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 Steve Carney, Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

Getting more mileage out of a tankful of new molecular entities?

The article by Schmid and Smith [1] in a recent edition of *Drug Discovery Today* represents one of the most thoughtful articles on pharmaceutical strategy in recent times. Rather than a blanket scenario of gloom and doom, the authors analysed in detail the successes and failures of the modern industry.

From the perspective of Pfizer (http://www.pfizer.com), a company that focuses on novel therapeutic uses for existing compounds, these authors highlighted a strategy that is more prominent at this multinational company than any other. The success Pfizer achieved with sildenafil (Viagra™) for the treatment of erectile dysfunction indicates the commercial value that an eclectic view of therapeutic utility can bring to a new class of molecule. As many will remember, the phosphodiesterase type 5 (PDE5) inhibitor program at Pfizer originally targeted angina and congestive heart failure. The efficacy of sildenafil in the treatment of erectile dysfunction was found as a result of a Phase I trial (in men), and the rest is history. Sildenafil is a major commercial success that has come from the consideration of this agent for a utility that was not the original focus when the discovery programme was started. It has also opened up a new therapeutic area, hitherto largely untreated, and led to competitor products based on PDE5 enzyme inhibition, for example, vardenafil [Levitra™ (Bayer; http://www.bayer.com) and tadalafil [Cialis® (Lilly ICOS LLC; http://lillyicos.com)]. This is good for the industry as a whole.

Schmid and Smith made the point that the stagnation in the number of new chemical entities per year does not mean an invariant number of new therapeutics because the use of a single agent in multiple indications is a growing phenomenon. This argument, although not without validity, cannot disguise the flagrant divergence between increases in US R&D spending, from approximately US$0.75 billion in 1970 to approximately US$25 billion in 2001 (a 35-fold increase) relative to approved new molecular entities (NMEs), which approximately doubled from 20 to 40 over the same period.

The current strategy followed by large pharmaceutical companies is to identify new uses for drugs that are already on the market and, in this regard, companies other than Pfizer are well advanced. As a class, the selective serotonin reuptake inhibitor (SSRI) anti-depressants have been extensively investigated, most notably by GlaxoSmithKline (http://www.gsk.com/index.htm) in their commercial treatment of Paxil™ (paroxetine). This SSRI was originally approved as an anti-depressant, but through the mid-1990s sales declined in the face of increasing competition; the approved indications were widened to include social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder and panic disorder, and as a result the sales decline was arrested and later reversed. A similar strategy was applied later to other SSRIs.

In an extension of this strategy beyond psychiatric indications, Lilly (http://lilly.com) has pursued other central nervous system (CNS) and some non-CNS indications for their anti-depressant duloxetine (Cymbalta™). This drug, classified as a serotonin-noradrenaline reuptake inhibitor (SNRI), is currently under consideration by the US FDA for depression and stress urinary incontinence, but is also in clinical studies for diabetic neuropathy and fibromyalgia. Developments of this kind are of potentially huge importance because they represent forays into areas of great medical need. Stress incontinence currently has no approved drug therapy in the US, yet is more prevalent than diabetes hypertension and depression among female patients in the primary care practice setting and, together with urge incontinence, costs approximately US$26.3 billion [2] (including incontinence-related care). Again, the market will need to be developed, but could potentially result in a dramatic new vista for the industry as a whole.

Although the benchmark for an acceptable safety and tolerability profile is not the same in all indications, and there are pricing and marketing issues for drugs in disparate therapeutic areas, this strategy seems to be gathering more widespread acceptance. In addition to the headline number of NMEs that are approved each year, greater attention should be placed on the number of new

1359-6446/04/$ – see front matter PII: S1359-6446(03)03011-3

drug applications to ensure that pharmaceutical industry productivity can be more realistically appreciated.

References

1 Schmid, E.F and Smith, D.A. (2004) Is pharmaceutical R&D just a game of chance or can strategy make a difference? *Drug Discov. Today* 9, 18–26

2 Wagner, T.H. and Hu, T.W. (1998) Economic costs of urinary incontinence. *Int. Urogynecol. J. Pelvic Floor Dysfunct.* 9, 127–128

David Cavalla
Arachnova Limited
St John's Innovation Centre
Cambridge
UK, CB4 0WS
e-mail: david.cavalla@arachnova.com

Multidimensional separation and hyphenated techniques in pharmaceutical research: practical considerations

With the widespread use of combinatorial chemistry, HTS, genomics, proteomics and metabonomics, pharmaceutical research is entering a new era. The increasing complexity of pharmaceutical research has led to the development and application of multidimensional separation methods and hyphenated techniques. Analytical scientists are now faced with the challenge of choosing the most appropriate technologies for solving practical problems. In a recent edition of *Drug Discovery Today*, Guttman *et al*. [1] summarized the latest developments in multidimensional separation techniques. Multidimensional separation can be comprehensive or simple. In the case of a comprehensive analysis, every part of the sample is subject to separation in each dimension. In the case of a simple analysis, only a portion of the sample components might pass to the next separation dimension. In addition, there are different combinations of separation techniques coupled with various detection or hyphenation techniques. The coupling of separation and detection or hyphenation can be simple, as in the case of liquid chromatography–mass spectrometry (LC–MS), or more extensive, for example, LC–UV–evaporative light-scattering detector (ELSD)–chemiluminescent nitrogen detector (CLND)–MS, which is used for characterizing combinatorial library compounds. Different separation and detection techniques can be used together, either on-line or off-line, to solve a practical problem, with different advantages and limitations.

Throughput versus information content

Often there is a need to obtain comprehensive information from complex samples. In the case of proteomics and metabonomics, multidimensional separation might be necessary even if the overall throughput is low [2]. However, using MS or nuclear magnetic resonance (NMR) as the detection method potentially affords a higher throughput because these techniques are capable of selective and simultaneous detection of multiple components. For example, the use of high resolution Fourier transform–ion cyclotron resonance (FT–ICR)–MS coupled with one-dimensional separation for proteomics has been demonstrated with excellent coverage for the bacterial proteome [3]. Another example is the analysis of combinatorial library compounds. Good separation is always beneficial, but the need for high throughput necessitates the use of generic one-dimensional reverse-phase HPLC (RPLC) or supercritical fluid chromatography (SFC) methods to analyze large numbers of library compounds coupled with suitable spectroscopic detections (e.g. UV–MS) [4].

Degree of hyphenation

MS is generally used as one of the detectors in a hyphenated system because of its sensitivity and ability to generate information that can be used to identify target compounds. It is the detection technique of choice in proteomics involving LC separation. In metabonomics, NMR and MS are used as complementary detection techniques. For combinatorial library compound purification and analysis, the combination of RPLC or SFC with MS is commonly used and is complemented by one or two additional detection techniques including, UV, ELSD, CLND and NMR. These different detection methods often provide complementary capability in detection selectivity, range of sensitivity and linearity of response. A recent example by Yurek *et al*. [5] describes the simultaneous determination of identity, purity and concentration of library components that were produced by parallel synthesis. The system uses an HPLC with diode array detector (DAD), ELSD, CLND and time-of-flight (TOF)–MS detectors. The use of the exact mass capability of TOF–MS with CLND yields a synergistic combination that enables target and side-product structures to be elucidated and the concentration and purity of the compounds to be determined in a single analysis. We have used LC–UV–MS to determine the stability of 644 diverse compounds from the Abbott Laboratory repository. MS was used to identify the target compounds and decomposition products while UV was used for quantitation of these diverse compounds at a relatively high concentration [6].

References

1 Guttman, A. *et al*. (2004) Multidimensional separations in the pharmaceutical arena. *Drug Disc. Today* 9, 136–144

2 Link, A.J. *et al*. (1997) Direct analysis of protein complexes using mass spectrometry. *Nature Biotechnol.* 17, 676–682

3 Lipton, M.S. *et al*. (2002) Global analysis of the *Deinococcus radiodurans* proteome by using accurate mass tags. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11049–11054

1359-6446/04/$ – see front matter PII: S1359-6446(04)03024-7