was going to be, and I have an awful lot of respect for every former head of R&D I have worked for because it is a consuming job. It can consume your life. Some of the best heads of R&D that I know held that job for 5 to 7 years. That's all you get, then you've done everything you knew how to do, so it's probably time for someone else to come in, with new ideas. So I'm not sure that it would be good for me to run R&D for another 5 years. Hopefully I am retired.

I love this industry, so hopefully I'll be doing something related to the industry while I am retired, maybe consulting,

'I absolutely love the pharmaceutical industry. I always did, and I always will.'

sitting on a board, even representing the industry in dealing with some of the issues we have spoken about, some of the political, regulatory and image issues. I can't ever imagine myself, even in retirement, not wanting to do something with this industry and for this industry. I absolutely love the pharmaceutical industry. I always did, and I always will.

Do you think you might get more involved in academia?

I could see myself, maybe not teaching at a university, but teaching science at an inner city school or at a small community college. I won't be looking for a large income, but rather for a way for me to give back. I live a fairly privileged life now, and I would like to give something back.

Bob Ruffolo
President
Research & Development
Wyeth Pharmaceuticals

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

A quiet revolution in lead optimisation services?

The article by Clark and Newton [1] in a recent issue of *Drug Discovery Today* on the outsourcing of lead optimisation is aptly sub-titled 'the quiet revolution'; lead optimisation is the cylinder block (i.e. the silent component) of the drug discovery engine. The lead optimisation stage of the drug discovery process is precisely where novel drug compositions are invented and new primary intellectual property is generated. Unlike many other areas of the pharmaceutical research and development pipeline that can be considered for outsourcing, the lead optimisation phase does not fit squarely into a compartmentalised, component model.

Several important issues are raised by the change of heart of the large pharmaceutical companies with respect to the outsourcing of lead optimisation. Currently, increasing numbers of quality medicinal chemists are employed by a growing number of service companies. Several such companies are located in India and China, where the economic laws of supply and demand create a comfortable environment for the client. There is no doubt that the issues of offshoring present a set of complex and real challenges for the lead optimisation service company.

In the mid 1990s, the intense demand for the new technology that was inherent in a collaboration with a combinatorial chemistry company led to these partnerships being structured with the supplier in mind, and the majority of deals incorporated a set of structured milestone payments, and perhaps royalties. Currently, contractual relationships are the order of the day. Indeed, cost restraint that is imposed by competition from relatively cheap offshore industries is driving down profitability for many European and US companies that offer lead optimisation services.

There is a danger that the economic parameters that govern today's market inadequately recognise quality among the various lead optimisation service providers – this is a cry that could become increasingly vocal from those companies that provide services at a relatively high cost. The generation of quality lead development candidates is difficult to benchmark because the output cannot be measured in simple terms. Therefore, although lead optimisation might not represent a hot new technology in the same way that combinatorial chemistry did ten years ago, it should not be considered a ready-made component of

1359-6446/04/$ – see front matter PII: S1359-6446(04)03133-2

pharmaceutical R&D. A purely contractual fee-for-service model might not be the best way of remunerating lead optimisation services.

Considering the future, the large pharmaceutical companies have benefited from an era of excess supply and of increasing use of service providers. An increase in the number of medium-sized pharmaceutical (and biotechnology) companies that use an outsourced approach has resulted in the growth of the market for drug discovery services. Service providers have become increasingly adept at generating intellectual property for their clients, and have changed their strategy towards discovering and developing their own products in-house. In part, this is a desire to move up the value chain in a competitive environment, but it is also partially because good scientists are not in inexhaustible supply. Several service providers that are based in Europe and the USA have become less profitable, others have built links with offshore competitors and some have ceased to operate. Furthermore, the role of the research coordinator at large pharmaceutical companies has changed with the advent of the outsourcing of the design and synthesis of new drugs. Beyond the purchasing of contract drug discovery services, large pharmaceutical companies are increasingly using licensing as a means to bolster thin R&D pipelines. The deals that are struck are based on staggered payments that reflect the value of the license candidate as development progresses, and typically include milestone and up-front settlements. The large pharmaceutical companies embody the partners of choice because they have the financial clout to develop and market a drug effectively. A wide range of license deals is possible, with the headline figures of the largest deals typically obscuring the frequently modest financial elements that characterise the bulk of the deals agreed. Risk is pushed upstream to the lead optimisation company: the success of the company depends not just on achieving hot leads in attractive therapeutic areas but also on performing this better than anyone else and turning hot leads into hot deals.

Is this the world of lead optimisation that we can look forward to in the next decade? It is actually a relatively positive forecast for the lead optimisation sector because future success depends on a healthy out-licensing market for pharmaceutical development candidates. Currently, the lead optimisation phase is an unusual stage to complete a license because potential licensees often have an abundance of opportunities from in-house research and are more attracted to products that are at early stages of clinical development (e.g. Phase II). It is not clear how this gap, should it remain unfilled, would be bridged and by whom. What is clear is that we can expect further 'quiet revolution' over the coming years.

Reference

1 Clark, D.E and Newton, C.G. (2004) Outsourcing lead optimisation – the quiet revolution. *Drug Discov. Today* 9, 492–500

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

The impact of cytochrome P450 allosterism on pharmacokinetics and drug–drug interactions

In a recent issue of *Drug Discovery Today*, Atkins [1] provides an excellent overview of cytochrome P450 (CYP) allosterism. The mechanism of CYP allosterism, and its impact on *in vitro–in vivo* correlation (IVIVC) and clinical metabolism-based drug–drug interactions (DDI), has yet to be fully elucidated. Atkins' summary has elegantly brought these topics to the attention of those scientists that are studying this new and emerging area of CYP research.

It is widely accepted that several CYP isoforms exhibit non-Michaelis–Menten (non-hyperbolic) kinetics *in vitro*, most notably CYP3A4, which is arguably the most important CYP with respect to drug metabolism. One of the proposed mechanisms of CYP allosterism suggests that the simultaneous binding of multiple homotropic or heterotropic substrates (and/or effectors) within the active site of a CYP results in a variety of atypical enzyme kinetics [2,3]. These multiple binding sites could be characterized as either discrete, static sites or a large dynamic site that could potentially hold more than one molecule, depending on the change observed in the apparent kinetic parameters (K_m and V_{max}) when interactions among the multiple substrates occur [3–5]. To address the complexity of multiple-substrate binding, many kinetic equilibrium expressions have been derived to fit observed data and to solve kinetic parameters that explain the kinetic interactions of multiply bound substrates [2,3,6]. The kinetic anomalies observed are the result of substrate–substrate, substrate–enzyme and/or enzyme–enzyme interactions. The binding of the first substrate to the active site of the CYP initiates a change in protein conformation that can either promote or inhibit the binding and catalysis of the second substrate [2].

In drug discovery and preclincal development, *in vitro* kinetic data (i.e. intrinsic clearance) have been increasingly used to scale and to predict clinical pharmacokinetics (i.e. hepatic and plasma clearance). Such predictions form the basis for the estimation of the systematic exposure (area under curve) of a drug and the drug dose that is needed to achieve the desired therapeutic targets (i.e. maximal- and trough-plasma concentration) [6]. Therefore, accuracy in the *in vitro* determination of the kinetic

 1359-6446/04/$ – see front matter PII: S1359-6446(04)03132-0