DEVELOPMENT AND SCALE-UP OF CONTINUOUS FLOW PROCESSES FOR THE MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENTS.

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An increasing fraction of new „small molecule“ active pharmaceutical ingredients (APIs) is discovered by small companies that focus on library synthesis and screening. The actual synthesis development, manufacturing and formulation is done by “custom development and manufacturing organizations” (CDMOs). Patheon, part of Thermo Fisher Scientific is among the biggest CDMOs worldwide.

Synthetic routes used in library synthesis are designed to allow for maximum substrate variability, but not for scalability and efficiency. Our first task as a CDMO is to scout for a synthetic route that can be developed into an efficient and reliable large-scale process: We investigate and compare details of the chemistry, the kinetics and thermodynamics of candidate routes and develop options to scale up the selected reaction sequence.

The lecture focuses on

- Criteria to select routes for scale-up, based on safety, materials efficiency and product quality.
- Ways to develop such routes into reliable processes using state-of-the-art process technology and analytics.

We pay specific attention to the development and application of continuous flow processes and their role in pharmaceutical manufacturing. Several large-scale examples have demonstrated the virtues of continuous processing in this field. Here we give examples to illustrate our way of identifying, developing and implementing continuous flow processes to render processes scalable and safe even if they require extreme process conditions such as low temperatures.

We give details on the chemistry, our considerations on analytics, on suitable reactors, and on options and methods for continuous improvement of such processes, with a focus on the multidisciplinary nature of such development tasks.