

recommendations on establishing antimicrobial stewardship programs and on the role of pharmacy services in antimicrobial stewardship. The publication is also available on the Australian Commission on Safety and Quality in Health Care web site along with other resources to assist hospitals implement antimicrobial stewardship programs <www.safetyandquality.gov.au/internet/safety/publishing.nsf/Content/PriorityProgram-03_Antimicrobial-Ss>.

I urge all pharmacists to read the publication and play their part in the global challenge to combat antimicrobial resistance.

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Death of the 'Blockbuster' and 'Pivotal' Clinical Trial: Rethinking the Drug Development Process

Unprecedented developments in genomics, proteomics, immunology and cellular biology have promised a plethora of new targets for pharmacotherapy. The hope has been that targeting pharmacotherapy to the individual patient based on the molecular characteristics of their diseases and/or genetic polymorphisms relevant to drug metabolism and toxicity will lead to superior clinical outcomes. But while this promise has been realised in the treatment of a limited range of malignant disorders (such as chronic myeloid leukaemia), for the most part pharmacogenomics has failed to impact significantly on the major chronic diseases of the developed world, particularly neurological and cardiovascular diseases. In fact, those tracking the performance of the pharmaceutical industry have observed that despite the promise of a 'genomic revolution', the 'pipeline' of new drug registrations has been reduced to a 'trickle'.¹

At the same time, the cost of bringing a medicine to market has ballooned, a recent estimate for a new chemical entity was US\$1.3 billion in 2005 dollars.² The risks involved for the pharmaceutical and biotechnology industries are astounding, of every 5 to 10 thousand discovery compounds, around 250 enter pre-clinical work-up, 5 make it to 'first-in-man' studies, and only one of these will make it through clinical development, with the chance of success declining yearly.³ The time taken to research and develop has also increased. New drugs that were registered by the US Food and Drug Administration from 2003 to 2007 are entering clinical practice after 3 to 6 years of discovery and pre-clinical development, and an average of 6 to 9 years in clinical development.⁴ The cost and complexity associated with running the mandatory large phase 3 clinical trials has also become increasingly prohibitive. Increasing regulatory requirements and demands for cost-effectiveness studies; the need to account in study design for sub-populations with different genetic profiles and test different combinations of drugs; and the escalating difficulty of recruiting for chronic illness studies all add time and cost to the process.⁵ Even when a new drug is successfully registered, only 3 out of 10 pharmaceutical manufacturers will recover the cost of their development and many of these falter when low frequency, but serious, adverse reactions start to appear once the drug is released on the market.⁶

At the same time, many of Big Pharma's over 30 current blockbusters (drugs that earn more than US\$1 billion in sales per annum), such as Lipitor (atorvastatin, US\$14 billion per annum), Singulair (montelukast, US\$4 billion per annum) and Plavix (clopidogrel, US\$8 billion per annum) have either come off patent recently or are just about to.¹ While, pharmaceutical companies have acted to try and maintain their profitability by seeking to reduce costs and acquire (rather than develop) the next (patented) 'blockbuster' through complex mergers and acquisitions, it remains unclear whether their efforts will ultimately be effective. Given these challenges, it is not surprising that over the last decade the stocks of Big Pharma have declined precipitously as investors give preference to more rapidly realised and less hazardous investments.¹

What is becoming clear, from both an industrial and a bioscientific perspective, is that the current model of drug development may need to be radically rethought if it is to continue to deliver effective pharmacotherapies.

A number of organisational, systemic, technical and conceptual changes are required. Organisationally and systemically, there is a need to better coordinate the pre-clinical science disciplines, e.g. to 'rationally' identify ideal drugs for specific sub-populations and to develop better surrogate measures to predict late-stage failures such as hepatotoxicity.⁷ There is also a need to adequately reward those whose work supports the discovery and early development of new medicines (e.g. through innovative public-private partnerships). Additionally, Pharma needs to be more willing to outsource to, and partner with, a range of public and private organisations in order to share its risks, increase its rates of success, and attract new investors.

Conceptually, there needs to be a willingness to give up on the idea of the 'pivotal' phase 3 randomised controlled trial, in favour of a diversity of approaches that involve analysing the totality of the evidence base, including 'real world' studies. Where populations are likely to become smaller as they are defined more and more accurately by genetic polymorphisms it will become both impossible and unnecessary to demand large scale randomised controlled clinical trials, systematic reviews and meta-analyses of clinical data. It is noteworthy, that Sir Michael Rawlins, head of the UK National Institute of Health and Clinical Excellence stated in his 2008 Harveian Oration that randomised controlled trials should no longer be considered the gold standard for evidence in support of registration.⁸

Another necessary conceptual shift will involve enriching our understanding of risks and benefits, especially as experience of the medicine in 'real world' settings evolves. Those investing in medicines need to use new information technologies (such as the eHealth record) to consider the 'therapeutic index' of a drug at each stage of its development lifecycle and regulators need to be more willing to accept such data. And those using medicines – clinicians and the public – particularly where they desire earlier access to medicines must learn to trust medicines information that is generated through 'real world' (post-marketing) safety research.

These transitions will not be easy. Organisationally and economically, the drug development process still privileges those who promise the next blockbuster (thereby supporting marketing, rather than research, and 'disease-mongering', rather than disease amelioration). And the entire evidence-based medicine 'movement' with all its substantive and rhetorical power remains tied to increasingly simplistic ideas of 'populations' and to established hierarchies of research evidence, which privilege systematic reviews and meta-analyses of randomised controlled trials of drugs for large populations.⁹

Nonetheless, unless these occur, unmet medical needs will remain that way and too many good 'leads' will remain unexploited. Those interested in quality use of medicines should, therefore, identify and promote better ways to discover and develop needed medicines that are safe, effective and affordable. We in hospital practice are a vital cog in the process, notably through our contribution to clinical research (both pre- and post-

marketing) and we need to be fully committed to such research. The publication of the Commonwealth's Clinical Trial Action Group recommendations earlier this year is very welcome and worthy of close attention by everyone involved in the clinical research enterprise.¹⁰

The institutions that make clinical research a strategic priority are too few in our country which, given our reliance on innovation to solve our unmet health needs, is an attitude we should try to alter.

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