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.

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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

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parameters is essential for the prediction of *in vivo* parameters. Although the effect of CYP allosterism on the IVIVC and pharmacokinetic DDI is not fully understood, CYP allosterism has been frequently observed in the screening of new chemical entities for inhibitory activity against CYPs. Substrate- and effector-dependent CYP inhibition have been found to exhibit the kinetic discrepancies that have hampered the understanding and interpretation of the data and the decision-making process at later stages in the drug development process [7]. Because multiple binding sites that have allosteric characteristics exist, the K_m and V_{max} values for a particular substrate can be changed by the presence of another substrate (or effector). The magnitude of the change is dependent on the concentration of the substrate that serves as an allosteric ligand. Thus, multiple, variable kinetic parameters could considerably complicate the prediction of the IVIVC.

As a result, a quantitative relationship between the substrate concentration (i.e. substrate and/or effector) and the kinetic parameters (K_m and V_{max}) should be characterized. Such knowledge could enable the accurate prediction of pharmacokinetics and DDI from the targeted drug concentration. Most importantly, to avoid severe clinical DDI, the influence of CYP allosterism on pharmacokinetics must be considered with reference to those factors that are known to alter CYP pharmacokinetics, including compounds that induce CYP expression and inhibit CYP activity.

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Fighting superbugs with superdrugs

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The annual *Superbugs and Superdrugs: A Focus on Antibacterials* conference, held on 1–2 March 2004, London, UK, gave an insight into what is happening in the global fight against drug-resistant bacteria. Various topics from the antibacterial drug discovery and development field were covered by leading specialists, including the strategies employed to identify novel targets and the regulatory incentives offered to spur the development of antibacterial agents.

It initially appears to be all doom and gloom in the fight against superbugs. The prevalence of superbugs, such as vancomycin-resistant *Staphylococcus aureus* (VRSA) and methicillin-resistant *Staphylococcus aureus* (MRSA), is increasing at a rapid rate both in the hospital sector and in the community. Recent surveys revealed that resistance rates were higher in bacterial isolates derived from in-patients when compared with those from out-patients or from general practice [1]. Furthermore, the increase in multiple antibiotic resistance appears to be linked to hospital cross-infection. In England and Wales, MRSA is now responsible for the majority of cases of adult bacteraemia. In 1990, only 0.9% of adult bacteraemia cases were recorded with MRSA as the causative agent, but this percentage had risen to 13.0% by 2000 [2]. Despite the media interest in these superbugs, the pharmaceutical industry appears to show little interest in including antibacterials in their research portfolio. So, what can be done to curb the growth of these deadly superbugs?

Promoting antibacterial development and education

The US FDA (http://www.fda.gov) has recognized the importance of