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 Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@current-trends.com

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Consider the following two opposite views of Process R&D: 'this is a core activity of significant value making important contributions to the business' and 'they only have to produce kilogram quantities of known compounds'. Do they strike you as being familiar? Are you in favour of one over the other or do you assume a position midway? Well, the main purpose of this contribution is to seriously try to influence those of you primarily belonging to the latter group to change your mindset towards the other end of the spectrum!

There are actually several timely reasons as to why this question is brought to your attention right now and I will focus on three of the most important ones. First is the ever-increasing pressure to achieve shorter times-to-market, from candidate drug (CD) nomination to launch. Second is the demand for considerable quantities of the chosen CD right from the start, and third is the structural complexities of the target compounds.

The idea of addressing these issues in a more concise way has grown ever since attending (as invited lecturer) a series of conferences and symposia during the autumn of 2000 (*ChiraSource 2000* in Lisbon, Portugal; *Chiral Europe 2000* in Malta, and the *18th SCI Chemical Process Development Symposium* in Cambridge, UK) largely devoted to endeavours in the field of Process R&D. Here, the current standing of the whole area was displayed before an international audience and the array of achievements reported was, in several cases, stunning or even spectacular. In many of the talks, the strength and ability to master many (if not all) of the intricacies they were confronted with (for example, multiple stereogenic centres, unconventional substitution patterns, regioisomeric features and arrays of functionalities) were amply demonstrated. It should therefore be evident to anyone in the business that the success potential for developing a new chemical entity (NCE) showing a high level of architectural complexity into a future drug rests on the ability to design, optimize and scale-up a chemical process to commercial manufacturing.

Just the fact that the three aforementioned major international events were organized in a time window as short as 2.5 months is testimony to the maturity that this 'science' has reached. Some people might raise their eyebrows when referring to Process R&D as a scientific discipline in its own right. The truth is, however, that during the past quarter-of-a-century, it has grown from being considered as a somewhat obscure and 'low-tech' shovelling of larger quantities of compounds of various types (performed mainly by unqualified workers!) to the present state-of-the-art, where unique production methods are devised that often brilliantly circumvent shortcomings or technical limitations of laboratory-based medicinal chemistry procedures. Needless to say, many of the processes thus developed have such creative and innovative qualities that they can be both patented and/or otherwise openly publicized for everyone to share (and eventually admire).

Taking the constantly ongoing trend to reduce the time-span from appointing a new CD to launch of a registered pharmaceutical product on the market (preferably on the entire global arena within the first year after approval by the authorities) into account, it is only too obvious that securing the availability of large volumes (meaning in reality non-laboratory accessible quantities) is a key driver in assuring that the narrow time-limits are met. This often poses an enormous logistical challenge on a Process R&D function in the sense that some kind of scalable procedure has to be quickly established while concomitantly trying to identify suitable external suppliers of starting materials and building blocks of frequently relatively high structural complexity (which are increasingly chiral in nature and requested in stereochemically defined form).

The fact that we, by far, focus our efforts on target molecules of unique structures previously never manufactured (except for the minute quantities required in initial screening) adds to the 'burden' in the sense that the compounds to be used for their construction are most likely not 'sitting' on the shelf waiting to be ordered. This is especially true as the synthetic strategy tends to be forward-integrated to reduce the number of required in-house transformations. Actually, the likelihood is that many of the

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products in contractors' catalogues have never been prepared in more than gram scale before and have previously used inferior methods unsuitable for further scale-up. Thus, with this background, finding out that a period of maybe 6 months (in worst cases even longer) has to elapse before the eagerly desired starting material is in your storage facility should not come as a surprise! With this in mind, the initiation of external contractors' work covering, for example, the production of a crucial building block should be evaluated and considered without for a moment ignoring the economical risk involved at this early stage before a CD has even been firmly chosen.

A solution to this dilemma that aims to minimize the obstacles already outlined and ensuring the speediest possible supply of materials will inevitably rely on the involvement of Process R&D already in the pre-CD phase. A conceptual model for how this can be arranged has recently been published[1] and hard facts expressed as 'time to first delivery' have in fact corroborated the validity of the procedure described therein. During the 6–12 months prior to nominating a CD, many of the issues around route discovery, process design, scale-up and technology, cost of goods, SHE (Safety–Health–Environment), lead times for raw materials, and patent/intellectual property questions can be addressed and fed back as an effective means of giving a qualitative input to the CD selection process.

The conclusive and clear-cut message from all this can be summarized as: *Drug discovery today needs more involvement from Process R&D*!

Reference

1 Federsel, H-J. (2000) Building bridges from process R&D: from a customer–supplier relationship to full partnership. *Pharm. Sci. Technol. Today* 3, 265–272

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Too many targets, not enough target validation ▼

'Correlation does not prove causation'. This aphorism, fundamental in selecting targets for drug development, must be re-emphasized given the great excitement generated by the recent publications from Celera Genomics (in *Science*)[1] and the International Human Genome Sequencing Consortium (in *Nature*)[2] describing the draft sequence of the human genome. In a recent issue of *Drug Discovery Today*[3], Philippe Sanseau described what this wealth of data means to the pharmaceutical industry. To date, the resources of the entire industry have generated drugs interacting with only ~500 molecular targets[4]. As Sanseau emphasized, our task now is to find the best drug targets among the thousands of newly identified genes. With fewer than 35,000 genes (discounting splice variants) in the human genome, this task could be slightly less formidable than first predicted (e.g. Incyte Genomics has reported >120,000 human gene transcripts, with 60,000 unique to its database; http://www.incyte.com/sequence/lifeseq/lifeseqgold.shtml).

How can the biological and chemical tractability of these potential targets be assessed? What are the criteria to justify intensive screening, chemistry and development efforts on each new gene product? In the past few years, the industry has been overwhelmed with targets identified using new tools such as gene expression arrays and expressed sequence tag (EST) databases, and this problem has only intensified with the release of the human genome sequence. Increased screening throughput is clearly not the solution, as this only forces the resource bottleneck downstream into lead optimization and development. Rather, a more rational approach is to eliminate poor targets before compound screening begins, through rigorous biological assessment of a gene product's role in disease.

Currently, the pharmaceutical industry has too many targets and not enough target validation. Target validation, crucial to rational drug design, is a concept often discussed but rarely defined. To address this, Sanseau described several 'discovery genomics' approaches to further evaluate targets uncovered in the human genome sequence. Mining of sequence databases, for example, has already added novel members to gene families of proven therapeutic value, such as G protein-coupled receptors (GPCRs)[5].

However, target validation requires more than just demonstrating correlation. A simple association of gene expression with disease (e.g. generated through a gene array) does not validate a role for that target in the disease. Even a human genetics approach to identify targets associated with disease does not necessarily generate chemically tractable molecular targets. Rather, the goal of target validation is to strengthen correlative data (from gene arrays, EST libraries and proteomics) by demonstrating a causal role for the candidate in a disease model. From a

Box 1. Approaches to assessing novel molecular targets

Correlative data	**Causative data**
Genomic sequence mining	Antisense oligonucleotides/ribozymes
Gene expression arrays	Neutralizing antibodies
Serial Analysis of Gene Expression (SAGE)	Knockout/transgenic mice
EST databases	Small-molecule agonists/antagonists
Proteomics	

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