Drug discoverers – you need us – Reply ▲

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

Reply from Kenton Shultis

Process chemistry is not just for manufacturers

Modern drug discovery is often compared with oil exploration: we are all comfortable with terms such as 'attrition rates' and 'dry holes' to describe the risky nature of the outcome. In drug discovery, as in oil exploration, if we are not successful in finding what we seek, we learn where to avoid searching. In addition, for a given class of compounds, we become better at exploration and discovery with each attempt.

Discussions about pharmaceutical R&D often extend the oil exploration analogy to the early stages of drug development, but this is where I believe the model ultimately breaks down. A drug development project's goal is to bring a new medicine to market; the unique characteristics of each particular compound teach lessons that do not often apply to the next project. If the project fails to produce a marketable drug, the development work, for the most part, is lost. I can think of no other commercialization process that is so regulated, meticulous, expensive and likely to fail as drug development. Because development programs consume enormous resources with little return for failure, it is crucial to the success of any pharmaceutical company for drug development to either progress to market as smoothly as possible or, conversely, terminate as soon as possible.

In his forum letter *Drug discoverers – you need us!*, Hans-Jürgen Federsel presented a dilemma faced by drug developers today. Devising a practical and scalable process to produce a new chemical entity coming from the modern drug discovery program is no longer an activity that simply happens without attention from development project managers. The chemical complexity of new compounds moving into the clinic has never been greater, hence the need to develop workable processes early in the project cycle. Together with the pressures of stronger process safety and environmental requirements, higher standards of purity and process control, and tougher deadlines as a result of a faster business tempo and drug regulatory changes, the process chemist and process engineer work at a standard of performance far higher than even ten years ago. Federsel captured the future of drug development perfectly; the bottleneck for drug development will often be process development.

One way to break the bottleneck is to 'telescope' the drug discovery and drug development processes by involving the process chemists in synthesis and procurement of drug discovery materials. This ensures that the supply chain for custom chemicals is in place and the process chemistry groups are familiar with the compounds, saving months of project time when a decision is made to proceed with a drug candidate. The process chemists also provide useful feedback with regard to candidate selection. Federsel reports good success with this practice in reducing time to first delivery of clinical supplies.

Often, small drug discovery companies view process development as an activity outside their scope because they have no intention of becoming manufacturers. Their goal is to get a drug candidate ready for licensing as quickly as possible. For these companies, process chemistry can have a strategic role. Telescoping helps advance the candidate drug more quickly and makes it more attractive to a collaborator.

Process expertise is a precious resource and must be used sensibly. Developing a full-scale process for each and every drug candidate is wasteful, given that most projects ultimately fail. However, process expertise should be used to streamline the operations for each compound. This practice ensures that every program gets the supplies it needs, when they are needed.

In short, process chemistry can both speed up a drug development program and provide an efficient and elegant process. The job of the successful project manager is to know when to switch emphasis between these two tasks.

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Efficacy of the anti-angiogenic approach to solid tumors ▼

The recent review by Hicklin and colleagues in *Drug Discovery Today*[1] provides a comprehensive overview of the use of monoclonal antibodies to block angiogenesis and, by doing so, inhibit tumor growth. The anti-endothelial growth factor (EGF) receptor molecules, Herceptin (approved for breast cancer) and C225 (Phase III), might owe some of their demonstrated *in vivo* efficacy to their ability to block angiogenesis.

It is unfortunate that the most-developed antibody specifically designed to be anti-angiogenic, the anti-vascular EGF (VEGF) antibody, which has completed three Phase II clinical trials, has not demonstrated dose-dependent efficacy and appears to have considerable toxicity. A Phase III trial of the monoclonal antibody combined with chemotherapy in

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metastatic colon cancer is underway. In addition, Vitaxin, the monoclonal antibody to $\alpha_v\beta_3$, is well tolerated in humans but has not shown efficacy. These studies raise questions about how effective an anti-angiogenic approach will be in human solid tumors. However, some of the other monoclonal antibodies that are currently entering Phase I trials, including anti-VEGF-receptor-2, appear to be non-toxic and significantly effective in therapeutic animal models with large, established tumors. Hopefully they will have a more successful clinical outcome than their predecessors.

Reference

1 Hicklin, D. *et al.* (2001) Monoclonal antibody strategies to block angiogenesis. *Drug Discov. Today* 6, 517–536

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