The Academy of Medical Sciences | FORUM

Safer Medicines Report

Pre-marketing (Clinical Phase I, II and III) assessment
Working Group report

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Key recommendations

Centre for drug safety

It is clear that there is currently only limited sharing of expertise, experience and information about drug safety gained from research studies between pharmaceutical companies. Such cooperation would improve understanding of drug safety and increase patient safety. There is, therefore, a need for a centre of excellence that would focus on drug safety. This centre could have a single location or more likely comprise a network of key facilities (perhaps using a 'hub and spokes' model). The centre would be formed from representatives of Academia and Industry, permit free exchange of information between scientists, toxicologists and clinical pharmacologists, and act as a repository of expertise in all aspects of safety evaluation in drug development. A role for this group should be considered in commissioning or undertaking research programmes in drug safety.

Clinical pharmacology

There is currently a widely recognised decline in the number of senior posts in clinical pharmacology and therapeutics, in sharp contrast with the other medical subspecialties, all of which are expanding. The 'visibility' of clinical pharmacology to potential clinical trainees is also reduced, because of changes in both undergraduate and postgraduate training. There is an acute need to reverse this trend, and to develop additional training opportunities, to strengthen the specialty. Clinical pharmacologists have a key role to play in improving quality prescribing, in the regulation and post-marketing assessment of medicines, and in the scientific investigation of the clinical potential and safety of potential new medicines.

Public Engagement

There is a gulf between what is recognised as a 'safe' drug by regulators and the perception of the general public (and indeed most clinicians). With support from the media, all drug withdrawals after licensing are seen as weaknesses of the system by the public, and often as scandals, rather than an inevitable consequence of a process that can never guarantee complete safety, and in which confidence of safety can only be achieved with exposure of a very large number of subjects to a drug. There is, therefore, a need for a dialogue with the public to improve understanding of drug safety, and engage them in the process. As a separate issue, all of us are likely to need medicines at various times through life, and it would be valuable if there was greater recognition of the importance for the public to engage with, and where possible become directly involved in, clinical research.

Chapter One - *Introduction*

The issues

1.1 Drug discovery has undergone major changes in the last two decades. A new drug is more likely to arise from screening chemicals against a molecular target than from observation of an effect on physiological systems. In many cases, relatively little may be known about the biological effects of manipulating pharmacologically the molecular target in vivo.

1.2 That said, clinical studies of new drugs in the pre-marketing phase have an extremely good safety record. In part this is because of the effectiveness of preclinical safety testing and because decision makers err on the side of caution when interpreting the data. It is also recognised that subjects are carefully selected for clinical trials and closely supervised, with clear pre-defined limits of dose-exposure.

1.3 It is a sorry and expensive fact that most New Active Substances (NASs) taken into humans fail to progress through to licensing. Recent data from the Centre for Medicines Research suggest that the failure rate is increasing. A study of 27 pharmaceutical companies (representing 79% of R&D expenditure in 2001) revealed that during 1997–2001, over 80% of NASs taken into man were terminated prior to reaching the market. Forty percent were terminated in Phase I and 43% in phase II. Seventeen percent were terminated during late development when costs are high. The major reasons for termination were concerns over clinical efficacy (30%) and portfolio considerations (28%). About 17% were due to concerns over safety and the remainder because of unsuitable pharmacokinetics and findings from toxicology.

1.4 Drug withdrawal post-marketing is not only expensive but often has a high profile in so far as it may receive widespread publication by the media. This can be unbalanced and inaccurate and increases anxiety in the general public.

1.5 Data on the reasons for drug withdrawal post-marketing are few. In a recent review of drug withdrawals worldwide over the past 4 decades, the top five safety reasons for withdrawals were: hepatic (26.2%), haematological (10.5%), cardiovascular (8.7%), dermatological (6.3%), and carcinogenic (6.3%) issues. Among the 87 products for which the timing of marketing was available, the median time on the market was 5.4 years, with about one-third withdrawn within the first two years. These data include the withdrawal of drugs that had received approval outside of Europe and USA. Information on drugs approved by European and USA agencies suggest a lower incidence of hepatotoxicity.

1.6 There is a need to reduce the failure rate during drug development while improving the safety of those drugs that come to market.

Challenges

1.7 Clinical trials are the cornerstone of drug development in modern medicine (see appendix 1). Most studies of new drugs in humans begin with studies in healthy volunteers who are given incremental single doses from a low starting level (there are exceptions where a compound may be too toxic to administer to healthy subjects, for example, some drugs used to treat cancer – see appendix 2). Subjects are carefully screened and closely monitored (including blood counts, liver function tests, plasma electrolytes, urine analysis, ECGs, and blood concentrations of the investigational drug). From these Phase I studies, which provide data on safety and tolerability and some evidence of pharmacological activity, a dose range is selected for repeat dosing studies, usually in healthy subjects, moving to patients suffering from the target disease but free of other illnesses that might complicate interpretation. These Phase II and III studies are designed to investigate drug efficacy, while collecting data on safety. The studies are conducted by experienced, well-briefed and motivated investigators following well-defined protocols. However, practical and cost

constraints on sample size, the strict inclusion/exclusion criteria and the fact that some adverse events are very rare mean that clinical trials have their limitations. This contrasts with the fact that licensed drugs are prescribed to less well phenotyped patients who are often not represented in the subject group(s) studied during development because of age, co-existing disease and concomitant drug therapy.

1.8 Drugs directed at novel molecular targets present particular difficulties when designing safety and efficacy studies. On the one hand, knowledge of the drug target permits an assessment of the specificity of the drug and may provide insight into the type of patient that might or might not respond. Some oncology drugs are examples of this. On the other hand, little may be known about the biology of the target and, more importantly, the effect of interfering with its function on safety. Recent experience with the cyclo-oxygenase-2 (COX-2) inhibitors illustrate the problems that can be encountered with introducing a new class of drugs.

1.9 The timeline of drug development is usually consecutive, with progression dependent upon the results of previous studies. A striking feature of this approach is the difficulty at any point of predicting the ultimate success of a novel candidate. In addition, the various studies that make up the registration package are often the responsibility of different groups in industry, with teams of people aligned by project or therapeutic area. In some cases there is a lack of an integrated approach within a project. Here there is a risk that little is learned about what questions have been asked or answered until the regulatory authority considers the submission for a marketing licence. In many cases, there is little sharing of experience between project teams. This slows down development as problems are revisited and lessons are relearned and inhibits the potential progress that may be made from pooling experience and ideas about mechanisms of toxicity.

1.10 A common problem with drug development is establishing the 'right dose'. Small subject numbers which include responders and non-responders coupled with the desire to see an effect may introduce a systematic error in the R&D process, forcing the selection of too high a dose.

1.11 Concerns about the effect of drugs on cardiac conduction have received a lot of attention. All are carefully screened for an effect on QT interval and their development is terminated if there is evidence that QT interval may be prolonged. This is erring on the side of caution as not all drugs that prolong QT interval have a high risk of causing arrhythmias (e.g. amiodarone). Bone marrow suppression, hepatotoxicity and idiosyncratic reactions are other common safety concerns. Preclinical screening for bone marrow and immunosuppression is effective. Decisions about the clinical implications of limited rises in liver enzymes are very difficult and limited guidance is available. It is widely recognised that the detection of idiosyncratic reactions is extremely difficult, as they are uncommon and unpredictable (and hence unlikely to be detected in the number of patients exposed in pre-marketing studies), and there are no animal models.

1.12 While there has been investment in molecular science, applied clinical science and toxicology have been neglected and the skill base in these disciplines has shrunk. The skill base for taking drugs through clinical development is thin. There is a need for more clinicians to be trained in clinical pharmacology and clinical research methodology. Clinical pharmacology is disappearing as a distinct, taught discipline in most if not all medical schools and the service-orientated approach to clinical training is reducing recruitment to clinical research. In addition there is a need for mathematically-minded biologists and systems biologists who are needed to integrate information about the drug from different sources.

1.13 It seems inevitable that the complete safety profile of a new drug will not be available until the product is exposed to a sufficiently large population post-marketing. While this should lead to caution when prescribing a newly licensed drug, this is counter to the Pharmaceutical Industry's aim of recouping on their investment as quickly as possible.

1.14 The general public have unrealistic expectations of what is possible with respect to drug safety. The fact that all drugs have the potential for adverse effects and that there needs to be continuous evaluation of drug safety may be unacceptable to the general public who have a poor perception of risk and an unrealistic expectation of safety when it comes to drug therapy.

1.15 In addition, the increasing potency and selectivity of novel biopharmaceutical agents means that it is likely that patients will be involved increasingly in very early phase studies. Recruitment for such studies will be easier if there is a wider acceptance in the general community that taking part in clinical research is a 'normal' and acceptable thing to do.

Opportunities and solutions

1.16 Drug development is an opportunity for greater creativity in disease-specific trial design. Information needs to flow from discovery into clinical studies and clinical studies need to be designed with the right questions in mind. This can be achieved by:

(i) Reducing the barriers between different project teams within Pharmaceutical Companies, through more open discussion of knowledge as it is acquired during the development process.

(ii) Greater sharing of information on drug safety between companies, while protecting intellectual property rights.

(iii) Closer links between Industry and Academia drawing on expertise from both sides.

1.17 Lessons can be learnt from the more scientific approach taken to assess biologicals, and from the R&D advances in some therapeutic areas (particularly cancer – see appendix 2). Here the traditional approach to drug development has had to be re-visited and there is a greater tendency for Academia and Industry to work together. Many biotech companies arose from and maintain close links with Academia. In cancer medicine, organisations such as CRUK and NTRC support the coupling of drug discovery and development in an academic environment.

1.18 There is a resurgence of interest in '*Experimental Medicine*' which employs an intelligent, question-based approach to drug development (see Cohen and colleagues, Scrip Magazine, May 2003). Detailed questions depend on the particular drug under consideration but the essential elements are as follows:

- *Does the biologically active compound/active metabolite get to the site of action?* This covers not just the kinetics of the drug but examines penetration into tissues (such as brain, tumour tissue) at the level of the molecular target.

- *Does the compound cause its intended pharmacological/functional effects?* This examines the mechanism of action of the drug, providing a better understanding of how the drug might best be used.

- *Does the compound have a beneficial effect on the disease or its pathophysiology?* This is traditionally asked in Phase III studies but should also consider effects on other physiological systems that might lead to side effects.

- *What is the therapeutic window of the new drug?* This examines the optimal dose and dosing regimen.

- *How do the sources of variability in drug response in the target population affect the development of the product?* Considering such sources as formulation, compliance, pharmacokinetics, pharmacodynamics, genetics, effects of the disease and co-existing diseases, other drugs and circadian rhythms.

1.19 This approach gives added value to studies of efficacy and is enabled by developments in applied basic science, which is providing a better 'toolkit' for studies in humans.

1.20 A recent report from the FDA has highlighted the need for a better "toolkit" for drug development. One important resource finding increasing use is imaging. Radioligand studies

are helpful in addressing questions about drug absorption and distribution. Positron emission tomography (PET) can be used to measure real time distribution of drugs in the human body as well as evaluating dose-receptor occupancy relationships in target tissues and so assisting dose selection for further studies. Accelerator mass spectroscopy (AMS) is also useful in pharmacokinetic work – it can be used to analyse drug and metabolite concentrations in humans after administration of micro-doses (human Phase 0 studies) in order to gain essential information on AUC, C_{max}, CL, V_d etc. There remain some concerns about whether the kinetics of micro-doses and pharmacological doses are similarly *in vivo*. These issues would need to be addressed before the widespread use of AMS is recommended. Modern imaging methods such as PET and functional magnetic resonance imaging can also be used to assess drug response; for example, the effect of a drug on tumour blood flow and viability. Using these technologies, data can be obtained in small numbers of patients and in a short time-frame (sooner than, say, waiting to assess a change in tumour size). This in turn allows decisions about drugs in development (go/no go, drug dose, etc) to be made more quickly and with greater confidence.

1.21 The Pharmaceutical Industry recognises the value of biomarkers in toxicity and efficacy studies and is putting considerable effort into identifying ones that are informative and well validated. Genomic, proteomic and imaging technologies in particular are being exploited with this in mind. These need to be developed and/or employed early on in the development process with a view to their utility in clinical as well as preclinical studies. Biomarkers have a particularly useful role in bridging the transition from pre-clinical to clinical studies, thereby enabling observations in pre-clinical studies to be followed up in humans. It would be helpful to have key indicators that inform effects on physiology rather than changes in structure (traditional histology). The Pharmaceutical Industry and regulatory authorities have a large database of preclinical and clinical data that can be mined to identify predictors of safety and efficacy. The value of some may be evident from the data available while a single additional trial may be all that is necessary to confirm the value of others.

1.23 Efficacy biomarkers could be used post-marketing to target drug use to specific patient subgroups that have been shown to benefit in early studies. One example is through the use of genomics to identify specific mutations or a particular pattern of gene expression and proteomics to detect a particular cell or tumour characteristic. Only patients with a biomarker demonstrated to be associated with a therapeutic response would receive the drug. This would assist doctors with prescribing and maximise the benefit to risk ratio for that patient subgroup. The use of metabonomics to identify metabolite profiles in patient urine that are indicative of response or toxicity also need to be further investigated.

1.24 The use of host genetic constitution to inform and predict drug response – a field of study known as pharmacogenetics or pharmacogenomics – is taking the lead in this regard. It is now routine practice to determine whether drugs are metabolised by polymorphic enzymes, for example CYP2D6, in preclinical studies. Currently, this knowledge may be transmitted into product information, but is not used to design phase I-III trials. The use of pharmacogenetic information in the design of trials may have several potential benefits: (a) better characterisation of the pharmacokinetics of the drug by studying genotypically distinct groups in phase I studies; (b) identification of sub-groups based on genetic polymorphisms that are responders to the drug from those that are non-responders in phase II studies; (c) the use of such data to design genotypically stratified phase III studies which may therefore be smaller and completed more rapidly than conventional phase III studies, thereby leading to cost savings. Although this strategy will not prevent the rare idiosyncratic reactions, it may allow an improvement in the overall benefit-harm ratio of the drug by identifying true responders and prevention of the more common dose dependent adverse reactions.

1.25 There is value in giving consideration to introducing new drugs in humans, a process which experience has shown is a relative safe

one for the subjects involved, earlier in the development process. Specifically, given that Pharmaceutical Companies may often have several related chemical entities as potential candidate agents, and it may not always be clear which will have the best characteristics for clinical development, it may be helpful to allow selection of a preferred drug at this early stage. In this situation, early comparative single dose studies for pharmacokinetics and dynamics might be supported by a more limited toxicological package that would not reduce safety but might allow the best medicine to be brought forward for further clinical development. This might lead to an overall reduction in animal use, in overall active drug exposure for volunteers, and increase the speed, efficiency and likely success of drug development.

1.26 Greater use can be made of computer modelling and simulation studies. This approach aims to maximise the information available from studies by integrating data from various stages of drug development. Using demographic, physiological, genetic and in vitro enzyme/transporter kinetic data, the knowledge base on a compound can be extrapolated and scaled up through biomathematical modelling to predict population pharmacokinetic-pharmacodynamic response. Such an approach permits the evaluation of heterogeneity and the active exploration of those who may be at risk. The prerequisite science base to conduct these studies is established and has FDA support but it is not widely used. A significant hurdle is the lack of sufficient scientists with appropriate expertise.

1.27 There is a need to strengthen and rebuild the relevant disciplines (notably physiology, pharmacology and clinical pharmacology) that bridge the path between the laboratory and the whole organism. In addition to providing training in traditional methods, there is a need to develop individuals with biomathematical skills and people creative in "proof-of-concept" studies that enable the rational assessment of drug activity in humans before a commitment to full-scale production is taken. This requires a commitment from Academia but also resources from Industry. This commitment extends to post-graduate development and supporting academic clinical research centres so that patients as well as healthy volunteers can be studied in an environment that meets current good clinical and research governance requirements.

Chapter two - *Proposals and recommendations*

Trial design

2.1 Drug development programmes should engage academics and individuals with specialist expertise at all stages of the development process to provide objective and critical insight into the design of studies.

2.2 There should be a centre of excellence for studying mechanisms of drug toxicity and providing guidance on the interpretation of toxicity data from early phase drug development. This centre may have one physical location or be networked but should include representation from Academia and Industry. It should be well resourced and encouraged and enabled to train. The current emphasis on disclosing data from negative as well as positive clinical trials should be encouraged and extend to sharing data on adverse events. A centre of excellence would offer a repository for such data.

2.3 The patients studied in early clinical trials need to be more representative of patients that will receive the drug once licensed. Genomics, proteomics and other technologies that permit the molecular classification of disease should be employed early on in clinical trials to identify those patient subgroups that respond best to a novel therapy. Individual variation in response to drugs should be identified early on in the development process, and this knowledge use to design trials in order to reduce the attrition rate and identify true responders. These technologies can then be used to identify the most appropriate patients to receive the drug post-marketing.

2.4 It is recognised that confining drug exposure to defined populations will improve the benefit risk ratio for a drug but may deny some the benefit of a drug. Furthermore, limiting exposure will reduce the possibility detecting unsuspected (idiosyncratic) adverse events. Regulatory authorities might consider fast tracking restricted approval of drugs that have been shown to benefit a specific patient subgroup (restricting the licence to that defined subgroup) while further studies are conducted in other patients in an attempt to extend the licence.

Biomarker and technology development

2.5 To facilitate the development of useful biomarkers, large databases from previous clinical trials and epidemiological studies on natural disease history should be mined to assemble existing data on the association of marker with outcome. Where there is an uncertainty in the relationship it may be possible to clarify the relationship in a single additional study.

2.6 Technologies such as PET, AMS and magnetic resonance imaging/spectroscopy should be developed and applied to assess the efficacy and safety of drugs early in development as valuable information can be obtained from exposing small numbers of subjects to the drug. This includes the dose relationship to drug binding in the tissue of interest and assessment of response through surrogate markers. Several questions need to be addressed that might extend the use of the techniques further, such as (a) the relationship between micro-dose PK and pharmacological dose PK, (b) whether micro-dose PK can be fed into *in silico* PK/PD models to better define the doses to be used in conventional Phase I studies and (c) whether combining AMS/PET studies permits PK and PD data to be obtained in one study. If the research programmes demonstrate the utility of the micro-dose approach and the data acceptable for regulatory submission, then it may be cost-effective to consider micro-dose studies for many first in human and first in patient studies.

Education

2.7 There is a clear need to support and encourage more training programmes in clinical

pharmacology, clinical investigation and in the broader field of biomathematics, especially as applied to pharmacology. Elements of this could be supported through the establishment of a national centre of excellence.

2.8 Both the general public and physicians need to be educated with respect to the acceptable level of risk associated with new drug licensing.

2.9 In view of the need to recruit suitable patients and for endpoints in clinical trials to reflect patient needs and values, a greater effort should be made to engage the public in trial design and methodology. The proposal is that a program is established to promote the value to society and the individual taking part in clinical research. It is worth considering establishing a national network for the recruitment of subjects into studies.

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Appendix 1- *Experimental Medicine in drug development*

It was hoped that the sequencing of the human genome would lead to the identification of a large number of new drugs targets and a cornucopia of important new therapeutic agents coming forward. The first expectation has been fulfilled with over 300 G-protein coupled receptors, 600 kinases and about 1000 proteases, many of them novel, revealed in the human genome. All of these are potential drug targets. But over the same time period the submission of new chemical entities and new biological therapeutic agents to the U.S. Food and Drug Administration has fallen progressively (Fig 2).

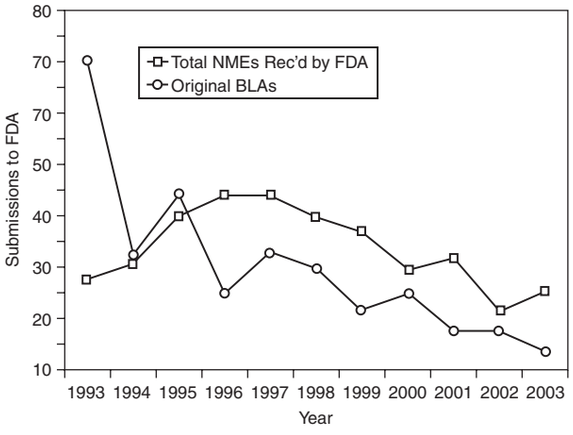

Figure 2: 10-Year trends in Major Drug and Biological Product Submissions to FDA

The figure shows the number of submissions of new molecular entities (NMEs)–drugs with a novel chemical structure – and the of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

Over the same period U.S. Pharmaceutical Company expenditure on research and development has risen sharply and at a higher rate than research expenditure by the National Institutes of Health, that is itself well ahead of inflation (Fig 1).

This situation has begun to give rise to considerable concern because, like it or not, the pharmaceutical industry is responsible for the discovery of many and the developer of almost all of the new medicines the world so badly needs. The United States Food and Drug administration had circulated a white paper entitled 'Innovation and Stagnation: Challenges and Opportunity on the Critical Path to New Medical

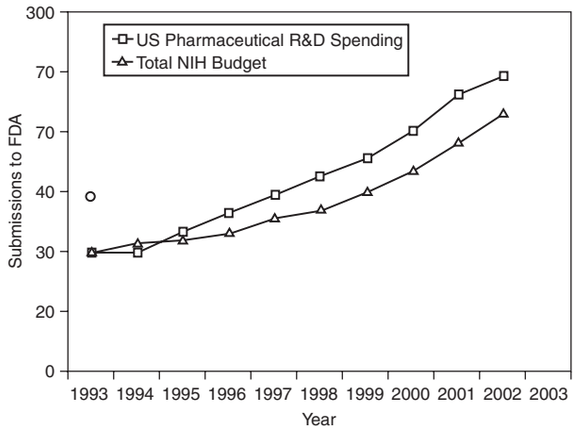

Figure 1: 10-Year Trends in Biomedical Research Spending

The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993–2003) and by pharmaceutical complnies research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003).

Products' (www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). Amongst the major causes of failure this paper identifies safety issues and lack of efficacy. The FDA paper places great emphasis on problem solving with new technologies such as imaging, biomarkers to establish efficacy. These will play a part but one of the core issues is targeting new therapies at deranged pathophysiologic mechanisms that are substantial etiologic factors in causation of the target disease. Answers to these questions will only come from intensive study in patients with the target disease, a type of medical research often known as 'Experimental Medicine'.

The early stages of drug development in man

Phase I

Most studies of new drugs in man begin with studies in healthy volunteers who are given incremental single doses from a low starting level. (There are exceptions where a compound may be too toxic to administer to healthy subjects, for example, some drugs used to treat cancer). The volunteers are very closely monitored for safety (blood counts, liver function tests, plasma electrolytes, urine analysis,

ECGs etc) and the blood concentrations of the investigational drug are also measured. Once a dose has been reached that attains a pre-set safety limit based on animal studies, causes safety concerns or a plasma concentration deemed sufficient for the desired action the single dose study ends. Other human volunteers will then participate in 14 day repeat dose study to obtain further data about safety and plasma concentrations. Where possible indications of pharmacological activity e.g. sedation, dry mouth etc will be sought but in healthy subjects only rarely can relevant evidence about possible therapeutic activity be obtained. It is only when these observations, often termed Phase I, are complete that the first studies of efficacy are undertaken in patients suffering from the disease against which the new drug is directed.

Phase II

Traditional phase II studies to establish efficacy involve selection of a group of patients suffering from the target disease but free of other illnesses that might complicate interpretation. The methods of measuring efficacy are usually fairly simple e.g. sygmomanometer blood pressure readings for hypertension, peak expiratory air flow for asthma, a rating scale such as Alzheimer's Disease Assessment Scale (ADAS)- cognitive (ADAS-Cog) for dementia. Depending upon the degree of variability of response the numbers of patients required to obtain a statistically significant indication of efficacy the numbers of patients needed may be quite large, for example about 300 for a new drug used treat schizophrenia.

The traditional method works well for drugs directed at a validated target but when the target is unprecedented the failure rate is very high (over 90% of projects that reach man, fail). It is for this reason that there has been a resurgence of interest in experimental medicine.

Experimental Medicine

Mechanism or efficacy?

Experimental medicine studies can be divided into two broad categories, (a) those intended to demonstrate that the proposed pharmacologic/ biochemical mechanism operates in man and (b) those designed to demonstrate that the new compound has efficacy in modifying the disease process.

Mechanism based EM studies.

Examples of mechanism based studies include the use of positron emission tomography with an ^{11}C labelled compound that binds to the target receptor or enzyme and constructing a dose-response curve to displace the radio-ligand with increasing doses of the unlabelled new drug. From such "cold-ligand displacement" data it is possible, for example, to calculate receptor occupancy in the human brain. Pharmacological challenge in another widely used method, for example the inhibition of the wheal and flare after intradermal histamine by an anti-histamine compound.

A different approach, that gives an early indication of potential efficacy, involves the use of a biomarker to obtain an early read out of an effect upon a mechanism linked to the disease progress. To demonstrate that a new drug for treating osteoporosis has a beneficial effect in preventing fractures can take 2 to 3 years. Measurement of type I collagen N-telopeptide fragments in the urine can be used as a biomarker of degradation of bone mineral matrix and a change in excretion may be demonstrable in a matter of days with a compound that inhibits bone resorption.

Mechanism based studies not only help to substantiate the mechanism in man but provide valuable information about the dose-response relationship.

Fast forward to man.

Development of new, rapid, methods of measuring drug action in man, especially using biomarkers is a very active area of research. The existence of a validated biomarker/imaging method etc can make it possible to bring forward to man a new compound with very limited animal safety data, for example, a 4 day study in rats. This may only provide safety cover for single doses in man but these may be sufficient to show whether or not an unprecedented mechanism shows some indication of modifying a disease process if there is a suitable biomarker. Sensitive new (and existing) biomarkers of adverse effects upon specific tissues (liver, kidney etc) also have considerable value

in monitoring safety in early studies, particularly when toxic effects have been demonstrated in animals at low multiple of the predicted human exposure. The existence of a sensitive biomarker for the type of tissue injury that is a cause for concern makes it much more acceptable to proceed with carefully monitored studies in man. The lack of one necessitates adopting a much more cautious approach.

Experimental Medicine studies of efficacy.

The objective of experimental medicine studies of therapeutic efficacy is substantially different from a traditional phase II study. The traditional phase II study is designed to be part of the smooth and rapid progression of a molecule from laboratory to market while demonstrating activity in as wide a range of disease severity, age, gender etc as possible. In contrast an experimental medicine study is a therapeutic assay using (a) sophisticated methodology designed to improve the accuracy of measurement, (b) a carefully specified patient group designed to minimise variability and increase the likelihood of response (c) measurement of the parent drug and any active metabolites in blood and use of sophisticated mathematical modelling to predict concentrations at the site of action and relate these to the measured response (PK/PD).

The flow of new genetic information about processes linked to disease pathogenesis, allied to advanced clinical understanding of the disease phenotype, will be of particular importance in "enriching" or "fractionating" patient groups to optimise the chances of demonstrating an effect by an unprecedented mechanism. This approach also holds promise for predicting patients who may be particularly likely to suffer adverse effects. Early development of new drugs has to be much more closely linked to understanding patients rather than simply a step along a more or less mechanical path.

One distinguished clinical investigator, Dr EJ Moran Campbell, once put it that you do an experimental medicine study 'To find out what you are going to find out'. By this he meant that the study is essentially exploratory to develop a credible hypothesis rather than to prove it. The underlying assumption is that if no potentially useful activity can be demonstrated with an active molecule, in an enriched sample with very careful measurements then it is unlikely that the chosen target has a major influence on the disease process. The following are some brief examples of such approaches.

An approach to the study of anxiety is use of magnetic resonance methods to measure small changes in blood flow in different parts of the brain (fMRI). If a patient is shown pictures of threatening or smiling faces these evoke different changes blood flow in areas of the brain including the amygdala. Such changes can be modified by medicines that have an effect on anxiety. The traditional method of measuring responses of malignant tumours to treatment is termed RECIST (Response Evaluation Criteria In Solid Tumors) and this involves measurement of the tumour size on an image such as a CT scan. The method in insensitive and it may take months of treatment to show a change. Modern imaging methods to measure drug penetration, blood flow and tumour viability by positron emission spectroscopy, not simply size, may give an indication of useful activity in days rather than weeks or months. Many diseases cause inflammation in the body. These range from chronic bronchitis or rheumatoid arthritis to unstable atheromatous disease of arteries. One way of obtaining an early indication of response is to measure markers and mediators of inflammation in the blood such as the cytokine IL6, the acute phase protein CRP or enzymes released from inflammatory cells such as metalloproteases or myeloperoxidase.

Not all experimental medicine techniques are necessarily complex. The most sensitive observers of side-effects are the patients or volunteers who have taken the medicine and use of a patient completed questionnaires can help identify and quantify these effects. Very simple measurements such as body sway may help to demonstrate that a new medicine may cause unsteadiness or use of weighed dental cotton wool rolls to measure a tendency to cause dry mouth. The continuing role of serendipity, the ability of a skilled observer to notice something unexpected – as in the discovery of the erectile action of Viagra – should not be underestimated.

The range of possible techniques is enormous and considerable skill and knowledge of human physiology is required to make best use of them but they offer a faster and safer way of identifying useful compounds and more quickly discarding those that do not perform. By deploying these methods the chances of progressing useful molecules to the later, and very expensive, stages of drug development will be much

improved and the prospect of delivering the coming fruits of the genetic revolution in biomedical science to the patients who need them will be greatly enhanced

Conclusion

Experimental Medicine studies and the concomitant development of new biomarkers, imaging techniques etc has the potential to reverse the worrying decline in registration of new drugs referred to in the opening paragraphs of this paper while enhancing the safety of the whole process. 'Fast forward to man' may make it possible to undertake early human studies with more limited animal safety data. More sensitive methodology for testing the mechanism of action or deriving early evidence of efficacy will limit the number of humans who need be exposed before a decision is made whether or not to proceed. More sensitive biomarkers of tissue injury should make it possible to stop dosing before there is clinically significant harm. Combination of genetic and high quality phenotypic data will help to identify individuals who are particularly likely to respond, and equally important, those who are most vulnerable to adverse effects.

Appendix 2- *Cancer drug development*

A recent report has examined the risk-benefit of early phase non-paediatric oncology studies (Horstmann et al NEJM 2005). Four hundred and sixty trials involving 11,935 participants were analysed. The overall response rate (i.e., for both complete and partial responses) was 10.6 percent, with considerable variation among trials. The overall rate of death due to toxic events was 0.49 percent. The authors conclude, however, that 'reliance on a single estimate of the response rate or the toxicity-related death rate for phase 1 oncology trials is misleading, since rates of response and toxicity vary according to the type of trial.' Investigational treatments may have clinically meaningful benefits – reduced pain, increased appetite, energy, and activity, weight gain, reduced fatigue, or increased ability to perform daily activities. Some of these benefits might accrue from research participation itself; for some persons, contributing to research and potentially helping future cancer patients may also be an important benefit.

Recommendations for early phase oncology studies

For both targeted drugs and cytotoxic agents doses should be absolute (e.g. mg/patient) until such time as drug clearance is shown to be related to body size (i.e. surface area or weight) or some other physiological or genetic parameter (e.g. renal or hepatic function, genetic polymorphism) at which point an adaptive dosing strategy should be developed and validated, i.e. shown to be more reproducible than absolute dosing.

Pre-clinical toxicology using a non-rodent species is not routinely needed for first in patient studies, and non-rodent studies are only subsequently warranted where initial human experience identifies specific problems that cannot be addressed in rodents.

In Phase I trials of both targeted drugs and cytotoxic agents dose escalation should use pharmacologically and statistically guided methodologies to increase the dose as safely and as quickly as possible in the minimum number of patients. For example, in the absence of toxicity, one patient per dose level with dose doubling has been successfully used in a number of trials. If an individual patient tolerates an initial dose level that is subsequently shown to be below the MTD or optimal dose, he/she should be offered a higher dose on subsequent courses, i.e. intra-patient dose escalation should not be precluded by concerns about cumulative toxicity. Cumulative toxicity is essentially never an issue in Phase I trials and can only be rigorously addressed in Phase II and III trials.

Phase I trials of non-genotoxic targeted therapies in healthy volunteers can provide useful PK and, where a surrogate biomarker is available, PD data. However, measurement of tumour PK and PD should also be undertaken in Phase I. Furthermore, the tolerance of cancer patients to new drugs may be different to that of healthy volunteers due to the presence of malignant disease, which may be extensive, and prior, often toxic, therapy.

Phase II trial design should include at least two pharmacologically distinguishable dose levels (on the basis of PK and/or PD) unless there is overwhelming evidence from Phase I trials in patients showing that the MTD is needed for maximal activity.

Combinations of targeted drugs with conventional cytotoxic drugs or drug combinations should be based on a sound hypothesis. New combinations should be studied in Phase II trials prior to Phase III trials to exclude: toxicological and pharmacokinetic interactions, or a marked reduction in the efficacy of the cytotoxic therapy. Phase II trials should include biomarker studies to test the hypothesis on which the trial design is based. Pre-clinical toxicological studies are not required for the development of combinations of targeted agents and cytotoxic drugs, although pre-clinical pharmacological studies are required to support the hypothesis tested and validate biomarkers for use in clinical trials.

In addition to information on PK, PD, side effects, drug interactions and other clinical information, Phase I/II trials of targeted agents should define:

- *The level of activity of the drug in the specific tumour type.* Where stable disease, as opposed to tumour shrinkage, is the most frequent clinical response observed caution should be exercised in

progressing to Phase III trials as the relationship of this endpoint to survival following targeted drug therapy is currently uncertain.

- *The dose level for the Phase III trial.* If the two or more dose levels studied in the Phase II trial have not defined an optimal dose (i.e. the one that gives maximum activity with acceptable or no toxicity) the Phase III trial design should include 2 or more dose levels of the new agent, with early stopping rules to curtail less active or more toxic arms.
- *The relationship between activity and the presence of the drug target in the tumour, its level, and the extent of post-treatment drug-target interaction.* Initial Phase III design should then be limited to patients whose tumour molecular pathology and/or biomarker responses indicate the greatest likelihood of response.

Phase III trial design should exploit all available pharmacological, biomarker and clinical data in protocols designed to treat only those patients who are most likely to respond to the drug therapy. Quantitative measurement of the drug target in the tumour of all patients entering the trial should be mandatory.