Timely synthetic support for medicinal chemists

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In recent years, there have been significant developments made in the way new drugs are being discovered and developed. Such changes are driven by new technologies that have expanded the opportunities to prepare and screen large libraries of compounds in a rapid time frame by the use of high-throughput synthesis and screening techniques [1–3]. These strategies are driven by the need to shorten time lines for bringing discovery leads to the market [4,5]. As a result, the role and needs of synthetic chemistry in the discovery and development of new therapeutic agents has been altered [6]. This paper will explore the roles of synthetic chemists and how pharmaceutical companies respond to the evolving needs of synthetic chemistry challenges in their discovery and development programs

The introduction of HTS of libraries to uncover leads for molecular targets has been one of the biggest changes that has occurred in chemical discovery programs. Initial chemical leads are identified from HTS of thousands of individual compounds in sub-mg quantities that can be run in 384-, and even 1536-well plate formats [7]. The discovery approach to searching for leads has shifted generally through use of HTS from primary screens done with *in vivo* models requiring g quantities to *in vitro* screening that can be done with mg quantities in an HTS format. Interesting compound classes identified by HTS can be further optimized by library modifications to give refined lead structures. Synthesis of related-compound libraries is quickly accomplished by techniques of automated parallel synthesis [8–11]. Use of robotics coupled with solid phase and classical solution methods has greatly accelerated this optimization work. The preparation of libraries of large numbers of compounds has also been greatly facilitated by advances in preparative chromatographic methods that have also been adapted to automation. HPLC coupled with MS analysis has become highly automated, allowing the structural confirmation and purity determinations on the large numbers of compounds that have been prepared and purified by automated techniques [12,13]. The overall result of these improved technologies is that discovery and optimization of a lead structure can proceed much more quickly and with less material than were needed in the past. Automation, robotics, parallel reactors and combinatorial techniques have had a significant effect on the way synthetic work is carried out in medicinal chemistry groups [14].

Effect of new technologies on chemical synthesis by medicinal chemists

The emphasis on the initial preparation of large numbers of new structures requiring mg quantities to screen has clearly had an effect on the synthetic work of the medicinal chemist [15]. This is a key point that we wish to make: the scale of synthesis in medicinal chemistry has become directed to preparing smaller quantities but with a much larger number of new structures being made. A result of this shift has been that the synthetic goals of medicinal chemists and scale-up chemists have evolved in different directions. Synthetic routes used

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by medicinal chemists have focused toward devising schemes that could be used generically to prepare a variety of structural modifications. These generic synthetic routes are usually adequate for elaborating SARs and for modifying the structure to optimize ADME properties [16]. This is not to say that optimization of leads and ADME properties can be addressed by preparation of mg quantities alone but rather that this approach has become highly utilized in discovery work. Retrosynthetic analysis differs between medicinal chemists and chemists charged with working out synthetic enhancements. Medicinal chemistry focuses on lead optimization and the synthetic strategy used is directed to preparing diverse sets of compounds. On the other hand, chemists involved in scale-up or developing synthetic improvements devise retrosynthetic strategies to facilitate the preparation of an individual compound. This approach, coupled with skills in purifying and isolating compounds in multi-gram quantities, are what differentiate medicinal chemistry and scale-up chemistry work. The medicinal chemist identifies the lead of choice and looks to the synthesis optimization chemist to make larger amounts for development.

As minimal amounts (usually mg quantities) of compound are needed for optimization of leads, the routine use of chromatographic methods for purification and isolation of synthetic intermediates and final products is the accepted medicinal chemistry tool in synthesis work. It is more efficient at the lead optimization stage of a program to use chromatography for purification than to search for more efficient, higher-yielding, alternative synthetic routes. For example, it has become more expedient in the short term to prepare racemic or diasteromeric products and rely on chromatographic methods to isolate isomerically pure products than to devise clever synthetic routes and isolation procedures for these products [17].

The quantities needed for identifying and advancing drug candidates are now much smaller in the exploratory or discovery phase of programs than was necessary in the past. Yields have become of lesser concern to the medicinal chemist because only mg amounts are needed to evaluate leads at this stage. At later stages of development, when muti-gram levels of material are needed, yield optimization is imperative. Once a promising lead is identified and larger amounts of it are needed to advance the lead for further studies, large-scale synthesis becomes a problematical bottleneck. The bottleneck results from the fact that the original medicinal chemistry synthesis of the lead was often done through a synthetic route that used procedures that were inefficient, too costly, too time consuming or had safety concerns related to the larger scale.

Another issue that results from the synthetic methods used by medicinal chemists to prepare a lead is that less attention is paid to addressing the physical, solid-state properties of the lead [18]. Because most compounds are being purified by chromatography, they are frequently isolated and screened as amorphous solids. When salt formation options are available, these too are often made and tested as amorphous solids. When the lead becomes of sufficient interest for further *in vivo* efficacy evaluations, multi-gram batches of drug are needed. It then becomes necessary to more rigorously establish the physical properties of the lead and develop a suitable formulation for its administration [19]. This is a very necessary preliminary step for establishing suitable PK profiles that are critical for use in initial safety evaluations [20]. The synthesis, isolation and purification methods for the lead at this point must address any less-than optimal physical properties before it can proceed to further development. Purity requirements of a lead that is advancing become more stringent and, with it, identification of minor impurities in the lead becomes of major importance. When preparing multi-gram quantities of a lead it becomes critical to have a robust synthesis route and have methods for isolating the lead in a consistent, reproducible substance with good purity.

Options for synthesis support for the medicinal chemist

Due to time pressure to accelerate all aspects of the drug discovery and development process, the synthetic methods used by medicinal chemists and the synthesis optimization chemists who address scale-up have clearly diverged [21]. The medicinal chemist's focus must be on the rapid synthesis of thousands of new structures, relatively few of which might require timely and efficient synthetic enhancements. The scale-up of these compounds, however, must be timely and efficient. Different strategies can be employed for supporting synthesis optimization for medicinal chemists. One strategy is to outsource the scale-up of selected leads and the synthesis of library components and scaffolds. Several companies in North America offer this support to major pharmaceutical companies. Pharmaceutical companies are also exploring offshore use of chemists in Asia and eastern Europe to expand discovery activities. The largest use of these chemists appears to be directed to the synthesis of compounds that enhance the chemical diversity with a company's compound bank. The prime benefit of this strategy is that expenses for this work might be lower than when done in-house. It is potentially less expensive to reach a critical mass of chemists supporting a project using this strategy. The weakness of this strategy is that when scale-up resources are needed to advance a project, technology transfer and timely interactions between the medicinal chemistry owners of the lead and the off-site chemists may be severely compromised by distance and timeliness of the response.

Another strategy many organizations use is to apply the in-house Chemical Development group for all the scale-up support to discovery work. This strategy has the advantage of allowing close interaction between medicinal chemists and scale-up chemists while providing the

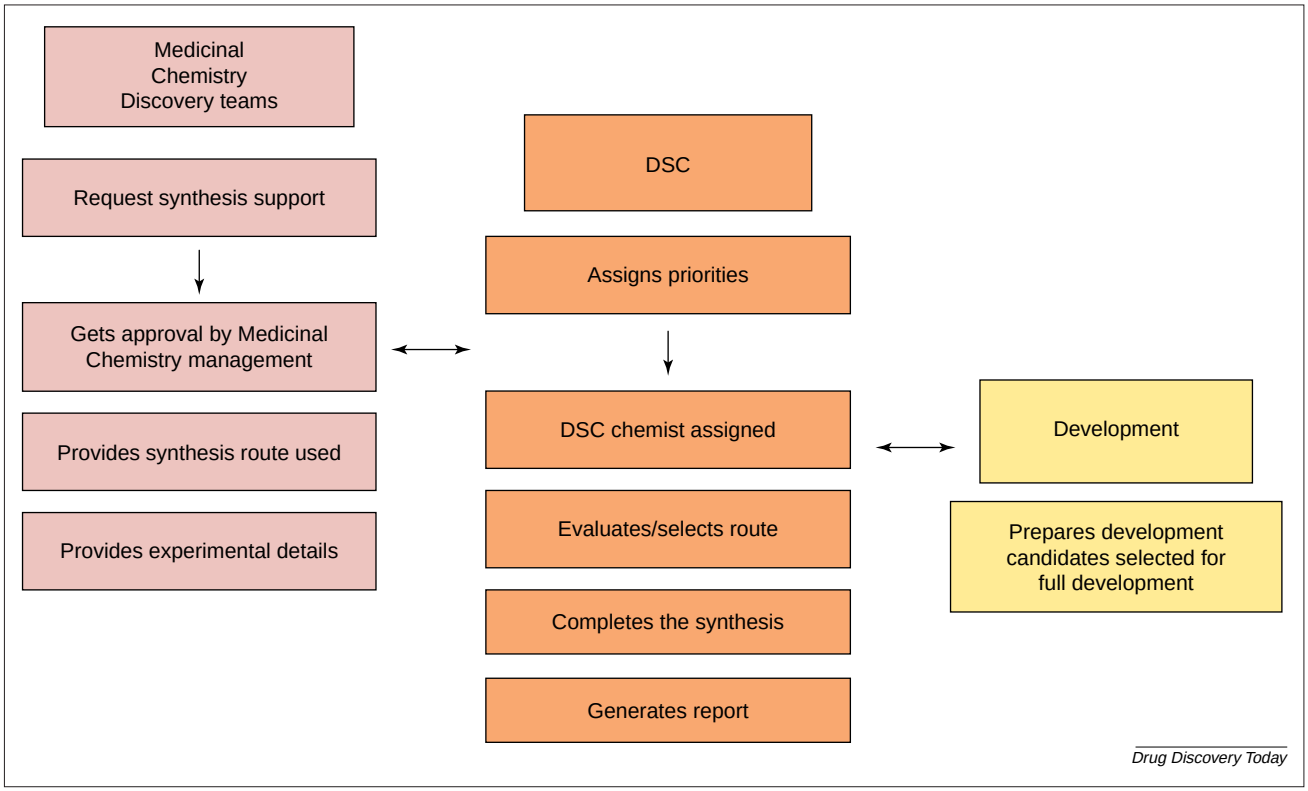

FIGURE 1

Workflow: process for assigning synthesis support from Medicinal Chemistry through Discovery Synthetic Chemistry (DSC) to Development.

development organization a great start on developing scale-up chemistry for a promising lead. The difficulty with this strategy is that in the current discovery environment, discovery projects that need timely, initial scale-up support or synthetic improvement are far too numerous for a Development group to react quickly at early stages and on all projects when attrition of lead compounds is high and quantities are still <100 g [22].

A third strategy for scale-up support is to have a versatile, multipurpose synthesis enhancement group within the discovery wing itself. This group would partner with medicinal chemistry groups working in all therapeutic areas within discovery to provide support to discovery teams by preparing up to 500g quantities of intermediates for use as scaffolds for libraries, preparing key intermediates for SAR refinement and providing reference or benchmark compounds for assay and screening development. In addition, this group would examine first generation synthetic improvements necessary for larger scale synthesis. By supporting medicinal chemistry work in this way, the group would free the efforts of medicinal chemists to work exclusively on lead discovery and optimization. As the identified leads progress from *in vitro* screens to *in vivo* models, material requirements grow and the discovery scale-up group would bring resources to these projects. Synthesis of a batch (up to 100g) of a selected predevelopment lead would be the transition point for a project as it moves to development.

Wyeth's Discovery Synthetic Chemistry group

Wyeth has adopted a strategy of using a synthetic chemistry group within the discovery organization to support synthesis enhancement needs for medicinal chemistry. The goals for the Discovery Synthetic Chemistry (DSC) group are to bring timely scale-up synthesis support to all medicinal chemistry projects, to improve processes, to develop routes and procedures that allow for efficient and practical preparation of batches of promising leads and to serve as a key interface with Chemical Development. An important role for DSC is the preparation of material needed for chronic efficacy and safety studies. A major aspect of this work is delivering the material in an acceptable salt or polymorphic form. To be effective, the group must carry out this role under significant time constraints and from a short-term perspective.

The DSC group provides synthesis support to all medicinal chemistry teams. Its involvement in discovery projects is variable and depends on several factors such as maturity of the discovery program, the amount of intermediate or product that is needed to move the project forward and the resources that are available in DSC and medicinal chemistry at any time. Projects are prioritized through interactive dialogue between medicinal chemistry management, DSC and often, Chemical Development to determine who is best equipped to deliver material in the quantity needed (Figure 1).

Tactics utilized by DSC are highly predicated on time-lines. The amount of material needed to move the project to the next decision point has an impact on the chemistry used for the scale-up [23,24]. On receipt of an assignment the DSC scale-up group evaluates the original chemistry route and procedures, considers any other possible routes and makes a judgment on how to proceed given the amounts and time-lines desired for project. Primary considerations in this evaluation are the efficiency of the route, the number of synthetic steps, the availability of starting materials and the need for chromatographic purifications. Pragmatic judgments are made if minor improvements on a medicinal chemistry route will be sufficient or should a whole new scheme be implemented. The overriding consideration is minimizing preparation time rather than making a perfect manufacturing process. Throughput, efficiency, work-up conditions and process safety are factors that often need to be addressed in the synthesis routes and procedures provided by the medicinal chemist. As a result, systematic improvements in a synthesis (conditions for each step) or in overall strategy (type and number of steps) are investigated.

Upon deciding on a selected route, the DSC group frequently prepares a pilot batch in 5g scale. This batch is used to assess preliminary information on crystallinity, polymorphism and purity and can be used for salt-selection work if necessary. An important benefit of this batch is to identify the impurities in the product and determine where they arise in the synthesis. This information is then incorporated into the work in preparing subsequent batches that are used further in formulation and safety studies. In advancing their series, medicinal chemists rely on chromatography and not on crystallization techniques for isolation and purification. To avoid chromatographic bottlenecks, the DSC chemist preparing larger amounts of material must be adept at developing crystallization conditions not only for final products but also for purification of large batches of intermediates. In the past year, DSC has facilitated advancement of leads in a variety of therapeutic areas. Examples of DSC impact on lead advancement were two projects in which compounds were brought forward by medicinal chemists who had used preparative HPLC to isolate isomerically pure leads. In one of these projects an efficient chiral synthetic route was developed for the synthesis of the optically pure product and in a second project a new synthetic route was provided that allowed crystallization of diastereomeric salts for purification. Both of these routes eliminated chromatographic separations and were subsequently utilized in development.

Keys to minimizing synthesis time for any scale-up of a lead are to have an early notice of the potential structures of interest, to use this opportunity to evaluate the degree of synthetic difficulty and then to be able to explore at risk some new synthetic approaches for the structure. Thus, timely communication is especially valuable in the early stages of projects. The interaction of scale-up chemists with medicinal chemistry colleagues must be very close and the understanding and respect of the roles of each of these chemists is essential. Keeping an ongoing dialogue between discovery chemists and scale-up chemists is crucial and best facilitated by having these groups geographically close and in frequent formal and informal contact. Assigning DSC staff to monitor individual discovery teams in medicinal chemistry and actively participate with these programs through the synthesis of intermediates and final products is a valuable way to foster this communication. If the synthesis of key intermediates poses scale-up concerns, the scale-up chemist can address these issues while the medicinal chemist is refining structures to reach the optimal lead. The familiarity with the synthesis of these intermediates gives the DSC group a fast start when the lead advances and larger amounts of it are needed. This synthesis scouting work is often done on 'at risk' basis in consultation with the medicinal chemistry management. As a lead structure becomes more interesting, limited synthetic efforts are initiated before the need of multi-gram amounts become a critical-path issue.

The DSC staff is comprised of scientists who are entirely focused on issues related to synthetic chemistry and scale-up, work that entails more of a development perspective than a medicinal chemistry perspective. Emphasis is placed on taking what comes from the medicinal chemistry and adding value to the project by resolving issues surrounding synthesis, purity, and problems with salts and polymorphs. The group recognizes that the time devoted to any project is necessarily short and this is the biggest issue the DSC must address. The short time frame on a project puts great demands on the initiative and creativity of the staff. Finding opportunities for making significant impact on projects is challenging. The perfect synthesis solution will rarely be found, although measurable value in synthetic contributions can usually be realized. The process provides opportunity for the staff to submit composition of matter and process patents. The staff has come to recognize their key place in the discovery process and have a positive self-image in this role.

Relationships with development functions

Organizationally, the DSC group at Wyeth is part of discovery research and is evaluated by its contributions to discovery goals of providing new chemical entities for development to drug products. The DSC group bridges the gap between the medicinal chemistry efforts on lead identification and refinement of the lead to a development candidate when it is presented to development functions. Important relationships must therefore exist between the DSC chemists and scientists in Chemical and Pharmaceutical Development. The experience DSC gains in preparing intermediates and initial leads in medicinal projects is useful for providing a valuable platform of information for development scientists to get an expeditious

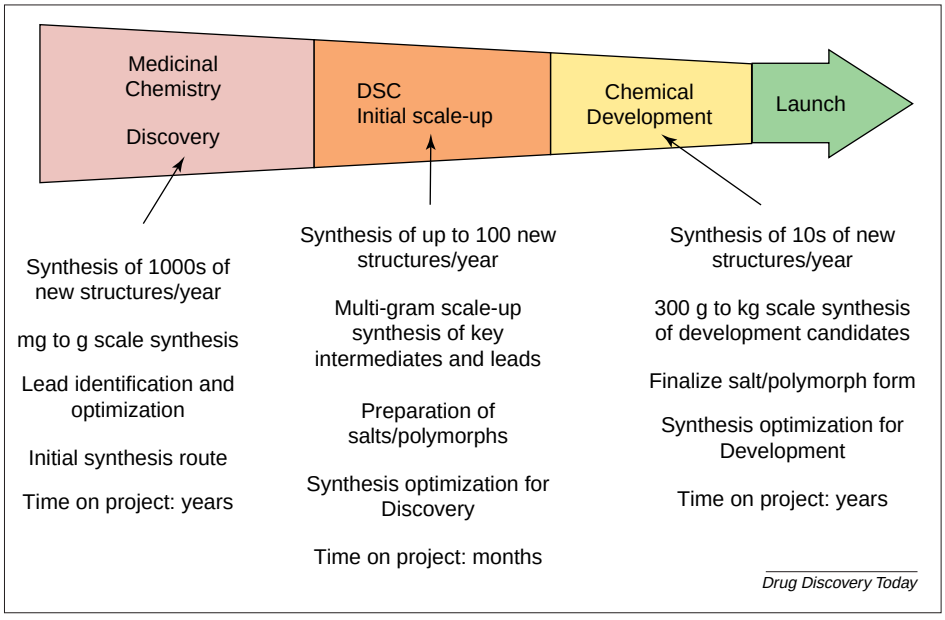

FIGURE 2

Synthesis roles for Medicinal Chemistry, Discovery Synthetic Chemistry (DSC) and Chemical Development

start in phase 0 work. The Wyeth DSC group provides documentation that captures all medicinal chemistry and DSC synthesis work done up to the time the project moves to development. This documentation provides archival benefits as well as advantages in technology transfer to Chemical Development. The improvements made in the synthesis of the lead as it advances from the initial medicinal chemist synthesis of mg quantities to the synthesis by DSC of multi-gram quantities are presented. The routes and procedures offered by medicinal chemistry are evaluated and critiqued and changes in routes or procedures are discussed by describing what was changed, why the change was made, and what was the outcome of the change. DSC offers practical insight from hands-on experience in issues ranging from synthetic details to addressing physical characteristics (crystallization techniques, polymorphism and salt forms) on lead molecules. Through the effort it devotes to solid-state properties, DSC frequently makes positive contributions to projects by providing the crystalline salts and favorable polymorphs for leads that could not be crystallized in medicinal chemistry.

The DSC group routinely keeps development functions alerted to leads further back in the discovery pipeline. Early notice gives Chemical Development opportunities to investigate and identify potential sources for critical starting materials and aids in shortening lead times for obtaining key raw materials if a lead moves further into development. In return, DSC often receives large quantities of intermediates and starting materials useful in newer projects along with highly developed laboratory procedures that are adaptable to new structures being made in discovery programs.

The DSC at Wyeth is seen as a transition group between Medicinal Chemistry and Chemical Development (Figure 2). Medicinal Chemistry provides a great number of leads for potential development and it is beneficial to have these leads filtered to give a smaller pool of molecules that are more fully profiled and merit the full resources of a development group. Chemical Development would not have adequate resources to address all early lead issues that merit scaling up beyond medicinal chemistry capacity. Having a discovery support group to prepare adequate material to more fully evaluate all leads before proceeding to development is one of the major reasons for establishing a DSC group. Through the efficient preparation of sufficient quantities of early leads, a better profiling of these can be achieved and elimination of weak candidates can occur without investing the resources of development. Chemical Development involvement could be more efficiently utilized for more-robust leads that make it through the gate to full development. Having a DSC group being the initial scale-up group discovery does mean that there is an additional technology handoff before a project reaches development. Transferring technology potentially results in occasional duplicated efforts, lost information and missed communication. However, through close interactions with Medicinal Chemistry and Development, DSC involvement actually streamlines and adds value to the transition of projects from discovery to development.

Conclusion

The new challenges for medicinal chemists to discover selective and safe leads for new targets within ever shrinking timelines have had a great impact on the synthesis methods used by the medicinal chemist. To meet these challenges the medicinal chemist has taken advantage of the new technologies of high throughput, parallel synthesis techniques, purification, analysis and screening. These technologies have been highly successful for the medicinal chemist. To maximize discovery efforts, it becomes highly valuable for companies to provide, timely dedicated resources that allow medicinal chemists to proceed with their primary discovery mission of providing new highly selective and safe therapeutic leads. The synthesis work focusing on synthetic optimization must be interactive and highly collaborative with medicinal chemists. The medicinal chemists and DSC have common goals and share the objective of providing leads for development. To meet these goals, medicinal chemists and the scale-up chemists will exhibit complementary skills in synthesis and scale-up work. Scale-up synthetic chemistry requires a mindset regarding synthesis, purification and isolation requirements that is different from that of medicinal chemistry today. Wyeth's support for

the medicinal chemist begins with a discovery synthesis group (DSC) designed to react interactively with Medicinal Chemistry needs on the one side and then to provide the starting point to Chemical Development involvement on the other side. Pharmaceutical companies may address the area of scale-up synthesis support for Medicinal Chemistry in many different ways, what is offered here is one approach in which Wyeth has found beneficial.

References

1 Golebiowski, A. *et al.* (2003) Lead Compounds Discovered from Libraries. *Curr. Opin. Chem. Biol.* 7, 308–325
2 Bunin, B.A. (2003) Increasing the Efficiency of Small-Molecule Drug Discovery. *Drug Discov. Today* 8, 823–826
3 Goodnow, R.A. (2001) Current Practices in Generation of Small Molecule New Leads. *J. Cell. Biochem. Suppl.* 37, 13–21
4 Elands, J. (2001) The Evolution of Laboratory Automation. *Drugs and the Pharmaceutical Sciences* 114, 477–492
5 Federsel, H. (1998) Building Bridges from Process R&D: From a Customer-supplier Relationship to Full Partnership. *Pharm. Sci. Technol. Today* 1, 387–393
6 Venkatesh, S. and Lipper, R.A. (2000) Role of the Development Scientist in Compound Lead Selection and Optimization. *J. Pharm. Sci.* 89, 145–154
7 Lesney, M.S. (2003) Gearing Up for Speedy Relief. *Modern Drug Discovery* 39, 39–41
8 Coates, W.J. *et al.* (2000) Successful Implementation of Automation in Medicinal Chemistry. *Drug Discov. Today* 5, 521–527
9 Merritt, A.T. (1998) Uptake of New Technology in Lead Optimization for Drug Discovery. *Drug Discov. Today* 1, 505–515
10 Lawrence, R.N. (2000) Current Approaches to Multiple Parallel Synthesis. *Drug Discov. Today* 5, 172–175
11 Labaudiniere, R.F. (1998) RPR'S Approach to High-speed Parallel Synthesis for Lead Generation. *Drug Discov. Today* 3, 511–515
12 Hughes, I. and Hunter, D. (2001) Techniques for Analysis and Purification in High Throughput Chemistry. *Curr. Opin. Chem. Biol.* 5, 243–247
13 Kyranos, J.N. *et al.* (2001) High-throughput Techniques for Compound Characterization and Purification. *Curr. Opin. Drug Discov. Devel.* 4, 719–728
14 Wess, G. (1996) Challenges for Medicinal Chemisty. *Drug Discov. Today* 1, 529–532
15 Hird, N.W. (1999) Automated Synthesis: New Tools for the Organic Chemist. *Drug Discov. Today* 4, 265–274
16 Caldwell, G.W. *et al.* (2001) and Z Yan, The New Pre-Preclinical Paradigm: Compound Optimization in Early and Late Phase Drug Discovery. *Curr. Top. Med. Chem.* 1, 353–366
17 Federsel, H. (2003) Facing Chirality in the 21st Century: Approaching the Challenges in the Pharmaceutical Industry. *Chirality* 15, S128–S142
18 Curatolo, W. (1998) Physical Chemical Properties of Oral Drug Candidates in the Discovery and Exploratory Development Settings. *Pharm. Sci. Technol. Today* 1, 387–393
19 Grant, D.J.W. and Byrn, S.R. (2004) A Timely Re-examination of Drug Polymorphism in Pharmaceutical Development and Regulation. *Adv. Drug Deliv. Rev.* 56, 237–239
20 Huang, L. and Tong, W. (2004) Impact of Solid State Properties on Developability Assessment of Drug Candidates. *Adv. Drug Deliv. Rev.* 56, 321–334
21 Federsel, H. (2001) Drug Discoverers – You Need Us! *Drug Discov. Today* 6, 397–398
22 Shultis, K. (2002) The Dilemma of Process Development. *Drug Discov. Today* 7, 850–853
23 Federsel, H. (2003) Logistics of Process R&D: Transforming Laboratory Methods to Manufacturing Scale. *Nat. Rev. Drug Discov.* 2, 654–664
24 Hillier, M.C. and Reider, P.J. (2002) Stereoselective Synthesis from a Process Research Perspective. *Drug Discov. Today* 7, 303–314