

Submission to UK Royal Society Project on Pharmacogenetics from the Population Health and Use of Medicines Unit, St Vincent's Hospital and UNSW, Sydney, Australia

This submission outlines the process by which high cost biological drugs have been made available through the Australian national health system. It recognises that pharmacogenetics (including target identification; transport system; optimization of pharmacokinetics) has broad application in optimising outcomes of drug use.

The submission is focused on how pharmacogenetics has been, or could be, employed to guide access to a drug in Australia via the Pharmaceutical Benefits Scheme (PBS) using cost effectiveness evaluation. While the UK health system differs from the Australian, all health systems are grappling with access issues.

Our comments refer in the main to dot points 3 and 4 in the outline of the scope of your program in your call for information, relating to “social, ethical, legal and regulatory issues and the mainstream health system”. We also consider there are implications from our recent experience for “future clinical trials” (dot point 2 in your call for information) and for “relationships of regulators and industry consistent with those social, ethical, legal and regulatory issues.”

- **Evidence based approach to cost-effective targeting of high cost biologicals.**

The Australian Pharmaceutical Benefits Advisory Committee (PBAC), constituted as a Statutory Committee under the National Health Act, makes its recommendations to the government for placing drugs on the Pharmaceutical Benefits Scheme on the basis of comparative clinical efficacy, safety and cost-effectiveness. It values “health outcomes” not “products”. Given the very high price of the biological therapies, it has been argued that alternative models of access are needed, as the products are most unlikely to prove cost-effective in all patient groups. However the PBAC has thus far retained the same processes for these new therapies as apply to all new applications from sponsors.

To date, two strategies have been implemented through the PBS in an attempt to improve the cost-effectiveness of biological agents. The strategic options depend critically on the evidence as to the mechanism of action for the drug.

(1) *Population targeting backed by a collaborative stakeholder model:* The aim is to identify the subset of the population for which the drug is likely to be cost-effective compared with the main available treatment (which may be placebo where there is no standard pharmaceutical treatment). In the absence of specific evidence as to a precise genetically based mechanism of action, the PBAC has developed a collaborative model, working with the key stakeholders of the relevant branch of the medical profession and representatives from the pharmaceutical company and consumer organisations to specify restriction rules to govern subsidy, consistent with evidence that the outcome is of acceptable cost-effectiveness. The restrictions include detailed

initiation and continuation rules and require patients to sign a patient agreement form indicating that they understand the restriction and acknowledge that PBS-subsidised treatment will cease if the predetermined response criteria do not support continuation of PBS-subsidised treatment. This has been the basis for listing, for example, of the tumour necrosis factor-alpha inhibitor class of biologicals such as etanercept, adalimumab and infliximab as well as for anakinra, the interleukin 1 receptor antagonist. There are potential ethical issues in this form of targeting which relate to withdrawal of an effective therapy from patients who gain less than 'adequate' benefits. It is an imperfect way of targeting. Nevertheless it is ethically preferable to not making an effective drug available through the Pharmaceutical Benefits Scheme (or its equivalent in other jurisdictions) at all. It should be noted that population targeting using a collaborative model can be applied whether or not there is genomic basis to the targeting.

We submit to the Royal Society that:

1.1 The collaborative model which backs up population targeting in the current Australian system is a partial solution to the ethical concerns and could be useful in other jurisdictions. The more usual adversarial model is unlikely to achieve the same adherence to the difficult clinical situation inherent in population targeting.

1.2 We believe it is critical for research to be conducted to evaluate the collaborative process and outcomes of population targeting: a Ph D student working with one of us is currently engaged in such an evaluation for the tumour necrosis factor-alpha inhibitors. We recommend that future funding for policy-oriented research in parallel with scientific research is encouraged by your Enquiry.

1.3 It will be critical to evaluate how well a drug is targeted in practice using data from administrative databases. The studies of drug use and patient outcomes should be established at the outset.

As reimbursement authorities come under increasing pressure to fund new high cost biotechnology and other innovative, targeted therapies for the prevention and treatment of previously unmanageable diseases, health outcomes research will play a critical role in policy decision-making. This will require high-level cooperation of administrative databases which are usually not set up for such drug use evaluation studies. An example for us in Australia has been the evaluation of the use of transtuzimab, which was funded in 2001 by the Australian government for a period of four years and is now being reviewed.

(2) *Molecular targeting:* On the recommendation of the PBAC the Australian government has listed gefitinib from December 1 2004. The listing includes the requirement that "there is evidence that the patient has an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material. The

mutation(s) must be demonstrated by analysis of the DNA sequence of the EGFR gene.” This is the first time such a recommendation has been made in Australia. We are unsure if it has been applied in other jurisdictions. An important limiting factor in the wider use of molecular targeting in practice is that it is not universally required to be included in the drug developmental process. Moreover the mechanism for identifying the target population is not coordinated with the drug developmental process. This problem must be resolved if reimbursement is to be effectively targeted to the true target population. The clinical trials for therapies which may be guided by genomics do not necessarily pursue the target group where efficacy and safety may be most clearly observed. Data dredging or government funded research after the fact in an attempt to satisfy a reimbursement authority is clearly unsatisfactory. In a global industry Australia can do little to alter this situation, whereas your enquiry may have a global impact.

We respectfully submit to the Royal Society Enquiry that:

2.1 The ideal option for cost effective targeting of biological therapies to which we can apply a genomic basis is pharmacogenomic analysis, including molecular targeting. Indeed the argument can be easily made that this is the most ethical approach.

2.2 Molecular targeting should be an integral part of the drug development process, required as part of the early phase studies used for registration purposes.

2.3 The mechanism for identification of the target needs to be developed in parallel with drug development. This parallel development should be required as part of the registration process.

There is an ethical concern about genetic testing where the testing is done to detect the possibility of future disease, that there may be misuse of information. However, this concern does not logically apply where the disease is present and the genetic testing is done in order to ensure that good medical care can proceed. Indeed the potent ethical concern would seem to be to avoid exposing patients dying from their cancer to unnecessary treatment that it would be possible to avoid. In the case of gefitinib there was evidence of a highly variable response rate in the clinical trials and convincing published evidence^{1,2} that identification of the activating mutation of the EGFR gene would allow for targeting gefitinib to the population of patients who are most likely to achieve at least a partial response.

More generally, the nature of the characterisation of the target might depend on the type of therapeutic agent. For example, in the case of the EGFR tyrosine kinase inhibitors mutations may be important as the aim is to inhibit receptor activity and mutation may in itself may influence binding, conformation, etc. In the case of anti-EGFR antibodies, levels of expression of the receptor but not mutation may be the

important factor, although this is not yet definitive. The different assays required to identify these potentially predictive factors have different cost/logistic implications.

- **Two other strategic options not confined to biological therapies also exist:**

(1) **Price reduction:** In Australia this option is available for companies seeking to improve the cost-effectiveness of the drug in the requested restriction, since the PBAC makes its recommendations direct to the Minister. This option is not available in jurisdictions such as the UK where the evaluation of the drug is made quite separately from government processes. The Australian PBAC has offered this option to sponsors, when a drug is considered to be clearly very effective (at least in some patients) but also clearly *not* cost-effective.

(2) **Pharmacogenetic tailoring** to improve drug selection and optimal dose where the absorption, distribution and transport across membranes, metabolism or excretion are important to its clinical efficacy and toxicity and therapeutic index.

This option has not been applied in the Australian system for PBS listing but could maximise the chances of obtaining the desired drug effect. All patients might qualify for treatment but the dose/schedule might need to be adjusted, as opposed to a treatment that is an all or nothing qualification.

For example, inclusion in restrictions of a requirement for genetic testing of the cytochrome 2D6 isoenzyme for drugs where this pathway of elimination had been identified in pre-clinical development could in principle be offered to a sponsoring company. In this circumstance, testing for genetic polymorphisms may hold the key to reducing toxicity or enhancing efficacy. This could achieve more appropriate dosing and thus be of benefit to patients and doctors. An example is the identification of responders to perhexiline in angina where a benefit for a sub group of patients can be achieved with a much lower dose without the dose-related adverse effects. Warfarin is another important example.

There are many drugs for which pharmacogenomic tailoring may improve clinical practice. There will be some instances where this may be useful as a requirement for PBS listing as a means to guide access. However an evaluation would be useful to inform policy and clinicians.

In summary, good medical care and good health policy will correctly target the people who will have the benefit and specifically identify people where there will be no likely benefit or where there may be a high probability of adverse effects.

References:

1. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 2004; 304:1497-1500
2. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; 350:2129-2139