Editors' view

Medicines regulation and clinical pharmacology

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In December 2003 the Clinical Section of the British Pharmacological Society organized a symposium on 'Medicines Regulation and Clinical Pharmacology in the 21st Century' at its annual winter meeting, held at Guy's Hospital and hosted by the Department of Pharmacology of Kings College London. Papers from a selection of the presentations are published in this issue of the *Journal*.

Clinical pharmacology and medicines regulation are inextricably linked. First, the search for new medicines and new indications for old medicines is based in clinical pharmacology. Secondly, two of the most fundamental principles of clinical pharmacology, establishing a safe and effective dose range and critical evaluation of the complex data that underpin optimal drug use, are also the cornerstones of medicines regulation. Clinical pharmacologists are involved at different stages and in various guises during the regulatory process. Regulatory agencies employ them as assessors of drug applications, and independent advisory bodies, such as the Medicines Commission and the Committee on Safety of Medicines (CSM) in the UK and the European Committee on Human Medicinal Products (CHMP) are well supplied with clinical pharmacologists.

In the first two articles in this issue we read about the formation and work of two important organizations whose chairmen are clinical pharmacologists. Alasdair Breckenridge (pp. 571–4) writes about the Medicines and Healthcare products Regulatory Agency (MHRA), which was formed last year by combining the Medicines Control Agency and Medical Devices Agency, and

Michael Rawlins (pp. 575–80) writes about the National Institute for Clinical Excellence (NICE). Medicines regulation is defined in relation to the provision of medicines that are safe, effective, and of high quality, and these considerations underpin the safeguarding of public health. Both Breckenridge and Rawlins stress the relevance of their organizations to public health and the challenges that they face at a time when fewer new drugs are reaching the market and public expectations are on the increase.

Figures recently published by the US Food and Drug Administration show that the numbers of new licence applications submitted to them fell from about 70 per year in 1993 to under 15 in 2003 [1]. The reasons are complex, but in their report the FDA point to the fact that 'the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences'. They partly blame the way in which the reductionist approach, 'knowledge at the gene, gene expression or pathway level' has been fostered at the expense of the systems approach, and they call for 'strengthening and rebuilding [of] physiology, pharmacology, [and] clinical pharmacology'.

This is put into context by the next three papers in this issue of the *Journal*, which deal with important aspects of practical drug development. Garattini and Bertelé (pp. 581–6) point out that only 10–20% of the drugs that reach the market offer 'substantial advantages' over existing ones, and they give three examples purporting to demonstrate this. For instance, they cite the ALLHAT study as evidence that there is little advan-

tage to using an ACE inhibitor or a calcium channel blocker rather than a thiazide-like diuretic to treat hypertension. That is certainly true if monotherapy is your aim. However, there is evidence that combinations of different classes of antihypertensive drugs in standard doses can be as effective as the usual dose of a single agent, with fewer adverse effects [2].

What the figure of 10–20% shows is how wasteful drug development is, because of our inability to predict which drugs will be successful and which will not, until they have been developed and tried. Take for example, the following list of the 15 oral beta-blockers that are included in the current issue of the *British National Formulary*:

- propranolol, sotalol • oxprenolol, pindolol, acebutolol, atenolol ••• timolol, metoprolol • labetalol, nadolol ••••• celiprolol ••••• esmolol •••• bisoprolol, carvedilol ••• nebivolol •

The drugs are presented in chronological order of their first appearance in the published literature (data from Pubmed). Each of the dots represents another beta-blocker that has not made the grade. Although these 15 drugs represent only 27% of the grand total of 55 beta-blockers, they represent 86% of the total published literature on beta-blockers. Even omitting propranolol, which has the lion's share of publications, the other 14 represent 73% of the literature on the total of 54 beta-blockers. It could be argued that even among the 15 named drugs several did not offer 'substantial advantages' over their predecessors, and that the main reason that so many beta-blockers have been developed is simply that even a small share in a blockbuster market can be very profitable for a drug company. On the other hand, since no two beta-blockers are exactly alike, whether because of partial agonism or some secondary pharmacological property, having a choice may provide additional advantages for some patients.

Garattini and Bertelé also cite the example of typical and atypical antipsychotic drugs and correctly point out that emphasis on the lack of extrapyramidal effects of the latter has diverted attention from the weight gain that they cause. However, it is not clear what the benefit to harm balance is in this comparison, because we do not know to what extent the weight gain caused by the atypical drugs increases the risk of cardiovascular disease or diabetes later in life and how that compares with the relative freedom from extrapyramidal effects that they confer. A better example is that of the NSAIDs, highlighted by Becker *et al.* (p. 587–600). They point out that the COX-2 selective drugs seem to be a little

more gastroprotective than their non-selective ancestors, but also prudently remind us not to ignore the cardiovascular risks, first highlighted 4 years ago. The recent withdrawal of rofecoxib from the market has hammered that message home.

Finally, Walker (pp. 601–8) reminds us of the importance of careful pharmacokinetic and pharmacodynamic studies in drug development.

There are various potential solutions to the diminishing number of new licence applications. The FDA has called for a ‘new product development toolkit’ with collaboration across industry, academe, and the regulatory authorities [1]. The tools that they highlight are those of bioinformatics, genomics, imaging technologies, and materials science. In his article, Breckenridge gives an excellent example of a genomic marker of an adverse drug reaction, abacavir hypersusceptibility in association with HLA B57. Discoveries of this sort may lead to earlier recognition of adverse effects, allowing selective prescription, avoiding medicines in susceptible individuals. The teasing out of such susceptibility factors may also allow new medicines to be marketed that would otherwise fail because of toxicity, and may yield information that will inform the development of safer drugs. Another approach is to search for new uses for old drugs, as implied by the observations of Garattini and Bertelé. Whatever approaches are used, there is no doubt that clinical pharmacologists will play important roles.

Many clinical pharmacologists contribute to the discovery and development of medicines, but may be less familiar with the roles they can play in the regulatory and post-authorization phases. For example, the wider availability of medicines for chronic conditions without the initial intervention of a physician has complex implications in terms of cost-effectiveness and the balance of benefits and harms. These require the same intellectual rigour in decision making as the assessment of a novel drug, if the potential benefit to public health is to be maximized. We hope that this selection of papers will broaden the horizon of readers relatively unfamiliar with medicines regulation and how it is informed by clinical pharmacology.

References

- 1 US Food and Drug Administration. Challenge and opportunity on the critical path to new medical products. 2004. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html> (accessed 22 October 2004)
- 2 Aronson JK. Live long and prosper: a mass strategy for treating the factors associated with ischaemic heart disease and stroke. *J Med Screen* 2004; 11: 1–2.