledge gained.

F³ Factory continuous technologies set to benefit EU polymer production

Europoly – the joint Rhodia/BASF industrial project – seeks to demonstrate the suitability of F³ Factory concepts to enable the transition from batch to continuous multi-product plant for different polymers with widely varying properties.

Modular, intensified and continuous F³ Factory technologies offer a potentially exciting solution to the challenge of high heat production that characterises conventional high volume polymerisation in batch reactors.

Working with academic partners TU Dortmund (TUDO) and CRNS Nancy, BASF and Rhodia are seeking to demonstrate that a changeover to F³ Factory continuous technologies can improve the sustainability and competitiveness of European polymer production.

Two lab plants have been constructed in TUDO and CNRS to validate the concepts on two industrially relevant co-monomer systems:

Rhodia: Mildly viscous with similar propagation rates for M1 and M2

BASF: Low viscous with very different propagation rates for M1 and M2

Preliminary estimates suggest that investment savings of 30–50% (for a single product process of 10 kt/yr) and a 10 fold space-time-yield increase are possible through process intensification and successful transition from a 24hr batch cycle to a continuous process with <2 hr residence time.

The multi product aspect has also been studied by TUDO, showing that in a realistic range of cleaning and modification periods, utilisation of continuous plants operated in yearly/monthly campaign modes is higher than batch plant utilisations.

For the industrial demonstration of this project, three PECs - with internal changeable modules - have been conceived, with preliminary PEA and PEC designs advanced for a 10 kt/yr plant concept.

First polymerisation experiments at the TUDO lab have shown a good fit with the theoretical predictions.

The next phase of the project includes continuing validation of pilot scale trials with different grades of polymers and further study of the batch-to-continuous economics for a multi-product process. Final pilot scale demonstration in INVITE is scheduled for 2013.

The Europoly project complements Rhodia’s “factory of the future” programme and BASF’s interest in “smart scale” production. Both themes are focused on improved, faster ability to meet market and customer needs.

For further updates visit www.f3factory.eu
New production technologies for highly exothermic reactions

Partners across the Evonik sub-project are investigating the use and economic evaluation of new, modular production technologies for highly exothermic reactions.

Within the framework of the F³ Factory project – the new production technologies seek to optimise mass and heat transfer in the reaction units and simplify reactor design to enable parallel plant operation.

Two specific technologies are being investigated:
- structured catalyst packings
- jet-loop reactor with integrated ‘cold’ membrane separation

With a twin focus on use of different feed quantities and faster scale-up procedures, the project is being progressed via close collaboration between Evonik and three key academic partners - Technical University Eindhoven (TUE); Technical University Dortmund (TUDO) and the University of Newcastle.

Lab-scale experimental work on the ‘structured catalytic packings’ and ‘jet-loop reactor’ technologies have all progressed well in the first stages of the project with clear benefits identified.

Evaluation work on the two intensified technologies suggest there is potential for dramatic gains in space-time-yield (up to 50%) as well as significant reductions in reactor manufacturing costs (up to 50%) and energy use (-10-20%) - depending on the respective reactions investigated. Enhanced safety in plant operation as well as CO₂ and other savings are also projected.

As the project moves into its final year, work is well advanced on the design and engineering of a PEC for the hydroformylation process that will be demonstrated at INVITE in 2013.

Given the highly exothermic reactions involved - and potential parallel operation of different PECs within the INVITE facility – the Evonik PEC will use an inert gas purge that is connected to the waste gas system.
F³ Factory methodology targets faster, more efficient pharma development

Demonstration of a new “transformation methodology” for increasing throughput of early phase pharmaceutical development lies at the heart of the AstraZeneca sub-project.

Working in collaboration with project partners Royal Institute of Technology (KTH), Technical University of Denmark (DTU), University of Newcastle, Karlsruhe Institute of Technology (KIT) and Britest – this project seeks to develop a new, generic process design for conversion of various substrates - using nitro reductions as an example reaction class – and a generic transformation methodology to adapt this process to a specific substrate.

Modular continuous processing capability at the 10-100L scale – as defined in the F³ Factory project – will add significant production flexibility and enable faster, lower cost assessment of new material candidates for new drugs.

**Progress towards demonstration…**

Experimental investigations on a new “transformation matrix” for nitro reductions has identified two hydrogen transfer systems that will be validated in the new INVITE facility.

A new Substrate Adoption Methodology (SAM) protocol - developed in conjunction with Britest and DTU - has been defined for the process. It has also been applied to two further compounds, with results pending.

KIT has designed and tested new flow process reactor technology and is actively now developing the final lab scale reactor. A novel isolation method, solid supported evaporation (SSE) has also been evaluated successfully by KTH.

Lab-scale PEAs have been defined for the pumping equipment and slurry reactor and are running effectively at AstraZeneca’s large scale development labs in Macclesfield.

Experimental work will now seek to test the new process and iron out any technical issues before the project proceeds to full validation and demonstration in a PEC unit at INVITE in Q4, 2012.

If successful, this new flow chemistry process could be used for early stage pharmaceutical development across all therapeutics areas – potentially reducing pharmaceutical intermediate development time by up to 30%.

Difficulties in handling the highly viscous phase during polymerisation have so far prevented producers from developing solvent-free processes. The focus of this F³ Factory project has concentrated on development of intensified, high-strength mixing equipment.

A new twin-shaft, high-torque Buss-SMS-Canzler (SMS) kneader reactor has been shown to meet the key requirements of strength and operational flexibility.

Modular construction and many standardised parts also allow flexible adaptation to different products or processes, with ability to switch rapidly between different mixing rotor assemblies.

To realize the full potential of the intensified reactor, its complex geometry has required focus on several key durability issues. Their examination has been a classic model of F³ Factory project partnerships.

University of Paderborn (UPB) has been investigating mechanical integrity; modelling unit processes; radial and axial mixing; micro/ macro mixing and axial dispersion.

Numerical simulations have been performed by Technical University Eindhoven (TUE) to calculate the velocity and pressure fields within the kneaded material, leading to rotor strength and fatigue computations by SMS.

Online measurement techniques have been developed by BASF, with technology transfer to partners UPB and SMS.

BTS has derived a mass-balance for the reactor design, providing the liquid filling level as a function of viscosity, throughput and rotational speed. Following validation of the new reactor technology at lab-scale and successful polymerisation trials, a modular plant concept has been developed and the PEAs and PEC for demonstration have been designed. As the project now moves into the demonstration phase, partners in the collaboration are optimistic that the technology will bring both cost and environmental benefits to high viscous polymer production.

New reactor technology set to drive process intensification for high viscous polymers

BASF and Bayer Technology Services (BTS) are working closely on a project to demonstrate F³ Factory concepts for multi-product, small-to-medium scale production of high viscous polymers in a solvent-free manufacturing process.

For further updates visit www.f3factory.eu
The INVITE Research Center – a 50:50 joint venture between Bayer Technology Services GmbH and TU Dortmund University – officially opened its doors in September 2011. Its versatile container-based infrastructure will provide the open access backbone facility to support demonstration of the F³ Factory industrial case study projects. It will also serve other research projects both during and beyond the F³ Factory project lifetime.

As a non-university research organisation in applied sciences, specifically in the field of new production technologies, INVITE promotes the development of new ideas and integrates results in practical applications. Based at the Chempark site, Leverkusen in Germany, INVITE seeks to advance process innovation and technology solutions for companies in the EU chemical, pharmaceutical and biotechnology industries.

The INVITE Research Center combines a lecture hall and technical center equipped for research and process testing under realistic conditions. It is also engaged in the development and standardisation of modularised process equipment. The F³ Factory backbone facility - specially designed for the operation of modularised container plants (PECs) - is provided in a central, single facility configured to enable up to six different PECs to be docked alongside each other.

In the final phase of the project, the schedule for demonstrating the seven industrial case studies is nearing completion. This is an important part of the project and will enable a detailed impact analysis to be completed for each industrial case study demonstrated in the facility. With access to EU stakeholders beyond the F³ Factory consortium, the INVITE Research Center will be a prominent sign of the ongoing intention of the EU community to build a Flexible, Fast and Future Factory!

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F³ Factory progress showcased at key EU events

Dissemination activity for the F³ Factory project is now a key focus as the research and validation activities move to full scale demonstration.

Key developments in the project are communicated to EU stakeholders through the project website, newsletters, presentations at key industry events and open invitations to annual Interest Group meetings.

To date, over 80 formal presentations and/or scientific papers for peer review have been delivered to highlight project successes.

Pro-active engagement with EU stakeholders has been the focus of joint presentations and shared booths for key EU Framework 7 projects (F³ Factory, Synflow, Polycat and Copiride) at 2012 industry events including ACHEMA and CHISA.

Feedback from EU stakeholders on the pace of developments within the project and the openness in which these developments are being disseminated to the wider community continues to be very positive.

If you wish to be kept informed of developments within the F³ Factory project, receive our annual Newsletter, or attend future Interest Group meetings, please send your details to: contact@f3factory.com

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For further information visit: www.f3factory.eu

Project Coordinator: Dr. Sigurd Buchholz, Bayer Technology Services GmbH, Building E41, D-51368 Leverkusen, Germany
Phone: +49 214 30 67253 Fax: +49 214 30 50262 E-mail: sigurd.buchholz@bayer.com

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