End-to-End Process Design in Flow: from Flow Chemistry to Flow Reactor Networks

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In May 2015, the FDA opened a new era in chemical manufacturing and called on pharma manufacturers and CMOs to begin to switch from batch to continuous production which shall be completed in the year 2025 *[Brennan, Pharmatechnologist, 2015]*. In April 2016, the FDA gave Johnson & Johnson's Janssen drug unit the thumbs up for the continuous manufacturing process that it has been working on for 5 years. The agency approved a switchover from batch to the new technology for production of HIV drug Prezista on a line at its plant in Gurabo, Puerto Rico *[www.pharmamanufacturing.com]*.

Beyond this legislative authority push, the ACS Green Chemistry Pharmaceutical Roundtable, and thus the pharmaceutical industry, has endorsed the same view and declared continuous manufacturing as top-1 priority. The vision of a complete continuous end-to-end pharmaceutical manufacturing has been demonstrated by Novartis and MIT recently *[Jensen, Trout, Angew. Chem. Int. Ed. 2013]*. Bosch Company and the Formulation Competence Center RCPE in Graz/Austria have recently announced a collaboration on the continuous pill production until the packaged product *[Kleine Zeitung, 07.03.].*

Cascade reactions are key to end-to-end manufacturing and are a popular topic in batch-operated chemistry with > 30,000 publications. Commonly agreed advantages of cascades are high atom economy, high degree in structural complexity, reduction of waste generated, use of solvents, time and work procedure. Recently, flow cascade chemistry has been set on (116 publications). 'Novel Process Windows' *[Hessel, ChemSusChem 2013]* boosts chemistry to the limits and open new Windows of Opportunity.

Own end-to-end research will be reported. A micro-flow multi-step synthesis of rufinamide, an antiepileptic drug to treat the Lennox–Gastaut syndrome, has been realised. A fully solvent-free flow factory has been established and its sustainability is analysed by LCA. 'Chemergy' stands for the unanimously forecasted "Electrification of the Chemical Industry". Along these lines, the plasma-catalytic processing was applied for nitrogen fixation using air (N_2) to manufacture NO/NO_2 which finally is converted to nitric acid and fertilizers. A new business model considers distributed production enabled by mobile, compact container production platforms which are driven from green renewable energy sources. The whole OPEX and CAPEX scheme of the process is fundamentally changed providing a new window of opportunity. LCA studies supplement the sustainability analysis of the new processing.

Today's flow cascade systems are (inherently) very complex involving highly elaborated process machinery. Harmonization and synchronization asks for new biomimetic process schemes. Future might provide a complete game change through the 'Organic Chemistry Science Gateway' *[Ley, Chem. Commun. 2015]*. The 'March of the Machines' *[Ley, Angew. Chem. Int. Ed. 2015]* will relegate process monitoring to central computer systems under the oversight of the 'The Robo-Chemist' *[Pedlow, Nature 2014]*. We just started research along those lines in the European FET OPEN project ONE-FLOW, aiming at a merger of the cells compartmentalization with modern catalyst & process technology.