SPECIAL FEATURE SECTION
LABORATORY AUTOMATION IN PROCESS R&D

Editorial

Combinatorial chemistry and high-throughput screening have dramatically influenced the way compound discovery is carried out, and this has had severe implications for process R & D. In a short period of time, millions of compounds can be prepared, and after lead optimisation, candidates quickly enter the development pipeline as potential new products. The result is a vastly increased workload on chemical process R & D and chemical development departments.

At the same time, the increased candidate development costs have placed an emphasis on reducing time-to-market with particular stress on moving early development candidates quickly forward, resulting in less time for investigating new synthetic routes and for process optimisation.

In addition, the current requirement on the pharmaceutical industry for processes to be validated places an emphasis in late chemical development on optimisation of critical process parameters and robustness testing.

The response that process chemists and chemical engineers have taken to this "triple" challenge is to use the techniques, first elucidated in discovery chemistry, of automation and robotics to increase not only the productivity of process R & D in terms of the number of experiments per day but also the quality of the data produced. One reason for the latter statement is that automated techniques lend themselves to a combination with statistically designed approaches (design of experiments, DOE) such as factorial designs, simplex optimisation, and response surface designs. These methodologies allow the rapid assessment of the importance of key process parameters (reagent, solvent, catalyst, stoichiometry, addition time, concentration, temperature, pressure, reaction time, agitation, work-up conditions etc.) on yield, quality of product, cost, and space−time-yield.

These automated techniques are bringing about a revolution in the way process chemistry is carried out: faster development with an improvement in the quality—as well as the quantity—of data produced. The papers which follow illustrate the philosophy that different companies and research groups have used and the instrumentation they prefer—some of the latter has been custom-designed to meet the user's strict specifications.

On a personal level, I have been interested in this area for many years. In my time at ICI in the 1970s, an automated system for carrying out experiments was built in-house (I think it was called Merlin), and many of these systems, which today look rather cumbersome, were built and used effectively. At the same time Smith Kline and French, Rhone Poulenc, and a number of other companies were developing their own methods for automating organic chemistry. In my Smith Kline days, I purchased a Contalab system in 1984 for automating late-stage development, but the 2-L reactor size was a severe limitation. Similarly, other instruments such as the RC1 could be used for carrying out automated reactions, but the throughput/productivity was low.

Several companies began using the Zymark and other robots to design their own in-house systems for fully automated and rapid experimentation, and—as seen in the following papers—these robots and later upgraded versions are still popular. In the UK, Glaxo-Wellcome chemists pioneered the use of the SK 233 system with automated following of reactions by HPLC. I well remember a lecture from Martin Owen of Glaxo—I think it was at one of the SCI's annual Process Development Symposia at Cambridge and probably around 1994/5 when many process R & D chemists "saw the light" and realised the potential of not only automation, but also rapid screening of reaction parameters coupled to DOE. He subsequently helped me to organise a series of annual conferences on laboratory automation in process R & D, which have helped to bring process chemists and instrument developers together to talk about the present capabilities and limitations of equipment/software and to plan for the future. A number of equipment manufacturers have been active in seeking the assistance of experienced process chemists in a continuous dialogue, to aim to produce more efficient and user-friendly systems.

Organic chemists have primarily used these methods to optimise batch processes. Adaptation of the equipment to continuous processes has rarely been attempted, but in the bio-organic field (e.g., fermentation) robotic systems with feedback are being used to optimise continuous processes. The use of a feedback loop to integrate the information gained in one set of experiments to control automatically a second set of optimisation experiments is a dream that all process chemists have had, which is now close to reality. In the future, maybe, all the organic chemists should have to do, after preliminary experimentation gave a low yield, is to set up the automated equipment for optimisation, press the button, and come back the following day with the reaction optimised to 90−100% yield. A dream, maybe, but not too far from reality.

The papers in the following section have been submitted in response to the editor's request for this special issue on automation, and they make excellent reading. One or two papers were submitted but failed to meet the tight deadlines, and will appear in future issues of *Organic Process Research & Development*. My thanks to all of the authors for their contribution and to their companies for allowing publication of their work in this fascinating area.

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Editor

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