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

David Hampson
Division of Veterinary and Biomedical Sciences
Murdoch University
Murdoch, WA 6150
Tel: (08) 9360 2287
Fax: (08) 9310 4144
E-mail: D.Hampson@murdoch.edu.au

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

pigs, this is a major constraint, and total profitability for the drug company is based on high turnover associated with the clear economic benefits of the product. On the other hand, the market value of drugs for companion animals such as dogs or horses can be higher (although usually less than that for human beings).

Safety concerns are generally less for drugs for companion animals than they are for human drugs. For production animals, however, safety concerns are not just limited to the species themselves, but to the human consumers of the products from these animals. Furthermore environmental concerns may be greater for production animals, where large volumes of drugs may be used and be excreted into the environment.

Traditionally, human safety concerns associated with veterinary drugs have focused on the possibility of drug residues being present in animal products. In the case of antimicrobial drugs, this has been expanded to consider the possibility of the development of drug resistance and its transmission via resistant microorganisms or resistance genes, ultimately to impact on human health.

Given such broad-ranging concerns, it is not surprising that there is now limited interest in developing and registering new antimicrobial drugs for use in production animals.

Despite such difficulties, a new antimicrobial has recently been developed in Australia and been registered for use to control diarrhoea in young commercial pigs. CHEMEQ^{RTM} polymeric antimicrobial was discovered and developed by Dr Graham Melrose, working in Western Australia. Following his original idea for the new antimicrobial polymer, which was based on his extensive knowledge of polymer chemistry and activity, in 1986 Dr Melrose obtained provisional patents over the concept.

Literally working in a tin shed in north Fremantle, using personal money and money invested by friends, Dr Melrose developed and improved the manufacturing process. In 1989 he and his wife Olga established Chemeq Ltd, and shortly afterwards started to collaborate with the academic staff at Murdoch University to evaluate the efficacy of the drug in controlling diarrhoea in pigs (other studies were undertaken to evaluate its use in industrial and other settings). A number of animal trials confirmed that the antimicrobial polymer was safe, and had considerable potential for controlling intestinal bacterial infections.

By mid 1999, the company had lodged around 25 patents, and at that time became listed on the ASX. A pilot manufacturing plant was established in 2000.

In 2001 the FDA proposed fast-track approval for the polymer. The basis for this fast-tracking of the application process was that antimicrobial resistance problems were being recorded for many other antimicrobial drugs, and that alternatives to these were needed (CHEMEQ^{RTM} polymer has a novel model of antimicrobial activity, so that resistance problems are not anticipated).

In 2002, CHEMEQ^{RTM} polymer received regulatory approval for use in South Africa and New Zealand, and field trials indicated that it was effective for controlling diarrhoea in pigs. A manufacturing facility is now being constructed in Rockingham, south of Perth, and will start full production by mid 2003. Applications for regulatory approval for use in pigs are underway in Australia, the USA and a number of Asian countries. Applications for its use in poultry will follow.

The process of drug development from an initial concept to the first sales (from a company now worth around $200 million) has taken around 20 years, and has required an enormous effort and commitment from Dr Melrose and his supporters. The process did not start by seeking a drug to control piglet diarrhoea, and its application in this context was largely fortuitous. Nevertheless, the outcome has been good for Australia, with a new Australian pharmaceutical manufacturing company taking its place on the worldwide scene.

Figure1: Aerial view of the new Chemeq Ltd manufacturing plant being built in Rockingham, south of Perth (artist's impression).