The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Dr Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@drugdiscoverytoday.com

Are microwave instruments just expensive hot-plate stirrers? ▼

Larhed and Hallberg closed their recent article in *Drug Discovery Today*[1] with the words ‘with these advances, the age of high-speed chemistry will be here’, concluding a convincing case for the inclusion of microwave-assisted synthesis in the medicinal chemist’s ever-expanding repertoire of techniques. In their timely article, the authors highlight the beneficial effects of using microwave heating in synthetic transformations that are universally employed in medicinal chemistry laboratories. Those who have tried will know that it is often possible to complete a microwave-promoted reaction in the time it takes to set up a hotplate-stirrer and reflux condenser.

Perhaps inevitably, the bulk of published microwave research has relied on the expedient use of domestic microwave ovens to effect solution-phase chemistry. Numerous interesting reports along such lines have appeared[2,3], but there are many drawbacks to this technique. Aside from the danger of heating organic solvents in domestic ovens, there are serious issues of reproducibility associated with the crude degree of control and monitoring that such instruments provide. In addition, many reports fail to provide thermal comparisons to microwave promoted reactions. It might even be argued that these factors have done little to enhance the scientific credibility and wider acceptance of microwave-promoted chemistry.

If domestic instruments must be employed for whatever reason, it is prudent to restrict their use to solvent-free chemistry on inorganic solid supports. Quite correctly, Larhed and Hallberg[1] point towards the use of dedicated custom-built laboratory instruments as the best route to take.

Several companies now offer dedicated laboratory instruments of varying degrees of complexity and cost. There is some debate as to the merits of multi-mode versus single-mode (focused) microwave fields and there are commercial proponents of each technology. To an extent, this is irrelevant to the end user who simply requires a fine degree of control over the reaction conditions to obtain consistent and reproducible results, without being overly concerned about the microwave physics.

To be cynical, it might be advocated that microwave instrumentation simply constitutes an expensive stirrer-hotplate or that the technology provides yet another means of shifting the dreaded synthetic bottleneck. Taking these points in turn, it is now evident that microwave heating offers clear advantages in reaction efficiency and that, in principle, any thermal reaction should be enhanced by the application of microwaves. With regard to the second point, there might be some validity in this argument, however, the solution lies in the imaginative use of microwaves in confluence with other emerging technologies.

For example, the use of polymer-supported (PS) reagents in tandem with microwave technology[4,5] is especially attractive because the inherently slow kinetics currently associated with PS-reagents might be remedied by microwave heating. In turn, reaction work-up and purification is reduced to a simple filtration to remove the PS-reagent. The use of novel reagent display formats, solvent-free media, new supported catalysts, ionic liquids, on-line LC–MS and/or flow cell NMR analysis, automated liquid handling and integration with automated purification equipment, all provide ample scope for the advantageous application of this technique.

Lead discovery units might incorporate automated high-throughput microwave technology alongside automated purification technology for the production of libraries. Importantly, the rapid reaction times possible with microwave equipment allow sequential rather than parallel heating to become a viable option. Less elaborate manually-operated instruments might become a standard tool in lead optimization laboratories where smaller numbers of compounds are dealt with. Here, short reaction times provide opportunities for rapid screening and optimization of reaction conditions, quick investigation of novel chemistries and cleaner, more efficient conversions that require fewer equivalents of reagent.

References

1 Larhed, M. and Hallberg, A. (2001) Microwave-assisted high-speed chemistry: a new technique in drug discovery. *Drug Discov. Today* 6, 406–415

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2 Manhas, M.S. *et al.* (2000) Vinyl β-lactams as efficient synthons. Eco-friendly approaches via microwave-assisted reactions. *Tetrahedron* 56, 5587–5601
3 Banik, B.K. *et al.* (1999) Microwave-assisted rapid and simplified hydrogenation. *J. Org. Chem.* 64, 5746–5753
4 Ley, S.V. *et al.* (2001) A polymer-supported thionating reagent. *J. Chem. Soc., Perkin Trans.* 1, 358–361
5 Brain, C.T. and Brunton, S.A. (2001) Synthesis of 1,3,4-oxadiazoles using polymer-supported reagents. *Synlett,* 382–384

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Drug discoverers – you need us! – Reply ▲

Initial letter: Federsel, H-J. (2001) *Drug Discov. Today* 6, 397–398

Response from Nicholas Meanwell

In contemporary drug discovery campaigns, multi-disciplinary teams routinely focus attention on simultaneously optimizing several parameters associated with lead molecules including biological activity, physical properties, toxicological potential, metabolic stability and a broader range of pharmacokinetic attributes. The anticipation is that, by selecting compounds that meet stringent criteria, the overall objective of enhancing candidate success (measured by entering crucial proof-of-principle efficacy studies in Phase II human trials) will more probably be achieved. However, often of lesser concern during the discovery phase, but ultimately of paramount importance to the overall success of a drug candidate, is the facility with which significant quantities of bulk drug substance can be produced.

With all of the major pharmaceutical houses focussed on delivering new chemical entities in a predictable fashion against timelines that seem to be perpetually shrinking, the expedient production of significant quantities of drug candidates in a practical fashion while adhering to regulatory and safety guidelines represents a significant challenge. Against this backdrop, the appeal by Hans-Jürgen Federsel, in a recent letter to the *Discussion Forum*, that process R&D should be fully participating partners in the later stages of drug candidate identification seems to be not only reasonable but necessary and essential to orchestrate a seamless and flawless transition. Indeed, successful anticipation and implementation provides obvious benefit when timelines for first-in-man studies that were once considered ambitious objectives, but which are now routine expectations, are achieved.

The strategic model described by Federsel has merit, either as practiced by AstraZeneca or in a form modified to more effectively complement individual organizational structures and business cultures. The system relies on maintaining an awareness of developments early in the drug discovery process, largely through communication between chemists who together constitute a broader community of practice, with subsequent and timely practical involvement as the project enters the final phases of candidate identification. Such an interface offers the potential for mutual benefit with discovery chemists developing a heightened awareness for, and a deeper appreciation of, the issues associated with the large-scale production of compounds while providing process R&D scientists with the opportunity to observe the decisions required to successfully identify a drug candidate. An optimal arrangement, practiced where feasible at Bristol-Myers Squibb (BMS), has process R&D and drug discovery chemists working in close geographical proximity and collaborating to solve synthetic problems in a fashion that produces advances ultimately synergistic in nature.

The key issue implicit in Federsel's discussion is the need to educate those immediately outside of the process R&D environment about the challenges faced in producing bulk drug substance. To some extent, process R&D chemists could be falling victim to their own past successes where elegant and practical synthetic approaches to targets that presented a significant degree of difficulty have been developed. Two compounds that come to mind as specific examples from BMS' process R&D group are the thromboxane-receptor antagonist Ifetroban®[1–3] and the dual metalloprotease inhibitor Vanlev®[4], striking accomplishments that heighten expectations.

However, several factors are emerging that have the potential to contribute to enhancements of the discovery chemistry–process R&D interface. The effect of increased productivity realized over recent years as drug discovery has evolved into a more industrialized process has afforded a larger number of discovery scientists the opportunity to participate in project teams assembled to usher candidates through the early stages of the development process. These teams are providing important forums for discovery chemists to glean unique insights into a broader range of process R&D issues, an awareness that has the potential to influence their strategic thinking as they devise synthetic approaches to drug candidates. As perhaps an ultimate extrapolation, discovery chemists at BMS have accompanied candidate compounds into early development, being seconded for several months as part of an exercise designed to be mutually educational and beneficial. Second, with additional preliminary *in vivo* toxicology studies planned before candidate nomination, demands for substantial quantities of drug substance at earlier stages of the discovery continuum are increasing. This provides drug discovery chemists with the

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