Fast tracking drug development: balancing risks and rewards

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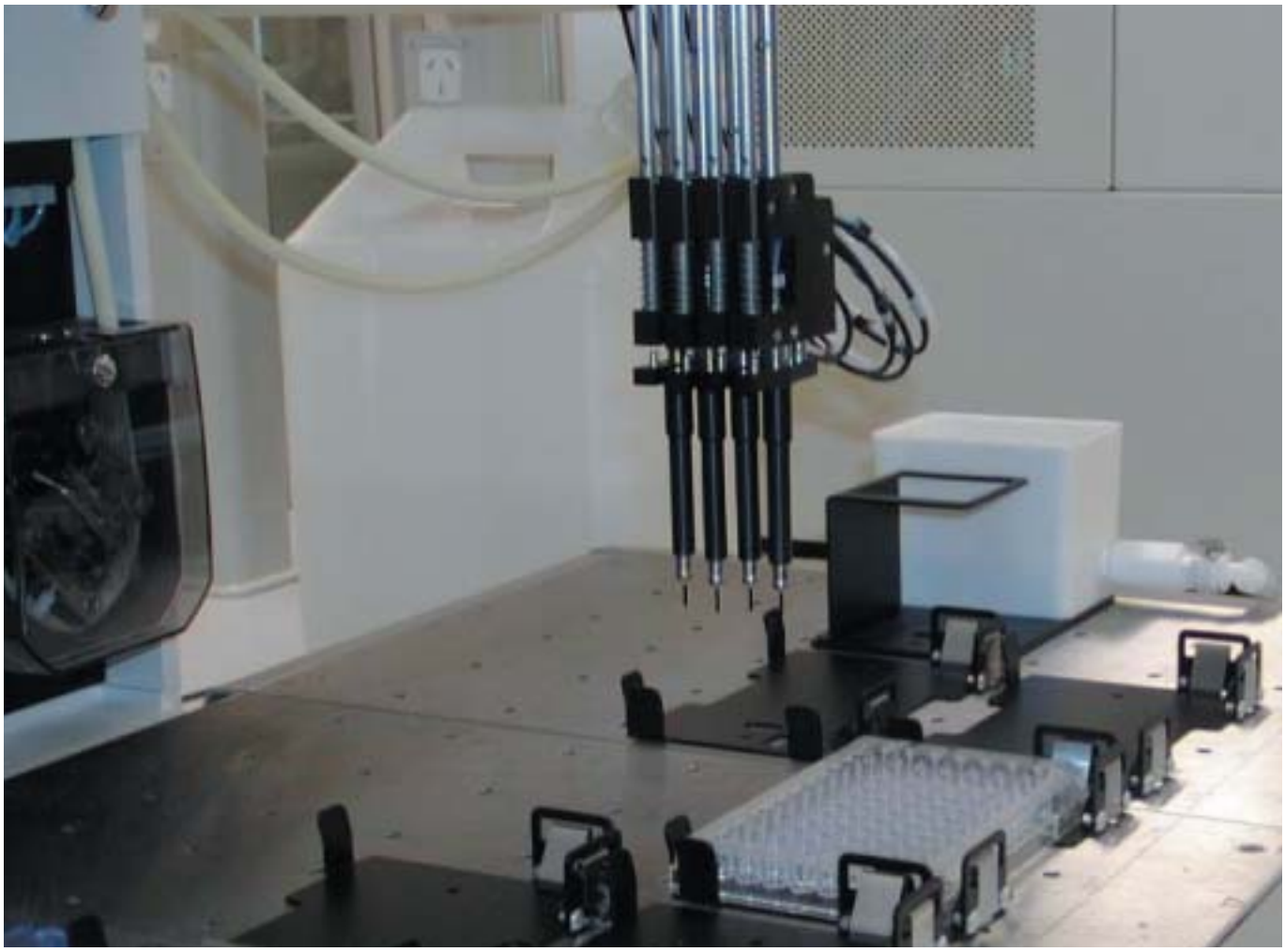
The biotechnology revolution offers great hope for new therapies based on rational approaches to target discovery and drug design based on genomics, proteomics, advanced chemistry (3-D modelling, combinatorial chemistry) and high throughput screening[1].

However, drug development processes are under increasing strain because of high cost of the new discovery paradigms. Drug approvals are static and the profitability of major pharmaceutical companies is linked into developing pipelines of market leading products in major disease areas. This has meant that increased emphasis is placed on more efficient development processes which cut both cost and time to market.

Major changes in drug approval processes occurred all over the world in the late 1990s to decrease the time for regulatory approvals and convergence of regulatory requirements particularly between the US FDA and the European system (and Australia). However, there is now an increased focus on the development process itself to speed up drug screening and safety testing and also to increase the capacity to handle vast chemical libraries which are generated by the new technologies.

Part of the new development requirement is to introduce pharmacokinetic and toxicology (drug absorbtion, metabolism, excretion and toxicity; ADMET) early into the development process of new drugs. This is a departure from the traditional view that ADMET is only carried out for regulatory compliance at late stage development. Statistics show that 50-60% of drugs fail clinical trails because of inappropriate characteristics in ADMET[2].

Late stage clinical trial failure is costly as the drugs have eaten up a large portion of the their R&D expenditure. It is estimated that in the USA in 1996



development costs of a successful drug were about US$500 million. Early stage screening for ADMET would substantially reduce total cost.

Moving back to an earlier stage changes the nature of ADMET studies. Firstly, it means that the pharmacologist, toxicologist and medicinal chemist are more profoundly involved in drug design in an interactive relationship.

Secondly, early stage screening implies that larger numbers of compounds have to be tested, particularly with combinatorial chemistry approaches. This is unsuitable for traditional animal testing models. Research is now replacing tests that involved whole animals with high throughput format cell and non-cell based tests to cope with the increased numbers of early stage compounds to be tested. This has stimulated the use of cell based technologies, particularly human, for ADMET.

More recently, computer simulations of ADMET properties of drugs using either 2-D or 3-D simulations of chemical structure have been developed [3]. The current limitations are the predictability of the *in silico* systems such as DEREK which in the case of toxicology are using toxicology databases relying on whole organism data [4]. Improvements will come when there is a more defined identification of drug toxicity at the cellular level through the molecular mechanisms for drug toxicity.

A bioinformatic approach is also being developed with different paradigms. For example, metabonomics is trying to relate patterns of NMR spectra in urine samples with disease and toxicity profiles with the aim of identifying patterns which predict problems [5]. Other approaches are in toxicogenomics which are relating patterns of gene expression to toxicologic consequences and individual variation in drug response [6].

As the predictability of such methods increase they will replace more laborious methods. Regulatory testing is likely to be slower to change with a safety first approach and the newer methodologies are most likely to be adopted in early phase screening with regulatory safety testing remaining more conservative and more prudent.

There are many examples why this prudence is required. In microbiology, particular issues relate to the need for new antibiotics and drug resistant bacteria. This has resulted in fast tracking of antibiotic approvals to deal with this issue through a special FDA programme. A fast tracking issue was the fluoroquinolone antibiotic trovafloxacin which was first described in 1993 and fast tracked by the FDA for clinical use in 1999 but subsequently found to be hepatotoxic and subsequently withdrawn from use [7].

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Trials and tribulations of veterinary drugs

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In general terms, the discovery and development of drugs for veterinary use follows the processes and procedures used for human drug discovery. Some interesting differences do arise, however. For example, when developing veterinary drugs it is necessary to be aware of the great diversity in physiology and disease profiles of the various species of animals, birds and fish for which new drugs may be sought. Hence, veterinary drugs may need to be targeted at specific species, rather than just for animals in general. Routes of delivery also can be very important – for example it is desirable to treat fish through the water, or chickens either through the oral or respiratory routes, rather than having to handle large numbers of individuals.

A clear advantage for developing veterinary drugs over human drugs is the possibility of testing them for efficacy and safety in the target species within the early stages of drug development. A disadvantage for veterinary drugs is that their retail price is limited by the actual and perceived value of the animal, and this constraint can greatly reduce potential profitability (and hence investment in drug discovery).

For production animals of relatively low economic value, such as chickens and