

Safer Medicines



A report from the
Academy of Medical Sciences FORUM

November 2005

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Registered Charity No. 1070618

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ISBN No. 1-903401-10-0



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Acknowledgements

The Academy of Medical Sciences is most grateful to Dr Geoffrey Schild, FMedSci, Dr Gwyn Morgan, Sir Colin Dollery, FMedSci, and Sir John Skehel, FRS, FMedSci, and to the members of the Working Groups for undertaking this report. It would also like to thank the Review Board, Chaired by Professor Patrick Vallance FMedSci, for their instructive comments and support.

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Cover image: Selection of medicinal pills in a hand.
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Contents

	Page
Summary and recommendations	7
Chapter one: <i>Background</i>	11
Chapter two: <i>Pre-clinical evaluation of safety</i>	15
Chapter three: <i>Safety assessment during pre-marketing clinical trials</i>	19
Chapter four: <i>Safety assessment after marketing</i>	23
Chapter five: <i>Biologicals: vaccines and gene therapies</i>	27
Chapter six: <i>Assessment, communication and management of risk</i>	31
Chapter seven: <i>Building capacity for better safety assessment</i>	37
<hr/>	
Appendix 1: <i>Remit</i>	39
Appendix 2: <i>Working Group membership</i>	41
Appendix 3: <i>Glossary and abbreviations</i>	44
Appendix 4: <i>References</i>	45
Appendix 5: <i>Working Group reports on CD-ROM</i>	Inside back cover

Summary and recommendations

The development of a drug that is both safe and efficacious is a complex and challenging process. While the prime concern of the general public is that a drug is safe and works well, it is the unavoidable case that drugs bringing genuine benefit will always carry some degree of risk. This report seeks to explain the risks involved and to describe approaches that might be taken to minimise them. Greater transparency and communication about the risks and benefits associated with drugs would allow the identification of real risks where they exist and promote sustained public confidence in the safety of medicines.

Achievements in basic science and medical research, along with an ever-faster pace of advance in drug discovery and development, have made considerable contributions to the improvement of human health over the past 50 years. This is most strikingly demonstrated in the increasing longevity of populations in the developed world and in the improved quality of life for many people worldwide. But the traditional tools used to assess drug safety have changed relatively little over the past 30 years. This is perhaps unsurprising given that the validation of new techniques is lengthy and complex and requires long-term investment. That said, technologies derived from the ‘omic sciences (genomics, proteomics and metabolomics), as well as the validation of novel biomarkers and advances in medical imaging are potentially useful additions to the safety assessment toolkit of the future.

This project, initiated by the Academy of Medical Sciences and its industry FORUM, is distinctive in that it has brought together experts from across the relevant constituencies to take an integrated view of the evidence. The recommendations in this report will have implications for many stakeholders, among them industry, academia and the regulatory agencies, as well as patients themselves. The report’s recommendations focus on the following key areas:

- The application of new technologies, specifically to pre-clinical and clinical safety assessment
- The need to provide for a rapid and thorough investigation of emergent clinical safety issues

- The role of information, in particular large patient databases, in the detection and reduction of adverse drug reactions
- The opportunity to improve the safety of medicines through public engagement on associated risks and benefits
- The importance of building research capacity in safety assessment

Recommendation 1: Expedite the application of new technologies to pre-clinical and clinical safety assessment through collaboration between industry, academia and regulatory agencies.

The ability to analyse, very rapidly, large numbers of gene transcripts, proteins and metabolic products in blood, urine and tissues offers great promise. Advances in these areas have the potential to aid the detection of safety signals or characteristic fingerprints that define potential risk by improving the speed, sensitivity and specificity of analysis. Such advances may make it possible to achieve some reduction in the number and duration of exposure of animals used in safety tests, in addition to their ability to contribute directly to patient safety. These advances may also help to diminish the present high rate of attrition in the development of new medicines.

The application of new technologies to ensure that biological products, including vaccines, are free from potentially harmful contamination has already had success. Molecular genetic studies of vaccine organisms will also provide essential information in pre-clinical studies and improve the detection of potential safety problems.

Extensive collaboration will be required between research-based pharmaceutical companies, academic experts and regulatory bodies in order to carry out the thorough validation of the new technologies. A prerequisite is the willingness of industry to share safety data. There is an urgent need to facilitate such pre-competitive joint research, both nationally and internationally.

Recommendation 2: Rapid and thorough investigation of emergent clinical safety issues should be facilitated by international networks between countries with advanced healthcare systems.

Emergent, severe, safety issues, such as liver necrosis and severe cardiac arrhythmia, are a medical emergency both for the patients suffering the adverse effect and for all other patients who are, or might be, treated with the drug. Vaccination and gene therapy can also have potentially serious adverse effects. Currently, relevant information on these safety issues is often incomplete, collected too late (or not at all) and access may be barred by data confidentiality and legal considerations.

Countries with advanced healthcare systems have a responsibility to develop international networks to investigate emerging safety issues (liver injury would be an appropriate pilot project). Such networks would enable doctors caring for patients with possible new drug-induced toxicity to respond quickly by contacting a coordinating centre. The centre would then use a common protocol and could suggest additional investigations including DNA sampling. Such an approach might allow a useful drug (or class of drug) to remain on the market by identification of genetic predisposition, drug or disease interactions, and consequent screening of potential recipients of the drug. Where an adverse reaction has occurred with a biological product, this should also be vigorously investigated, including identification of product and host-related factors in the reaction.

Recommendation 3: Build and use large databases of patients to speed the detection of adverse reactions that increase the incidence of common diseases.

Recent highly publicised examples of adverse drug reactions, such as the increased risk of suicidal thinking in adolescents taking serotonin re-uptake inhibitors (SSRIs) and the increase in heart attacks in patients taking COX-2 inhibitors, illustrate the difficulty of recognising adverse effects that change the incidence of a common disease. This problem could be addressed through the effective use of information stored on large patient databases. These databases could be scrutinised

by sophisticated computer software, searching for disproportionate changes in disease incidence. Such databases should be used in combination with large-scale, long-term clinical trials and patient follow-up.

The UK National Health Service (NHS) offers capabilities for combining clinical and prescribing information. In principle the whole NHS could be available to seek and test safety hypotheses using anonymised data. The UK clinical research networks for clinical trials, currently in development, have considerable potential for collecting long-term data on safety as well as efficacy, because of their ability to maintain long-term follow-up. Further investment in NHS capacity to evaluate drug safety should be a priority for Government and industry and might well attract international investment.

Recommendation 4: Reduce the risk of adverse drug reactions through greater public engagement.

Although adverse reactions to newly marketed drugs receive much publicity, some of the most frequent and potentially dangerous reactions arise with long-established drugs. Examples include the anticoagulant warfarin, the heart stimulant digoxin and non-steroidal anti-inflammatory drugs such as aspirin. The incidence and/or severity of many of these adverse reactions could be reduced by more intelligent use of medicines by medical practitioners and better understanding of their risks and benefits by patients. Access to the internet and the new NHS network offer opportunities to explore new methods of communicating intelligible, up-to-date information, and of checking on patient progress and safety.

There is considerable individual variation in the understanding of benefits and risks associated with treatment thus research will be needed to find optimum methods of communication. Developing better means of communicating absolute and relative risk to patients should be a priority. This is the responsibility of all stakeholders; industry and regulators must improve communication with physicians, and physicians must improve in communication with their patients. We recommend the development of an agreed, standardised system of presenting the risks and benefits of medicines.

Recommendation 5: Steps should be taken to address the decline in capacity in safety assessment.

Historically, pathological examination of animals exposed to high doses of a particular drug has been an important component of pre-clinical safety evaluation. More recently, the development of the safety pharmacology discipline and the use of drug metabolism to measure exposure levels in blood (rather than dose) have played an increasing role. In practice, the safety assessment of medicines requires input from many disciplines.

The application of new technologies requires skills in pharmacology, genomics, proteomics, biochemistry and bioinformatics, in addition to the established skills in pathology, drug metabolism and toxicokinetics. For

clinical safety assessment, skills in pharmacokinetics, epidemiology, genomics, statistics and risk/benefit analysis are required. With such a variety of disciplines involved in safety assessment, the skill of integrating many different sources of information to make a balanced judgement is becoming increasingly important.

So far, only limited effort has been made to train non-clinical and clinical scientists to adopt an integrated approach. Training in safety assessment within academia has not kept pace with developments in industry and it has become an orphan discipline in UK higher education. The education and training of specialists in safety assessment will require exposure to both active academic research centres and industrial expertise with encouragement from a national sponsoring body. The Academy proposes to examine how best this can be achieved.

Chapter one - *Background*

- 1.1 The pharmaceutical revolution, which is still only about 70 years old, has transformed medical care and made a major contribution to the increased longevity and quality of life in the developed countries. For example, survival rates in childhood have been improved dramatically over the past 20 years; the death rate following heart attack has nearly halved since the introduction of effective treatments; and patients with human immunodeficiency virus (HIV) infection have a substantially improved life expectancy. In addition, the prevention of many serious and life-threatening infections of children and adults by specific vaccination has led to profound improvements in child survival and public health.
- 1.2 Despite these advances, there still remains a large unmet need for effective therapeutic agents in diseases such as most cancers, degenerative diseases of the nervous system and osteoarthritis. New developments in therapeutic approaches, such as those involving gene therapy, offer promise in the treatment or prevention of diseases for which current approaches are ineffective. Vaccines are likely to have an increasingly important role in the prevention and therapy of some cancers.
- 1.3 Spectacular developments in pharmacology and therapeutics have been accompanied by progressive improvements in safety assessment by pre-clinical testing in animals and careful monitoring of patients. Most pharmaceutical therapy is now very safe if the drugs are used appropriately. The exceptions are mainly in the field of cancer chemotherapy where the margin between killing malignant cells and damaging normal tissues may be small or non-existent.
- 1.4 Patients generally expect that the medicines they are prescribed will be highly effective and very safe. The reality is that many useful modern medicines given to large numbers of patients can cause serious harm in a small minority. For the best results improved methods of patient selection are required, and safety issues also need to be identified early in the course of the introduction of new therapies. Medical care with drugs is a continuum from pharmaceutical research to patient. While manufacturers and regulatory authorities bear a heavy responsibility for ensuring that medicines are effective and safe, major responsibilities also rest on doctors and patients. Many instances of drug toxicity are potentially avoidable by greater skill and knowledge in the prescribing doctors and greater care and understanding by patients.
- 1.5 The tools used to assess safety of medicines (animal toxicology and clinical trials prior to marketing) have changed relatively little over the past 30 years. The basic processes of safety assessment involve exposure of animals to graded doses of the drug for up to a year, including levels higher than those that would be used in humans. The animals are monitored clinically, tested for changes in blood and urine composition and, after they are killed, detailed examination of 40 or more different tissues is carried out. In the early clinical phase patients are carefully monitored and, again, regular measurements of blood and urine composition are taken. In addition, if any specific concerns are raised either by the mechanism of action of the drug or potential problems identified in animals, appropriate parameters will be monitored wherever feasible. These methods should not be undervalued because severe toxicity in human has become rare, but there is evidently room for improvement.
- 1.6 Concerns about safety remain the biggest cause of failure of potential drug molecules to progress as medicines. One measure of the success of existing methods for the assessment of safety once a drug is entering the development phase is the proportion of new chemical entities (NCEs) that progress from 'first-in-human' studies to registration with regulators. The numbers vary according to therapeutic targets, but the average success rate of all therapeutic areas is estimated at 11%. In the year 2000, toxicology and clinical safety issues were

¹ *Kola and Landis, 2004.*

estimated to account for approximately 30% of all instances where a potential new drug failed to reach the registration phase.¹ The total cost of developing a new drug has been estimated to be in excess of 800 million dollars.² If a drug is withdrawn from use before these development costs are recouped, there may be serious financial implications for the manufacturer.

1.7 While current methods of safety assessment appear to have been quite successful in screening out compounds that might cause toxicity in a substantial proportion of patients, they have sometimes been less successful at predicting serious adverse effects that occur only in a relatively small minority of patients (less than 1 in 1000) and those where the adverse effect is to increase the incidence of a common disease. Examples of the former include troglitazone-induced liver injury and skeletal muscle toxicity (rhabdomyolysis) from cerivastatin. Examples of the latter include increases in suicidal thinking in depressed adolescents treated with SSRIs and the increase in heart attacks in patients taking certain COX-2 inhibitors used to treat arthritis. These events have shaken public confidence in the present methods of assessing safety.

1.8 It should be emphasised that, over time, differences of emphasis have emerged in the pre-clinical evaluation of drugs in comparison with biologicals. For drugs, the general approach indicated above provides common ground for evaluation of different types of drug. In the case of vaccines, classical toxicology is of limited relevance in many instances, and animal and other pre-clinical tests vary according to the specific nature of the agent involved, including its pathological characteristics. Particularly in the case of live vaccines (containing live attenuated infectious agents), animal models are of value to investigate that the infectious agent is stably attenuated and lacks pathogenicity or reversion to virulence. They also contribute to information that the product is free from contamination with infectious agents derived

from the source biological materials and does not possess potentially harmful immunological properties.

1.9 Advances in science and technology over the past decade have opened new possibilities for detecting and, in some instances, predicting susceptibility to drug toxicity but most of these methods have yet to be tested in large-scale trials or accepted by the regulatory bodies that decide whether a new drug can be marketed. There is a disparity between what is recognised as a 'safe' drug by regulators and the perception of the general public. The launch of a new drug is often accompanied by a large amount of favourable publicity, which may encourage unrealistic expectations from prescribers, the media and the general public about its safety and efficacy. Drug withdrawals after licensing are then seen as failures of the system, rather than an inevitable consequence of a process that can never guarantee complete safety.

1.10 The pharmaceutical industry has a clear obligation to society to ensure that drugs are as 'safe' as they can possibly be, as it is society that pays the price when serious adverse events occur. In the most serious cases, the after-effects of drug safety failures can be felt for many years after the event and may delay the development of important new therapeutic agents. Studies suggest that adverse drug reactions are responsible for over 6% of acute hospital admissions, leading to a projected annual cost to the NHS of almost £0.5 billion.³ However, even highly toxic drugs do have a role when used under the right conditions and knowledge – for example, thalidomide is regarded as a 'bad' drug, but is useful in treating leprosy.

1.11 Regulatory agencies are subject to much scrutiny following announcements of drug withdrawals, whether they relate to safety, efficacy or both. The regulatory environment is increasingly challenging, with rapid growth in knowledge resulting in increasing demand for specialisation. Significant cross-disciplinary skills and knowledge are needed to integrate

² Tufts Center for the Study of Drug Development, *Impact report 5*: <http://csdd.tufts.edu> (accessed 5 October 2005).

³ Pirmohammed *et al.*, 2004.

diverse sets of data from often unrelated fields. These skills are in short supply both in regulatory agencies and industry and are poorly developed in universities. Regulatory authorities are under such pressure to ensure safety that they may be viewed as increasingly conservative; this has the potential to increase drug development time and withhold potentially useful new medicines in areas of unmet medical need.

1.12 In the light of all these circumstances, the Academy of Medical Sciences, through its FORUM with Industry, resolved to re-examine present methods of assessing drug safety and to make recommendations that might secure improvements. This project is distinctive on several counts: it has brought together interested parties from industry, academia and the regulatory agencies; addressed issues relevant to both pre-clinical and clinical disciplines; and covered biological as well as chemically synthesised products.

1.13 The scope of the project ranges widely across the life sciences, from cell biology, pharmacology, pathology and drug metabolism to pharmacogenetics, pharmacogenomics, bioinformatics and molecular and clinical medicine. The project remit can be found in Appendix 1. A total of seven Working Groups

were set up to look at various areas in the safety assessment of drugs, namely:

1. Pre-clinical toxicology
2. Safety pharmacology
3. Pre-marketing (clinical phase I, II and III) assessment
4. Vaccines
5. Gene therapy
6. Risk-benefit assessment
7. Post-marketing surveillance

1.14 Full versions (in electronic form) of each Working Group report can be found in Appendix 5 on the attached CD-ROM.

1.15 This report represents a distillation of the important conclusions from these working parties and is one step in a longer-term strategy, the object of which is to advance the progress of safe and efficacious new therapeutic modalities for the benefit of all patients. The Academy of Medical Sciences will continue to build links with other interested parties in taking forward the present recommendations and to support, where appropriate, the initiatives of other bodies. The Academy greatly welcomes feedback on any of the points raised in this report.

Chapter two - *Pre-clinical evaluation of safety*

- 2.1** The objective of this chapter is to review, briefly, the present methodology available to assess drug safety before administration to humans and consider opportunities to apply new technologies.
- 2.2** Pre-clinical safety assessment of drugs relies heavily on macroscopic and microscopic examination of organs and tissues from at least two species of animals, using a range of drug doses for periods of up to six months or more. Application of these methods requires highly skilled scientists who are familiar with both animal and human pathology. The main improvement in methodology in recent years has been to measure the concentrations and kinetics of the drug in the blood and tissues of the animals used in the safety tests. This is necessary because small animals often metabolise drugs much more rapidly than humans. Equivalent doses on a bodyweight basis might therefore involve much lower exposure to the drugs in animals than would be achieved in humans given the same dose per kilogram. Much higher oral doses may be needed to match human exposure. It is now standard practice to calculate the maximum exposure in animals that causes no adverse effect. This is known as the NOAEL, meaning no observable adverse effect level. Human exposure is normally kept below the NOAEL, and five- to tenfold below if the initial toxicity is of a serious kind, such as injury to the heart or liver.
- 2.3** For drugs and some biological products these standard methods are supplemented by a wide range of more specialised safety tests in animals or isolated cells. These include testing for teratogenic effects upon the embryos of pregnant animals, genotoxicity assessed by damage to DNA *in vitro* and *in vivo*, and very long term exposure (years) of animals to assess the risk of carcinogenicity. Assessment of the risks associated with reproductive toxicity and carcinogenicity is made almost entirely using pre-clinical data, as it is not possible to obtain corresponding data in clinical trials or in a timely way through patient monitoring.
- 2.4** Although traditionally the application of conventional toxicological tests has not been regarded as generally relevant to vaccines, there are instances where specialised safety tests are of value, particularly for novel biologicals such as those being developed for gene therapy or those which contain agents that are potentially teratogenic.
- 2.5** Advances in chemical analytical methodology, particularly mass spectrometry, mean that it is usually possible to have a sensitive and specific analytical method available for measurement of plasma concentrations in animals and humans. It is normal practice to synthesise a species of the drug molecule labelled with carbon-14, a long-lived radioactive isotope of carbon. This can be used both to study the tissue distribution of the molecule in rodents and to obtain more detailed information about routes of metabolism.
- 2.6** Studies of the rates and routes of metabolism of the drug molecule will also have been undertaken, using freshly isolated liver cells (hepatocytes) or hepatic microsomal fraction from humans and animals and *in vivo* studies in the animals. These data are of particular value in making predictions about initial doses in humans but may also indicate potential problems from formation of reactive entities. Such *in vitro* studies are subsequently followed by studies of metabolism in animal species used in toxicity testing, and in humans, to ensure that exposure to metabolites has been achieved in animal species. Early findings in humans may require further testing in animals, for example if humans produce abundant quantities of a drug metabolite that was seen only in much lower concentrations in animals.
- 2.7** An increasingly important area of safety evaluation before administration to humans is termed safety pharmacology. The aim of this step is to make sure that there are no important functional effects upon vital systems, such as the conducting system of the heart, blood pressure, breathing, consciousness, liability to fits, etc. at exposures above those likely to be achieved in humans. Safety pharmacology studies can also

be conducted to provide a mechanistic understanding of adverse effects observed in humans that were not predicted from earlier testing.

2.8 Everyone concerned with assessing drug safety wishes to minimise the number of animals used but it is important for all concerned to understand that there are, in most cases, no alternatives. Isolated cells, such as hepatocytes, are very useful for limited purposes such as assessing metabolic routes, but they quickly lose many of their specialised properties when grown in culture. Furthermore, the mechanism leading to toxicity may require the interaction of several different cell types; consequently much drug toxicity depends on long-term complex effects upon integrated functions that can only be assessed in a living animal.

2.9 For several vaccines and other biological medicines there are examples of the use of sensitive and specific molecular assays, such as the gene amplification (polymerase chain reaction, PCR) test for the detection of extraneous contaminating viruses, reducing the need for biological and animal tests. They are already also routinely in use for the detection of blood-borne viruses in blood donations used in the manufacture of blood products where they provide a highly sensitive and reliable method for detecting hepatitis B and C viruses and HIV. There are examples of vaccines where characterisation of the product by physicochemical methods is of value for quality control and related safety; one of these is the structural analysis by nuclear magnetic resonance (NMR) of the polysaccharide-based meningitis vaccines now in common use.

Problems and gaps in the present approaches

2.10 *Inferences drawn from very high exposure.* The highest doses used in animal safety tests are intended to cause some toxic effect to elucidate what type of adverse effects may occur in humans. Some of these may not preclude administration to humans but will require special additional monitoring, whereas others may be so serious that it would be unacceptable

to risk their happening in humans, for example irreversible damage to cells in the retina. There has been a long debate about the significance of toxic effects seen only at very high exposures. At very high exposures, a compound may generate a substantial amount of a chemically reactive metabolite that swamps the capacity of the normal mechanisms that exist in the body's cells, particularly the liver, to inactivate them. At lower doses the same compound producing the same metabolite, but in much smaller amounts, may be non-toxic because the reactive species is removed efficiently, for example trapping by glutathione. It is therefore important to understand that the full dose-response curve for each compound should be characterised.

2.11 *Interspecies comparisons.* Predictions of safety between species (for example rat, dog and human) are good but not perfect. A longer-term hope is that knowledge of the genome of the main species of laboratory animal, and of humans, will increase the reliability of predictions. However, the mechanisms involved in toxicity are a complex mix of injury, defence and repair so progress in understanding may be slow. A special case is when a drug is so selective for the human target that it has little effect in the animal species used for safety assessment, as is the case for most monoclonal antibodies and some organic chemicals. Some types of pathology are more common in animals used for safety assessment than in humans, and a few pathologies seen in animals do not have any known human counterpart. Changes in the bile ducts are relatively common in rats probably because they are more efficient at excreting drugs in bile than are humans. These situations put a premium on the skill of experienced pathologists who have knowledge of the typical pathology in different species, and on the ability to integrate data on exposure with the microscopic findings.

2.12 A suitable animal model may not exist for studies of the safety and efficacy of a new vaccine under development. However, modern mouse genetics provide possibilities of developing transgenic mice strains with the required degree of susceptibility to the organism against which the vaccine is being developed. A

successful example for this approach is the use of transgenic mice susceptible to polio (normal mice are not susceptible) which are now widely used for safety tests of poliovaccine.

2.13 *Mechanism of toxicity.* Toxic events can be divided broadly into those caused by the main pharmacological action of the drug and those that are unrelated to it (off target). The pharmaceutical industry is exploring many novel targets derived from the human genome, and background knowledge about the biological role of the target receptor or enzyme is often fairly limited. This limits to some extent the ability to predict the possible unwanted effects of the pharmacological action, although the use of modern techniques to define the distribution of the target in the body provides an insight into the likely organs that may be affected by a new medicinal product. Greater openness with the academic community would be mutually beneficial. Non-target-related toxicity poses even greater problems: a detailed understanding of the mechanism of toxicity at a molecular level is rarely available although considerable progress is being made concerning the role of chemically reactive metabolites. Even so, the fact that a reactive metabolite is generated is far from proof that there will be safety issues in humans. There is a need for greater scientific investment to expand knowledge in this area.

Opportunities with new technology

2.14 *Application of the 'omics.* This term is often used to describe a range of new technologies. The main ones are: (a) transcriptomics, a method for examining the expression of thousands of genes using a DNA chip, often from the Affymetrix company; (b) proteomics, the identification of changes in the pattern of the thousands of peptides and proteins present in plasma or other biological samples; and (c) metabolomics, the investigation of changes in the pattern of endogenous chemical products of metabolism in plasma and urine.

2.15 Several pharmaceutical companies are known to have undertaken studies using transcriptomics

to examine the effects of known hepatotoxic compounds after short-term administration to rodents. These methods appear promising on two grounds: a signal can be detected before the microscopic injury is visible, and the changes in the pattern of gene expression give valuable clues about the mechanism involved that may not be readily apparent under the microscope. To move this area forward inter-company collaboration and collaboration with regulatory bodies should be a priority.

2.16 Proteomics and metabolomics have made less progress, partly because the analytical throughput of present methods is much lower than transcriptomics. However, because of the difficulty of obtaining human tissue for transcript analysis, these methods may come into their own when translating animal findings to humans. Eventually such approaches may lead to a database of characteristic 'omic fingerprints that warn of likely hazard.

2.17 *Imaging.* The great advantage of imaging techniques is that they are non-destructive and so the same animal can be examined at several time points to assess the evolution and reversibility of a drug-induced lesion. This technology is also often directly transferable to humans.

2.18 Advances in the application of 'omics and imaging methods require a broader commitment to the principles and practices of knowledge management. Full exploitation will require the development of computational resources and people capable of curating and analysing the resulting data. These databases should enable efficient interrogation of all the information generated and permit the relationships between animal toxicology data and clinical drug data to be ascertained. Such resources will also develop; as toxic signals emerge datasets can be re-probed to re-assess safety of molecules in the pipeline or already in the marketplace.

2.19 The more established technologies are also advancing. Wider use is being made in safety assessment of more sophisticated microscopic techniques including electron microscopy and

immunocytochemistry. Rapid advances in the knowledge of the role of transporter molecules in cells are being used to better understand what determines the concentration of a drug molecule within cells - where the toxic effect is usually manifest. For example, many drugs are organic acids (e.g. the statins) and these can achieve concentrations within liver cells of ten to a hundred times higher than in plasma by the action of organic anion transporters in liver cell membranes.

2.20 Sophisticated mathematical modelling (Systems Biology) has an important part to play in

integrating information gathered about the drug from many sources and making predictions that may be difficult and/or expensive to test experimentally.⁴

2.21 The proliferation of promising new approaches has not thus far been matched by a corresponding increase in academic research or national research investment outside industry. Several of the Academy Working Groups argued that a national centre for drug toxicology was needed to give impetus to research on the new approaches and maintain international competitiveness.

⁴ *The Academy of Medical Sciences is currently undertaking a project with the Royal Academy of Engineering on Systems Biology and these opportunities and challenges will be addressed further in that project.*

Chapter three - *Safety assessment during pre-marketing clinical trials*

Current process and procedures

- 3.1** This chapter deals largely with safety issues in clinical trials but it must never be forgotten that it is the balance between efficacy and safety that is most important. Patients will accept quite severe drug toxicity for potential benefit in deadly diseases such as cancer and HIV; conversely drugs intended for less serious conditions such as the treatment of obesity or mild allergy must be very safe and well tolerated. The question of risk assessment and the communication of risks and benefits is the subject of a later chapter.
- 3.2** Phase I. Before a new drug is given to humans for the first time, usually in healthy volunteers, there is an extensive review of the safety data on NOAEL in animals (paragraph 2.2) to identify any concerns that might require exceptionally intensive or specialised monitoring. The predictions made about a likely effective dose will also be reviewed, and the starting dose is normally set at a fraction of the dose that is anticipated to have any observable effect.
- 3.3** It is a testimony to the effectiveness of the methods used in pre-clinical safety assessment that serious, unexpected, toxicity in humans during early phase studies is very rare indeed. The effects most likely to be missed are less serious ones such as headache, sedation, inattention, nausea and fainting that are difficult to detect in animals.
- 3.4** The first phase consists of a placebo-controlled single dose-rising study in groups of 12–16 volunteers that will stop when either a pre-set exposure level has been reached (say one fifth of the NOAEL), there are dose-limiting symptoms, such as nausea and vomiting, or there are biochemical/haematological safety tests that can raise an alert. Blood samples are taken at frequent intervals for full blood counts and biochemical tests that may give an indication of damage to the liver, the kidney, skeletal muscle, etc. Urine and electrocardiogram (ECG) examinations are also made and any reported symptoms recorded. Pre-set upper limits for these tests at which dosing must be stopped will have been defined. An important part of this early study is to obtain reliable data on the plasma concentrations and duration of exposure.
- 3.5** The next stage is to give a series of doses, usually for 14 days, at levels based on the data from the single dose study. Similar safety measurements are made. It is well recognised that small increases (up to two to three times higher than the upper limit of normal) of the ‘liver’ marker alanine aminotransferase (ALT) activity may be observed on both active drug and on placebo. In many cases these appear to be more related to the circumstances of housing in an investigational unit and dietary changes than to a drug effect. This illustrates the difficulty in distinguishing between adaptation and toxicity.
- 3.6** *Phase II.* The course of phase II varies depending upon whether the compound has a precedented action or whether its action is so novel that there is no precedent. For a precedented action, studies will be undertaken in patients with the disease in which that type of activity is known to be effective. For an unprecedented action, more exploratory studies in experimental medicine will be undertaken using intensive measuring techniques, sometimes in patients with several different possible target diseases. As the objective is to demonstrate an action, if there is one, the groups of patients are carefully selected as being healthy in other respects and, increasingly often, are chosen as having features that increase the likelihood that they will respond. The number of patients involved is usually small in phase II, ranging from approximately 30 to 200, and the duration of exposure is usually short, rarely more than 6 weeks.
- 3.7** One of the main challenges at this stage is to find the right dose or range of doses that will be effective but not run a needless risk of toxicity from overdose. For some diseases this is

relatively easy (e.g. asthma or hypertension), whereas in others it can be very difficult (e.g. schizophrenia, Alzheimer's disease). Where the response is difficult to measure, advanced technologies such as positron emission tomography (PET; to measure receptor occupancy) may be employed. It is a truism that the most common property of a new drug that the industrial sponsor gets wrong is the dose. As the choice of dose is often ultimately based on the most favourable balance of efficacy to safety, obtaining good dose-response data for both is of critical importance.

- 3.8** Several special safety issues have to be addressed in phase II. The two most common investigations are evaluating the effect of the new drug on the ECG, and studying its potential to cause drug interactions by speeding up or slowing down the rate of metabolism of other critically regulated drugs such as the anticoagulant warfarin.
- 3.9** Several commonly used drugs with unrelated actions (e.g. the antihistamine terfenadine) have been found to prolong the re-polarisation phase of the ECG (long QT) and this predisposes to a serious irregularity of the heart beat called 'torsades de pointes'. It is now a requirement that compounds should undergo an exhaustive testing in healthy subjects with multiple ECGs to characterise and exclude those compounds causing anything more than minimal changes in cardiac re-polarisation.
- 3.10** The magnitude of effect and duration of action of most drugs is determined by their speed of elimination from the body. In many cases this involves metabolism by enzymes in the liver. If a new drug speeds up or slows down the rate of metabolism by one of these enzymes it will decrease or increase the concentration of all other drugs that are metabolised by the same enzyme, which can have serious consequences. If pre-clinical studies with human drug-metabolising enzymes suggest that such effects may occur in the range of expected therapeutic concentrations, a panel of test substances metabolised by different members of the enzyme family chiefly responsible (usually cytochrome P450s) will be administered with the test compound to normal volunteers.

3.11 The first part of phase II (IIA) ends when it is shown that the drug has an action with potential utility in a human disease, termed proof of concept or PoC, or that it has not. If the PoC is positive it is followed by phase IIB, which is used to finalise the dose and make a better assessment of therapeutic activity. Phase III involves very large confirmatory trials to achieve the necessary data for registration of the product. Phase IIB/III involves much larger numbers of patients, usually several thousands.

3.12 *Phase IIB/III.* These large trials determine whether a drug will be accepted by regulatory bodies for general use. Their primary aim is to demonstrate efficacy but they add valuable information about safety because of the larger number of patients.

3.13 Patients in these late-phase trials are monitored at intervals in a similar fashion to those in the earlier studies, although not necessarily so frequently. Each trial usually has its own safety data monitoring committee comprising several experts who are independent from the main study but have access to, and conduct a regular review of, data from the study. If serious safety issues arise, a trial may be suspended while the issue is clarified. A recent example is the suspension of trials with drugs that affect adhesion molecules, which are necessary for white cells to migrate from the blood into tissues. One compound in this class, a monoclonal antibody (Tysabri), was associated with several cases of a rare and serious viral disease of the brain. Studies with compounds with a similar mechanism of action were placed on clinical hold.

3.14 A limited amount of work is done on the effects of intercurrent disease of vital organs; for example it is usual to study changes in the kinetics of the new drug in patients with moderately severe kidney or liver disease.

Problems and gaps in the present approaches

3.15 *Exposure.* Although phase IIB/III trials often involve 5000–10,000 patients, the duration of exposure is often only a few weeks or months.

The total number of ‘patient years’⁵ of exposure may only be in the mid-hundreds and only a small minority will have been on the drug for as long as a year. If toxicity is cumulative over time, pre-marketing trials are not sensitive enough to detect it. When toxicity arises because of a low-frequency human genetic polymorphism, the number of individuals involved in the trials and the limited duration of exposure make it unlikely that it will be detected. Yet once a compound is marketed, human exposure may quite quickly increase by hundreds or even thousands of fold.

3.16 A recent example relating to the size of the phase III trials concerned a rotavirus vaccine under development. Phase III trials involving several thousand subjects failed to detect a serious neurological adverse reaction, Guillain-Barré Syndrome. This only became apparent by post-marketing surveillance during the wider routine use of the vaccine, which was subsequently withdrawn. There is an increasing awareness that recombinant therapeutic biologicals, although of human sequence, may after repeated application induce specific antibodies in recipients. This is the case with some interferons and growth factors.

3.17 *Generalisability.* The careful selection of patients for clinical trials means that the trials may not detect safety issues arising from serious intercurrent disease, environmental factors, such as high social drug intake, or administration of multiple other medicines simultaneously.

3.18 *Biomarkers.* It is usually impractical to obtain samples of human tissue to assess safety during clinical trials, so reliance has to be placed on substances that can be measured in accessible fluids, mainly blood and urine. These substances are often referred to collectively as ‘biomarkers’. When safety issues arise, such as a signals of liver toxicity, they are almost always detected by established biomarkers in clinical trials before significant tissue injury has taken place, because of the intensity of monitoring. However, there are some types of pathology

that are more difficult to detect at this early stage. A good example is a condition termed phospholipidosis.

3.19 Phospholipidosis is a relatively common finding in animal safety tests and involves infiltration of many tissues with phospholipids, probably because their normal breakdown by metabolism has been impaired. Despite its frequency in animal safety testing it is rarely found in humans, although it is often sought. The only reliable way of detecting the condition in humans, short of finding tissue infiltration with phospholipids, is to make electron microscopic examination of circulating white cells in blood. Phospholipidosis is used here only as an example; there are others.

3.20 Even when there are existing safety biomarkers there is often room for improvement. The markers used for detecting liver injury, such as ALT, are not liver specific, and liver biomarkers that are both more specific to that organ and that give a better indication of the type of liver injury would be of value.

Opportunities with new technology

3.21 Development of *new biomarkers* for both efficacy and safety (if feasible) could be of great value in improving the accuracy of conclusions reached in the clinical phase, particularly in its early stages. Acceptance of such biomarkers for anything more than internal management decisions will require extensive collaboration between the pharmaceutical industry and regulatory authorities. That progress is possible is beyond reasonable doubt but its extent and timescale is rigorously debated.

3.22 *Imaging methods* continue to advance. Although imaging is mainly used for efficacy measurements, this does affect safety. For example it is now technically possible to measure the effect of treatment on the size of a malignant tumour, the penetration of a radiolabelled drug into it, changes in the tumour blood flow and the viability of the cells within it.

⁵ *Number of patients × fraction of year exposed to drug.*

In time these methods will make it possible to detect tumour response earlier, optimise doses better and achieve a better balance between efficacy and safety. Imaging is expensive and it is difficult for any but very well funded academic centres to compete, but it is of great importance for the future.

3.23 *Developability.* Many of the problems associated with predicting drug interactions, variable absorption, reactive metabolites and the like are being addressed efficiently by pharmaceutical companies who screen their compound libraries for these properties. But the ability to make accurate mathematical models of interactions with drug-metabolising enzymes or the cardiac potassium channel (which is largely responsible for cardiac re-polarisation) may ultimately mean that such problems can be avoided when molecules are designed by medicinal chemists.

3.24 *Mathematical modelling of clinical trials.* As noted earlier, sophisticated modelling has great potential and it is possible to envisage a time when models could be used to test a greater range of possible situations than it is practical to address in affordable clinical trials. 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.

3.25 *Genomics.* The potential applications of genomics to safety are vast. The study of DNA sequence variation in relation to differential drug response is the basis for the application of pharmacogenetics in the development of personalised patient safety.⁶ Pharmacogenetics has the potential to transform pharmaceutical R&D processes and create new industry standards in efficacy and safety, in terms of focusing effort in phase II–III trials and providing the tools for ADR profiling in pharmacovigilance. A gene chip (Amplichip; Roche) has recently been made available commercially that makes it possible to screen individuals for common polymorphisms of two of the important drug-metabolising enzymes (CYP2D6 and CYP2C19).

3.26 No doubt chips to detect enzyme polymorphisms that lead to low frequency severe toxicity with important drugs such as azathioprine and 5-fluorouracil will follow. The importance of single nucleotide polymorphism (SNP) profiling in safety assessment has been demonstrated by the association of the hypersensitivity reaction to abacavir (a drug used in the management of HIV) with two genes, TNFalpha-238 and HLA-B57. However, it would be wrong to assume that this approach will abolish unwanted effects. Indeed it is unlikely to provide a ‘safe’ or ‘not safe’ signal, but rather to give an indication of the altered probability of experiencing an unwanted effect. Of particular importance is the possibility to reduce, or largely avoid, toxicities that have an immunological component, as animal safety tests are of little value in predicting them.

⁶ For more information please see the summary of Allen Roses’ presentation to the Academy’s inaugural FORUM meeting at www.acmedsci.ac.uk/p50evid7.html (accessed 5 October 2005).

Chapter four - Safety assessment after marketing

4.1 Once a drug is approved and licensed for marketing, the most challenging test of drug safety begins. Many of the patients to whom the drug is prescribed may have other disease conditions and be taking other medicines. It is also likely that these patients will be less carefully monitored than those involved in clinical trials. Almost all recent safety concerns have arisen after the compound had been on the market for an appreciable period of time and been taken by large numbers of patients. There are several processes in existence for detecting toxicity after a compound is marketed:

4.2 *Spontaneous reporting by healthcare professionals or patients.* An example is the 'Yellow card' system in the UK and 'Medwatch' in the USA. These are maintained by the national drug regulatory agencies, in these cases the MHRA and the FDA, respectively. Manufacturers also receive reports directly and from their field representatives and are required to make regular reports to regulatory agencies. Sophisticated computer programs have been devised to scrutinise these databases for a disproportionate excess of clinical events related to a particular form of treatment. The problem is that only a very small proportion of serious adverse effects are reported, even in Sweden where reporting is mandatory.

4.3 Formal post-marketing surveillance is an increasingly common requirement by regulatory bodies, in the form of post-marketing clinical trials or observational studies to increase the safety and efficacy databases. Such trials involve carefully supervised patients and the incidence of adverse events is usually low, therefore the studies need to be very large.

4.4 *Monitoring large patient databases.* It is increasingly recognised that large-scale observational datasets may be of particular value in assessing safety signals as they represent what

happens under normal conditions of clinical practice. Some have been established specifically for the purpose of monitoring safety signals, but the greatest opportunity lies in those that simply collect routine clinical data.

- Prescription event monitoring (PEM), operated by the Drug Safety Research Unit, uses NHS prescription data to collect information from GPs about clinical events experienced by patients taking a selection of newly marketed drugs.⁷
- Databases such as the General Practice Research Database (GPRD), which is a population-based primary care research database of computerised, anonymised patient records from the major GP software systems.⁸ The GPRD includes about 300 UK family practices. Other databases of this type include THIN,⁹ Mediplus and DIN-link (both of which are commercially run)¹⁰ and Q research (run by the University of Nottingham).¹¹
- MEMO, a record-linkage database run by the Tayside Medicines Monitoring Unit, incorporates data on dispensed medication from general practice, inpatient data and information from other national datasets for patients in the Tayside region.¹²
- Disease registries: there are over 100 databases listed in the directory of clinical diseases.¹³

4.5 The information in these databases is of variable quality. They do, however, reflect routine usage in the general population and provide denominator data. Several UK databases, particularly the GPRD, are used internationally, which indicates the strength of the information they hold.

4.6 In North America, the databases used for pharmacoepidemiological research are generally health maintenance organisations (HMO) claims databases and as such are more designed for administrative purposes and contain limited

⁷ www.dsru.org/main.html (accessed 5 October 2005).

⁸ www.gprd.com (accessed 5 October 2005).

⁹ www.thin-uk.com (accessed 5 October 2005).

¹⁰ www.imshealth.com (accessed 5 October 2005).

¹¹ www.nottingham.ac.uk/~mczgres/ (accessed 5 October 2005).

¹² www.dundee.ac.uk/memo/ (accessed 5 October 2005).

¹³ www.docdat.org (accessed 5 October 2005).

clinical information. As a result of this, the specific information needed to assess a safety issue may not be available.¹⁴

- 4.7** Important initiatives in Europe include Eudra-Vigilance, a European pharmacovigilance database set up as a result of the EU Clinical Trials Directive (in addition to the EudraCT trial registration database). This will include data from an annual safety update, but is not currently intended to be accessible to other researchers. This seems like a missed opportunity, and we believe this database should be made more widely accessible.
- 4.8** NHS connecting for Health, which is implementing the NHS National Programme for Information Technology (NPfIT), plans to implement a single system linking NHS patient records from any source in an electronic Health Record. This presents a unique opportunity to link drug prescribing to adverse events at all levels of care, and to allow an analysis of drug safety at a national level. The NPfIT is limited to England, while other systems are being developed in parallel in the devolved countries. It is important that the different systems are compatible to allow a UK-wide approach and maximise the opportunities for major advances in pharmacovigilance.
- 4.9** Existing databases also provide opportunities which have yet to be exploited. PEM is mainly used for signal detection, with MEMO and the GPRD being used to strengthen and refute signals, to quantify absolute and relative risks, and to identify subpopulations at risk. Some important issues, such as the impact of maternal drug exposure on pregnancy outcome, neonatal and early childhood health, and the use of medicines in children, could be addressed using the systems (with the appropriate ethical review and approval).

Problems and gaps in the present approaches

- 4.10** The main problem with all the spontaneous reporting systems is the very small percentage

of serious adverse events that are reported despite energetic attempts to increase them. There are several explanations. One of the most important is that if an event is well understood, for example bleeding on an anticoagulant or a low white cell count during cancer chemotherapy, physicians see no need to report it. Cancer specialists might need to file a report on every second patient on intensive chemotherapy. The second problem is that a small change in the incidence of a common disease caused by a drug is unlikely to be recognised unless a sequence of such events in a short time forces it upon a doctor's attention. There is a better chance that an event will be reported if it is unusual or known to be a sign of serious toxicity, such as jaundice or a very low white cell count for no apparent reason.

- 4.11** Formal post-marketing studies are likely to run into the same problem as pre-marketing trials. They are performed in selected patients who are closely supervised and may be less likely to suffer adverse events; if they do the drug will probably be stopped promptly before they become very serious. The most severe adverse events are likely to occur when a patient persists with a drug despite the onset of symptoms or when the drug is reintroduced after a short period without it. This was the case with some instances of severe liver toxicity with the anti-diabetic drug troglitazone and serious skin reactions with the anti-epileptic drug lamotrigine.

- 4.12** *Large-scale controlled clinical trials.* The cardiovascular safety issues with rofecoxib (Vioxx) and celecoxib (Celebrex) were detected because large-scale and long-duration controlled clinical trials were in progress for efficacy endpoints such as Alzheimer's disease or prevention of colon carcinoma. These provide the most secure scientific evidence because of the randomly allocated comparison group. However, to launch large-scale trials whose sole endpoint is safety presents ethical difficulties and it might be hard to persuade patients to take part.

¹⁴ These databases include Puget Sound, Kaiser Permanente, United Health, MediCaid and Saskatchewan.

4.13 Large databases. The use of large clinical databases for safety evaluation is increasing rapidly and the more comprehensive the clinical information the more useful they are. Their only real drawback is that patients are not allocated to treatment randomly and an excess or deficit of events might reflect the prescriber's judgement about the disease features in that patient. To some extent this problem can be managed by making statistical adjustments for disease severity. Unless the databases are very large they are of limited value for less widely used drugs.

Opportunities with new technology

4.14 The expansion and enrichment of searchable clinical safety databases is of the utmost importance in improving the safety monitoring of marketed medicines. An important factor in the use of these datasets is improving the links between them. The implementation of NPfIT is potentially of great importance, but it will also be necessary to maintain and strengthen the use of current databases, such as the GPRD, until NPfIT can at least replace their research capacity.

4.15 There is significant frustration within the research community about the constraints on sharing and research use of patient data in pursuit of public health objectives. It is important that clear guidelines for the interpretation of the Data Protection Act are developed to allow the sharing of valuable drug safety data while preserving patient confidentiality.

4.16 One approach to the issue of consent, particularly in circumstances where it is impossible or very difficult to obtain consent from all individuals but it is important that all are included (as in the case of pharmacovigilance), is to ensure that all data are completely anonymised. From a legal standpoint, there is provision within legislation to obtain patient data without consent where there is 'overriding public interest'. It may be argued that disclosure

of information relating to the safety of drugs is in the public interest, provided that such disclosure is to a specific authority and patient confidentiality is respected.¹⁵

4.17 The process of ethical review may benefit from being more streamlined. At present, a researcher may have to go through several approval processes including the appropriate funding body, an NHS ethics committee, an independent scientific panel (for example when using databases such as the GPRD), data protection officers and sometimes the R&D departments within each hospital trust. There have also been significant costs associated with using some of these datasets derived from NHS patients. For example, for several years access to GPRD data was so expensive that the bulk of the work using it could only take place in groups in the USA. It is essential that NHS datasets that could be used to pick up safety signals, verify safety profiles or test hypotheses related to safety can be accessed by researchers.

4.18 The limitations of these databases are largely related to the breadth and quality of the data they contain. Both the GPRD and PEM schemes contain information from GPs only, and therefore are unable to provide information on drugs which are mainly used in hospitals, for example cancer chemotherapy. PEM is a voluntary scheme which does not provide any financial incentives, and as a result at least 30% of GPs choose not to complete the appropriate paperwork. This creates a potential bias in the data, the effects of which are unknown.

4.19 Another limiting factor is that for some of the databases GPs do not record social data such as occupation, marital status and employment status in a routine and standardised format. As a result the accuracy of these data in terms of categorisation is variable.¹⁶ Investment in expertise to adjust data for social class and develop techniques to allow stratification for other social factors could allow better use of the resource. It may also form the foundation for

¹⁵ *The Academy of Medical Sciences is undertaking a project 'Personal Data for Public Good: using health information in medical research' to develop proposals on key issues of consent, security of data, confidentiality and public engagement; therefore these issues will not be covered in detail in this report.*

¹⁶ *Wong, 1999.*

beginning to use NHS datasets to pick up safety signals as well as testing specific hypotheses. Analysis of large routine clinical datasets in the USA demonstrated that the Vioxx risk was detectable once the risk had been identified in clinical trials, but development of statistical and

bioinformatics tools will be needed in order to use such resources to identify warning signals. We recommend investment in such expertise, some of which is already available within the defence industry in the scanning of electronic traffic for unexpected signals.

Chapter five - *Biologicals: vaccines and gene therapies*

5.1 Biologicals make increasingly important contributions to the prevention and therapy of diseases. The rate of development and introduction of new biologicals has accelerated over the past two decades. New products include vaccines and recombinant-derived therapeutics including interferons, hormones, immunoglobulins and blood factors. Monoclonal antibodies for therapy, targeting of drugs and diagnosis are other examples of the expansion of biologicals. In some cases recombinant-derived products have replaced substances extracted from human or animal tissues, for example human growth hormone, with clear advantages for product safety and consistency.

5.2 There are contrasts in the approaches taken to secure the safety of biologicals, compared with chemical drugs, arising out of their nature and production. In general, the toxicological approaches applied to chemical drugs are of only limited relevance to biologicals. Biologicals are molecularly complex and often heterogeneous in composition. They cannot, with few exceptions, be characterised in precise chemical terms and require biological assays for their characterisation. For drugs, detailed chemical analysis is the key approach to quality and product consistency. Biologicals have a greater potential for batch-to-batch variation in production. Arising from the biological nature of the source materials, there are special safety issues concerning potential contamination with extraneous agents and special attention needs to be given to ensuring that harmful agents are not present.

5.3 Despite the historical differences in approach to securing the safety of biologicals and chemical drugs, recently there has been a trend towards a common approach, so that similar principles are applied to both groups of medicines by the major international and national regulatory authorities. This is a positive development which will favour the adoption of the most valuable aspects of the approaches taken for biologicals and chemical drugs.

5.4 It is not the intention to address the whole range of biological medicines here, but to use vaccines as examples of products widely used and gene therapy as an example of new medical developments.

Vaccines

5.5 As vaccines are used to prevent infection and disease in healthy individuals, primarily children, there is a major emphasis on safety by manufacturers, vaccinators, regulatory organisations and the public. In particular, standardisation is recognised as a key element in the assurance of quality and safety, reflecting important lessons learned from past events. International guidelines relating to the manufacture and testing of well-established vaccines are provided by the World Health Organization (WHO)¹⁷ and, for example, the European Pharmacopoeia. The production of vaccines and securing their efficacy and safety has much benefited from the availability of international biological reference preparations distributed on behalf of the WHO. These provide 'yardsticks' for internationally accepted units of measurement and are used as key reagents in the standardisation of laboratory tests. Several hundred biological standards, relevant to a wide range of products, are distributed by the UK National Institute for Biological Standards and Control on behalf of the WHO.

5.6 Another special feature of the regulation of vaccines is the requirement in the UK and other EU countries for batches of each production lot of vaccine to be independently tested by a national or international authority for compliance with licence specifications. This includes biological assays relevant to safety.

5.7 To complement and in some instances to replace biological tests, progress is being made in the application of advanced physicochemical methods to characterise the structure of vaccine

¹⁷ See WHO Guidelines on Principles for Non-clinical Evaluation of Vaccines.

materials. NMR spectroscopy has, for example, been found to be of value in the characterisation and quality control of meningitis vaccines involving bacterial polysaccharide–protein conjugates. It is recommended that efforts be made to expand such structural studies, which are likely to make a contribution to safety as well as efficacy.

- 5.8** Testing in animals is required for some vaccines. However, there are important opportunities for replacing some animal models by using, for example, molecular markers for virulence, as is the case for poliovaccine. In addition, *in vitro* assays in cell culture are being developed to assess the presence of toxins for some vaccines, thus replacing animals.
- 5.9** Research work to develop and evaluate non-animal alternatives should be given high priority by industry and funding bodies. There is currently a strong contention that the validation of surrogate tests is crucial but underfunded.
- 5.10** The quality and safety of a vaccine depends to a large extent on the source materials and manufacturing conditions under which it is made. Methods for the control of starting materials for production, as for the vaccines themselves, and the detection of potential contamination exist in many cases, but there remains an important need to develop and introduce additional and more sensitive tests, for example for the detection of prion materials.
- 5.11** Many vaccines are based on attenuated, live viruses or bacteria. The securing of safety depends on an understanding of the mechanism of attenuation and its genetic stability. In addition, better understanding of the pathogenesis of the natural infection, including sites of replication and mechanism of cell and tissue damage, is important to safety and research in this key area and should be increased.
- 5.12** Regarding clinical trials of vaccines, more information could be extracted from these by studies of the response to vaccination using, for

example, the 'omics technologies described earlier in this document. The use of these newer approaches may be expected to improve predictions of the likelihood of adverse events. Long-term follow-up of vaccine recipients with active surveillance for potential adverse reactions is important and will benefit from linkage to vaccine databases. The availability of such long-term information would have been a considerable advantage in dealing with the recent issue of the safety of the measles, mumps and rubella (MMR) vaccine, which was based on speculation derived from a handful of clinical observations.

- 5.13** Valuable input into the content and conclusions of this report was provided by a symposium *Progress Towards Assuring the Safety of Vaccines* organised by the Academy of Medical Sciences in collaboration with the UK Health Protection Agency in April 2004.¹⁸

Gene therapy

- 5.14** Gene therapy is perhaps the most recent novel and highly innovative approach to developing treatment for a variety of diseases including some that have proven difficult to deal with by existing approaches. The strategy is to transfer functional genetic material into human somatic target cells, in order to supplant the defective gene function of the patient. Genes relevant to therapeutic or preventative functions of the host are delivered in specifically designed vectors, generally of viral nature.
- 5.15** No gene therapy product is yet licensed anywhere in the world, but a large number of small clinical trials are in progress in the USA, Europe and Japan. There is much research and developmental work in progress in academia, biotechnology companies and the pharmaceutical industry. Current clinical trials cover therapy of monogenic inherited diseases, primarily haematological disorders, cancers, cardiovascular disease and intractable infections such as HIV. Gene therapy has the potential to be the source of a valuable class of medicinal

¹⁸ See www.acmedsci.ac.uk/p50evid4.html for further details (accessed 5 October 2005).

products of the future should the clinical studies show successful results.

5.16 The main general safety concerns for gene therapy area as follows:

- The possibility of insertional mutagenesis in a region of the recipient genome that predisposes to malignancy.
- Adverse effects induced by the proteins expressed by the introduced gene. There is a potential for autoimmune responses and other harmful immune response as well as other manifestations of the expressed proteins, which may be produced in physiologically unusually large quantities and in abnormal sites.
- Exposure of germ cells to the introduced gene, which is specifically prohibited by current UK and EU rules.
- Contamination of the gene therapy products by potentially harmful viruses used in the production process.

5.17 Clinical trials of gene therapy approaches need to pay particular attention to measures to avoid adventitious exposure of the treated person with the genetically modified organisms used as gene vectors.

5.18 In relation to safety it is clearly important to develop and apply appropriate test methods for individual vectors, which will include studies in cell cultures and, where appropriate, in animal models. For example, recent clinical studies in very young children with severe immunodeficiency in relation to SCID-XI

treatment, which were associated with the onset of leukaemia, provided the stimulus for research in mouse models relating to integration and leukaemia development. The ability to predetermine favoured sites of integration in the genome so as to avoid harmful mutagenesis is a major challenge for long-term research.

5.19 Gene therapy has considerable potential to lead to effective treatments for conditions where none exist at present. It is important that the products themselves should be well characterised by laboratory tests for purity, specificity and consistency. Novel biological assays will be required for use in pre-clinical studies.

5.20 There is much to be done in studies assessing the risks of randomly inserted genes and in comparing vectors in relation to various cell populations. It is important that regulatory authorities address the complex issues of safety for gene therapy, that clinical studies are well designed to yield the maximum possible information and that great attention be given to the health and welfare of individuals involved in the studies. As yet it is too early to predict in a broad sense the adverse effects that may be encountered when more and larger clinical trials are undertaken.

5.21 It is a positive consideration that several of the regulatory and testing approaches which have served us so well in securing safe and effective vaccines, and some of the lessons learned from these, are entirely relevant to safety in the field of gene therapy.

Chapter six - Assessment, communication and management of risk

The present situation

- 6.1** Although great efforts are made to ensure that medicines are used safely, risk is inherent in any therapeutic intervention. There is no such thing as an absolutely safe medicine. Regulatory authorities pay close attention to the efficacy claims made, and precautions needed, for proper use of new medicines, and these requirements are reflected in the labelling of the medicine and in promotional material. But, under time pressure in medical practice and active promotion by company representatives, the detailed indications and warnings may be overlooked or forgotten. Considering the potency of many medicines, and their potential for harm if not used correctly, relatively little effort is expended on balanced, impartial education of medical students and practising doctors in therapeutics.
- 6.2** Publications of the results of clinical trials are prone to describe the efficacy of the treatment regimes in detail but often give only a relatively brief account of safety issues. This problem is not confined to industry-sponsored trials and may reflect the views of authors and editors that readers are less interested in such information. The lack of detail on safety results makes it difficult or impossible to carry out the kind of meta-analysis of safety data across many trials that are performed routinely for efficacy results, for example in Cochrane systematic reviews. Posting full safety data on company websites would be very helpful and academically sponsored trials should aim to do no less. A standardised format for the presentation of benefit and risk would help.
- 6.3** Medicines are often launched onto the market amid a flood of generally favourable publicity, including lectures by leading medical experts who have worked on the drug (known in industry as Key Opinion Leaders or KOLs). No
- doubt most are motivated by genuine enthusiasm but they rarely convey a balanced view. The volume of publicity may encourage unrealistic expectations in prescribers and the general public about the safety and efficacy of the new drug.
- 6.4** As the time taken to develop a drug increases, there is a consequent reduction in the period before patent expiry for marketed drugs. This has led companies to attempt to grow sales as fast as possible to maximise returns - assisted in the USA by direct to consumer advertising. However, unless companies are allowed to promote new products responsibly patients may fail to benefit from them and the UK is one of the slowest to adopt new products in the developed world. The appropriate period of commercial exclusivity for a new drug needs international consideration in conjunction with proposals for more controlled entry into the market for a new drug.
- 6.5** In the UK, advertising from pharmaceutical companies focuses instead on prescribers, as highlighted in a recent House of Commons report.¹⁹ Drugs that are available over the counter (OTC) may be advertised to patients, but those that are available by prescription only may not.
- 6.6** While considerable efforts are made by regulatory authorities and responsible pharmaceutical companies to monitor safety issues and alert prescribers about them, until recently this has been regarded as an activity somewhat separate from the critical need to demonstrate efficacy.
- 6.7** In the rush to achieve maximum sales it is important that safety concerns are not minimised. The perception that important safety data on some COX-2 inhibitors were not revealed in a timely manner has the potential to

¹⁹ *The influence of the pharmaceutical industry, 2005.*

cause problems for the entire class of drug and more than outweigh the marketing advantage initially created by overemphasising the potential benefits.

- 6.8** Carefully planned risk management can be very effective, and several companies have been able to keep on the market important medicines with a safety profile which might otherwise have been considered unacceptable. An example is the use of intravenous aminoglycoside antibiotics such as gentamycin in severe infections. These drugs can severely damage hearing and balance if the concentration is too high, as can easily happen in a very ill patient whose kidney function is impaired. Physicians' knowledge of this problem and routine monitoring of the plasma concentrations of the antibiotic have largely avoided severe toxicity. Another, more recent, example of effective risk management is the use of the HIV drug, abacavir (see section 3.26).
- 6.9** One of the most difficult areas is the provision of intelligible information for patients. A minority of patients read the package inserts provided with medicines and a very few read them in their entirety.²⁰ These leaflets present a long list of side effects with no attempt to categorise by incidence or severity let alone likelihood for an individual. The short average contact time between family doctors and their patients restricts the amount of person-to-person information imparted, although this type of contact probably has the highest impact.
- 6.10** Specialist patient support organisations such as CancerBACUP provide some of the most dependable information. More patients are turning to the Internet for information about their diagnosis and their treatment, but the many sources available on the web vary greatly in reliability. A basic difficulty is that most patients have a very limited knowledge of biology and medicine: words that have a very precise meaning to a doctor may convey relatively little to a patient.

²⁰ Raynor and Knapp, 2000.

²¹ Kohn et al., 1999.

Opportunities for improvement

Informing prescribing doctors and involving patients

- 6.11** The front line of drug safety is in the doctor's clinic when he or she writes a prescription and hands it to the patient. Clear warnings and carefully worded advice at this stage can have a real impact. Many serious adverse reactions occur not with new products (although these achieve most of the publicity) but with longer-established ones that are supplied largely by generic manufacturers. High on the list are anticoagulants such as warfarin, non-steroidal anti-inflammatory drugs and drugs used to treat heart disease such as digoxin. Given the very wide variety of human disease and the greatly expanded range of treatment options, some mistakes are inevitable but great efforts must be made to keep these to a minimum. The USA Institute of Medicine report *To Err is Human: Building a Safer Health System* reviews many of the issues arising from medical errors.²¹
- 6.12** One option that already exists but needs further development is to use intelligent software within the prescriber's IT system to remind her or him when a problem seems likely. This is not as easy as it sounds because the software has to be intelligent enough not to keep issuing warnings when the problem is non-existent or relatively minor, for if it does it will eventually be turned off or ignored. This is an area that needs further development. Given the rapid expansion of knowledge about mechanisms of toxicity it is reasonable to assume that most practitioners are not fully up-to-date on safety issues and educational efforts are needed. In this connection the Academy notes with regret the apparent decline in teaching of clinical pharmacology and therapeutics in many medical schools.
- 6.13** The patient is the person who cares most about the outcome of treatment. Development of improved methods of communicating the risks and benefits of drugs, in order to assist the

doctor's prescribing and the patient's understanding, is important. For example, relating the risks and benefits to common situations and giving absolute as well as relative risks may aid understanding. Industry, regulators and the National Institute for Health and Clinical Excellence (NICE) ought to work together to develop standardised approaches to presentation of risk and benefit. A recent article in the *New England Journal of Medicine* used a matrix of open circles, some of which were filled in black to illustrate degrees of risk.²² A generally agreed method of portraying serious risks and major benefits, extensively tested with patients and doctors, would be very valuable.

- 6.14** Most households now have Internet access. Many patients now use the web as an important source of information. Its capability is only just beginning to be exploited as a means of helping patients on long-term drug therapy and there is a need to help patients identify reliable sources. It is readily possible to foresee the day when as well as a 'Dear Doctor' letter from a pharmaceutical company advising physicians of a drug safety problem there will be a confidential 'Dear Patient' letter sent almost simultaneously via the Internet by doctors to all their patients (by name) who are recorded as having an active prescription for the drug in question. The use of the web as a means of periodic bidirectional communication between doctors and their patients, to check on progress and to remind and advise, could also have important applications in achieving safer use of drugs. Communications between doctors and patients in the UK NHS are very slow and primitive by current standards.

Regulatory and industrial oversight

- 6.15** Considerations of efficacy and safety should be inseparable for all medicines. For that reason the Academy does not consider that a separate agency dealing with safety is desirable, but it would like to see greater emphasis on safety within existing structures. In the USA, the creation of a Drug Safety Oversight Board within the FDA's Centre for Drug Evaluation and
- Research has recently been announced. The UK and the EU should consider whether such a system would be helpful and how we could work closely with the USA. Within pharmaceutical companies there is a need for close integration of those staff dealing with product efficacy and those with safety.
- 6.16** This new American Board will be responsible for providing enhanced oversight and transparency on drug safety issues: managing information on risks; resolving scientific disagreements on safety data; developing drug safety policies; and in increasing the flow of data between doctors and patients. The new communication channels are: the Drug Watch web page, to include emerging safety information on newly approved and older drugs; information sheets for healthcare professionals; and patient information sheets to contain new safety information as well as basic information about how to use the drug. Placing data in the public domain is not enough: there needs to be a credible independent body to analyse the data, identify genuine safety concerns and dismiss false safety concerns. To be credible, such a board would need to be seen to be independent.
- 6.17** In the USA, collaboration on a new electronic medicine safety monitoring system 'MedNet' across government agencies and the private sector will create an active surveillance and evaluation programme for monitoring marketed drugs. It is of interest that the FDA has a contract with the UK GPRD to obtain safety information. The NHS provides an unrivalled opportunity to collect and analyse computerised data on clinical care that could be analysed to detect safety signals for drugs.
- 6.18** The new functions of the Drug Safety Oversight Board will be integrated with the current responsibilities of the FDA rather than creating an entirely new regulatory agency to monitor drugs after approval. Clearly, there are also implications for ensuring that pharmacovigilance and communication are optimised in Europe. Since drugs are used globally, it seems sensible

²² *Elmore and Gigerenzer, 2005.*

that safety systems are also globalised, and closer working between European and USA agencies should be a priority.

Conditional approval?

- 6.19** Other radical options are also being entertained as part of the continuing dialogue between companies and regulators. One of these is a provisional licensing system, with drug approval confirmed subject to evidence of efficacy and safety from widespread use. Defining the nature of the probationary requirements may not be easy, but lessons can be learned from the pilot schemes already agreed for risk sharing after approval. For example, studies on disease-modifying multiple sclerosis drugs²³ and a statin²⁴ represent partnership between the manufacturer and health services to deliver agreed performance in terms of cost effectiveness. However, if conditional approval becomes another burden of cost and delay in marketing new drugs, it will be counterproductive.
- 6.20** Conditional approval with monitoring of substantial numbers of patients might allow drugs to be approved with less onerous pre-marketing trials. It will also require consideration of the patent life for a new drug to ensure companies have an opportunity to obtain appropriate benefit from R&D investment. Currently many new drugs are used with little attempt to collect data. A conditional approval system could allow early entry of new drugs onto the NHS with the real prospect of generating important safety data.
- 6.21** While the focus of existing studies of this type has been on efficacy, the determination of safety is probably best suited to this approach whereas efficacy is better assessed in randomised trials. There should be further discussion of the costs and benefits of conditional approval. There will be difficult points to resolve in ensuring that post-marketing studies cover all of the relevant patient population, for example to reflect the

natural incidence of co-morbidities, rather than imposing exclusion criteria (excluding patients at higher risk) so as to accumulate a 'clean' data set.

Risk management

- 6.22** A vital part of product stewardship is risk management. The risk management strategy ought to go far beyond collection and analysis of safety reports. An essential part of risk management is to attempt to foresee the possible problems a compound may encounter when it comes into general use, including secondary pharmacological effects, formation of reactive metabolites, failure to observe contraindications, mistakes in dose, serious concurrent diseases and their treatment and, increasingly importantly, genetic polymorphisms. It is likely that new data on the impact of genetic polymorphisms and debates about their application will come to dominate future discussion of low frequency but serious adverse effects. Ought a pharmaceutical company to consider the impact of a polymorphism, or more difficult still, a combination of polymorphisms affecting the safety of their product present in 10%, 1%, 0.1% or 0.01% of a population? In the past products have been withdrawn (e.g. the antibiotic chloramphenicol that rarely caused agranulocytosis) when the life-threatening adverse effect occurred in only about 1 in 100,000 patients treated.
- 6.23** These are perplexing issues that deserve informed public debate. Companies are now required to have a risk-management strategy for each marketed product and one consequence is likely to be closer integration of the safety and efficacy aspects of product development. Regulatory agencies should make public the agreed risk-management strategy for new products. An effective, well implemented, risk-management strategy should allow many products with safety issues to remain on the market because the means to avoid the risk in vulnerable patients has been developed. Pharmaceutical companies, as well as patients,

²³ Miller, 2003.

²⁴ Chapman et al., 2003.

have much to gain from effective risk management and clear presentation of the approach.

Crisis management

6.24 During the seven decades or so of modern therapeutics there have been several serious crises. For example, deformed babies with thalidomide, serious eye, skin and peritoneal changes with practolol, liver toxicity with troglitazone, increased incidence of heart attacks with rofecoxib and other COX-2 inhibitors, etc. Several major crises in relation to vaccination have occurred. One in the USA in the late 1950s was the ‘Cutter incident’ that involved several hundred cases of polio in recipients of Salk poliovaccine. This occurred due to incomplete inactivation of the virus during vaccine production, and was subsequently remedied by improvements in production techniques and testing. The event precipitated a major improvement in emphasis on quality control and safety testing. The misconception in recent years that measles, mumps and rubella (MMR) live vaccine was associated with chronic inflammatory bowel disease and autism in children provoked serious public concern and had a lasting negative impact on vaccine uptake and public confidence and vaccination safety.

6.25 Handling these crises has proved difficult. The initial reaction of pharmaceutical company staff, some of whose lives’ work has been the development of the compound, may be one of

disbelief or denial. Pharmaceutical companies and regulatory authorities appear to react slowly because the information reaching them at the outset is often limited and poorly authenticated. News media create a storm of concern that may lead patients to discontinue needed treatment. Lawyers begin trawling for patients who may have been harmed to launch class actions for damages and bar access to their clients when additional clinical details are sought. There ought to be a better way of handling crises. There is a need to be prepared, and an essential element of a speedy and sensible reaction is to gain access to reliable, detailed, clinical data on index cases as soon as possible.

6.26 Large clinical databases are a promising source of information for crisis management but the existing ones all have some limitations. HMO databases in the USA have limited clinical information, and the UK GPRD does not include hospital information. As most severe reactions end up in hospital, and it is to some extent predictable what vital organs are most likely to be affected, for example liver, blood, kidney or heart, clinical networks organised by medical specialist societies (national and international) in collaboration with regulatory agencies could play a critical role, with appropriate IT support. In some places these arrangements already exist but they need to be put on a firmer basis. A truly independent body charged with responsibility for safety might be a mechanism to ensure that true safety concerns lead to prompt action and that false ones are rapidly dismissed.

Chapter seven - *Building capacity for better safety assessment*

Infrastructure, training, manpower and research requirements

- 7.1** Safety assessment for pharmaceutical products is a rapidly developing and evolving, multi-disciplinary activity. As populations age it is likely that in future approaching 50% of the population will be taking a therapeutic drug and most older patients will be taking several different medicines at any one time. Given this high exposure of the population it is surprising that drug safety does not figure higher on the national medical research agenda.
- 7.2** It is a testimony to the considerable efforts made by the pharmaceutical industry and the regulatory bodies that most medicines are relatively safe when used as recommended. But, as the use of medicines extends to less severe medical conditions and enhancing quality of life, the safety requirements become ever more stringent. The boundary between social drugs, such as caffeine and alcohol, and therapeutic agents designed to enhance intellectual or physical performance in older people may become ever more blurred.
- 7.3** The number of disciplines that contribute to safety assessment has continued to increase and it is readily foreseeable that human genetics and social and environmental sciences, particularly the former, will play an increasing role. While the largest pharmaceutical companies have expanded their capacity in safety assessment across a wider range of disciplines, the regulatory bodies and the major academic centres have lagged behind. The skill of integrating many different sources of information to make a balanced judgement is relatively rare and only limited effort has been made to train non-clinical and clinical scientists to adopt an integrated approach.
- 7.4** At present most matters in relation to drug efficacy and safety are regarded by government and research funding agencies as, primarily, a financial responsibility of the research-based pharmaceutical industry. As a greater proportion of the medicines in use become generic, with active government encouragement, this position becomes less tenable.
- 7.5** It is doubtful that a major initiative on the validation of new methods of evaluating safety could be carried out in a single European country. Studies are likely to involve interdisciplinary and cross-sector collaboration. One example of this type of collaboration is that of a large consortium of pharmaceutical companies which has bid for funding from the European Framework Programme. The bid includes a proposal (called PredTox) to establish processes to improve the predictability of toxicology experiments by integrating the new 'omics technologies.
- 7.6** PredTox involves the construction of an integrated database with information on animal experiments of compounds with known toxicity profiles to compare traditional endpoints with 'omics data. One aim of the project is to facilitate access to new technologies for EU regulatory authorities, and to help define guidelines for use and interpretation of the data. This should be made available in the public domain.
- 7.7** There are a great many opportunities to progress better sharing of company safety data across similar classes of compounds and to embark on collaborative research. A commitment to partnership across the stakeholder constituencies can be expected to yield considerable progress in animal and model development and acceptance, clarification of contribution by new technologies and identification of ADR mechanisms. The assessment of safety needs to be seen as 'pre-competitive' and is too important to be left as a competitive activity with secrecy preventing progress. This collaboration could usefully be extended to training the next generation of safety scientists and physicians as a joint venture of companies,

regulatory agencies and academia. But to make this possible there would have to be a contribution of government funds. We recommend that systems to explore sharing of pre-competitive safety data are explored as a matter of urgency.

7.8 Academia needs to develop expertise in the biology and medicine of safety assessment. This will require establishing a limited numbers of centres of excellence with requisite critical mass in the ‘omics, bioinformatics, systems biology and imaging technologies, as well as expertise in *in vivo* studies in animals and humans such as experimental medicine to conduct mechanistic research on potential or real adverse effects in humans.

7.9 Several of the Academy working parties argued that there was a need for a UK National Centre for Drug Safety to span the wide range of disciplines involved and sponsor research, for example on new biomarkers from animals to humans and on genetic factors in susceptibility to toxicity. Such a centre could also draw up training programmes in consultation with interest parties in industry. They argued that its existence would enhance the competitiveness of the UK as a centre for pharmaceutical research.²⁵

7.10 The UK already has a substantial number of governmental (the Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC), NHS R&D) and charitable bodies (the Wellcome Trust, Cancer Research UK (CRUK), the British Heart Foundation (BHF), the Association of Medical Research councils (AMRC), etc.) supporting biomedical research and the Academy is hesitant about recommending formation of another without very careful consideration. Safety assessment transcends the remit of the main governmental research funding agencies as well as the regulatory agency, the MHRA. The Academy’s FORUM with Industry could form a model of how to develop a dialogue about how best to address a growing national need for a better coordinated approach to education and research in safety assessment and to convince government that investment would add value to the country as a research base for industry. The Academy proposes to invite representatives from the interested bodies for discussion about how best to progress this national need. The Academy does not, at this stage, rule out recommending formation of a national centre but will re-evaluate the question after consultations.

²⁵ *The Academy notes with interest the proposals from the European Platform on Innovative Medicines to establish a European Centre for Drug Safety as part of the 7th Framework Programme.*

Appendix 1 - Remit

Introduction

Animal research plays an essential part in the understanding of normal and disordered biological processes and in the development and evaluation of novel medicinal products. It will continue to contribute significantly in the foreseeable future, but there is wide acceptance of the principles of reduction, refinement and replacement, where appropriate, of the use of animals in scientific procedures. Advances in human genomics research, together with the sequencing of the main laboratory species, provide an important opportunity to understand the comparative determinants of toxicity and adverse reactions. It is the aim of this project to survey the current 'state of the art' in the assessment of the safety of medicinal products and to identify scientific opportunities, across a broad front, to improve safety assessment.

The safety of medicines remains a major public concern, and the goal of the Project is to improve the prediction of hazard while enhancing development opportunities and improving risk assessment by identifying newer scientific approaches.

The Project draws on the resources of the Academy's FORUM to bring together interested parties from academia, industry and the regulatory agencies, covering all relevant scientific disciplines and addressing issues for animal and clinical studies.

Project remit

1. The Project will examine and evaluate the methods available to assess and predict potential risk of adverse events associated with medicines; addressing both technologies and the process of assessment.
2. Case Study Analysis will be based on chemical drugs, conventional and recombinant biological products, vaccines and gene therapy products, in order to identify the principles needed for construction of the evidence base and for the development of risk assessment procedures.
3. A survey of current, relevant activities and developments in academia and medical research, industry and other bodies will be conducted in order to identify the research strengths,

weaknesses, opportunities and threats and to serve as the basis for developing recommendations.

4. The Project Steering Committee will take account of relevant activities by other bodies and will identify the particular value to be added by the Academy-based activity, for example in sharing best practice, identifying options and disseminating awareness more broadly.
5. Recommendations will cover R&D requirements and priorities and the issues for translational research, including the development of knowledge, skill sets and competencies and the value of public-private collaborations, in order to characterise the key elements of a national/European/international strategy to strengthen capability in this area. The Project will also advise on an appropriate approach to monitor subsequent outcomes.
6. The Steering Committee will consider the potential to initiate proof-of-concept studies in risk assessment in agreed target areas.

Target audiences and specific outputs

The primary deliverable is an authoritative Report and designated outputs are intended to be relevant for key stakeholder groups (in the UK and internationally) across industry, academia, government, regulatory authorities and policy-makers:

1. Improving safety of medicines by identifying and understanding the defects in current risk assessment approaches capitalising on new opportunities in science and technology.
2. Explaining role and responsibility of industry leadership in developing improved models in predictive toxicology – including alternatives to animal research – and importance of standardisation of tools, metrology and quality assurance procedures.
3. Informing and assisting Regulatory Authorities in the adaptation of new technologies; and identifying resources to provide expertise to advice regulators.
4. Educating public and media on the importance of science and technology and new approaches in safety evaluation.

5. Identifying skills and training needs in regulatory science; providing strategies for the training and advice for the next generation of toxicologists, pharmacologists and other relevant sciences and for the continuing professional development of the current generation.

Fields of science involved and style of working

The Project is expected to range widely in the life sciences, including cell biology, pharmacology, pathology, drug metabolism, genetics and genomics and informatics-based technologies, and molecular medicine, and to adopt interdisciplinary perspectives in developing the integrated mechanism-based approach to risk assessment.

The cross-sectoral Steering Committee will be constituted to function with transparency and will include experts from academia, industry and the Regulatory Authorities; predominantly drawn from the UK but with broad awareness of global developments and, in particular, European policy matters.

The Steering Committee will have the responsibility for collecting evidence across a wide front, analysing issues and generating options for recommendations. The study of several specific areas of the Project will be delegated to Working Groups and may be addressed in various ways (e.g. by organising a series of Working Group meetings, holding workshops or other consultative actions). Topics for Working Groups include: (1) Pre-clinical toxicology; (2) Safety pharmacology; (3) Pre-marketing (clinical phase I, II and III) assessment; (4) Vaccines; (5) Gene therapy; (6) Risk–benefit assessment; and (7) Post-marketing surveillance. Working Group Chairs will be members of the Steering Committee, to ensure coordination and leadership, and cross-sectoral membership of the Working Groups will be agreed by the Steering Committee. Further specification of working style, associated seminar events and timetable will be a priority next step.

As an activity initiated under the auspices of the Academy’s FORUM, it will be important for the Steering Committee to draw upon the FORUM, both as an initial resource and as a stakeholder group with whom to test emerging recommendations.

Appendix 2 - Working Group members

Editorial team

Dr Geoffrey Schild, FMedSci (Chair)

Dr Gwyn Morgan (Scientific Advisor)

Sir Colin Dollery, FMedSci

Senior Consultant
GlaxoSmithKline

Sir John Skehel, FRS, FMedSci

Director
MRC National Institute for Medical Research

Review Board

Professor Patrick Vallance, FMedSci (Chair)

Head of Division of Medicine
University College London

Sir Alasdair Breckenridge, FRSE, FMedSci

Chairman
Medicines and Healthcare products Regulatory
Agency

Dr Joseph DeGeorge

Vice President Safety Assessment
Merck & Co., Inc. (USA)

Professor Roderick Flower, FRS, FMedSci

Professor of Biochemical Pharmacology
William Harvey Research Institute

Dr Robert Temple

Associate Director for Medical Policy
Food and Drug Administration

Professor Jack Uetrecht

Canada Research Chair in Immunotoxicity
University of Toronto

Pre-clinical toxicology

Dr Sandra Kennedy (Co-chair)

Vice President, Safety Assessment UK
GlaxoSmithKline

Dr Lewis Smith (Co-chair)

Global Head of Product Development
Syngenta

Dr Graham Betton

Senior Principal Scientist, Experimental Pathobiology
AstraZeneca

Dr John Haselden

Head, Metabolic Profiling
Investigative Preclinical Toxicology
GlaxoSmithKline

Dr E. Clive Joseph

Senior Director, Safety Evaluation
Pfizer

Dr George Orphanides

Head, Investigative Toxicology and Stage 1 Toxicology
Syngenta

Dr Christopher Powell

Director, Safety Assessment Europe
GlaxoSmithKline

Mr Henry Stemplewski

Pharmacotoxicologist
Medicines and Healthcare Products Regulatory
Agency

Dr Jonathan Tugwood

Principal Scientist, Molecular Toxicology Group
AstraZeneca

Safety pharmacology

Dr Rob Wallis (Co-chair)

Executive Director, Discovery Biology
Pfizer Global Research and Development, Sandwich
Laboratories

Dr Tim Hammond (Co-chair)

Vice President Safety Assessment UK
AstraZeneca

Dr Peggy Guzzie

Senior Director, Safety Sciences
Pfizer Global Research and Development
Connecticut

Dr Peter Hoffmann
Head Non-Clinical Drug Safety
Pharmaceuticals Division
F. Hoffmann – La Roche

Professor Ian Kimber
Head of Research
Syngenta Central Toxicology Laboratory

Dr Ian MacKenzie
Head of Pharmacology
Covance Laboratories

Professor Beatriz Silva Lima
Associate Professor, Department of Pharmacology
University of Lisbon

Dr Andrew Sullivan
Director of Safety Pharmacology, Safety Assessment
GlaxoSmithKline

Dr Konrad Tomaszewski
Senior Director, Safety and Risk-management
Pfizer Global Research and Development

Professor William Dawson
Managing Director
Bionet

Pre-marketing (clinical phase I, II and III) assessment

Professor David Webb, FRSE, FMedSci (Co-chair)
Christison Professor of Therapeutics and Clinical Pharmacology
University of Edinburgh

Professor Martin Wilkins (Co-chair)
Professor of Clinical Pharmacology
Imperial College London

Professor Adam Cohen
Director
Centre for Human Drug Research
University of Leiden Medical Centre
The Netherlands

Professor Colin Garner
Chief Executive Officer
Xceleron

Professor Paul Grasby, FMedSci
Chairman, Brain Disorders Section
MRC Clinical Sciences Centre
Hammersmith Hospital

Professor Mervyn Maze, FMedSci
Chair, Department of Anaesthetics and Intensive Care
Imperial College London

Professor David Newell
Professor of Cancer Therapeutics
Northern Institute for Cancer Research
University of Newcastle-upon-Tyne

Professor Walter Nimmo
Vice Chairman
Charles River Laboratories

Professor Paul Rolan
Medical Director
Medeval

Professor Geoff Tucker
Professor of Clinical Pharmacology
Head, Academic Unit of Clinical Pharmacology
University of Sheffield

Vaccines

Dr Philip Minor (Chair)
Head of Virology
National Institute for Biological Standards and Control

Dr Mike Corbel
Head, Division of Bacteriology
National Institute for Biological Standards and Control

Dr Elwyn Griffiths
Associate Director General
Biologics and Genetic Therapies Directorate
Health Canada

Professor Adrian Hill, FMedSci
Professor of Human Genetics
Wellcome Trust Principal Research Fellow
University of Oxford

Dr Christopher Jones

Head, Laboratory for Molecular Structure
National Institute for Biological Standards and
Control

Professor Elizabeth Miller

Head, Immunisation Department
Centre for Infections
Health Protection Agency

Professor Kingston Mills

Professor of Experimental Immunology
Department of Biochemistry
Trinity College, Dublin

Professor Peter Openshaw, FMedSci

Professor of Experimental Medicine
National Heart and Lung Institute

Dr Clive Sweet

Senior Lecturer, School of Biosciences
University of Birmingham

Gene therapy

Professor Klaus Cichutek (Chair)

Vice President, Paul Ehrlich Institute
Langen
Germany

Professor George Dickson

Professor of Biomedical and Molecular
Cell Biology
Royal Holloway, University of London

Professor Bernd Gänsbacher

Department of Surgery
University of Munich

Dr Anthony Meager

National Institute for Biological Standards and
Control

Dr James Robertson

National Institute for Biological Standards and
Control

Professor Adrian Thrasher

Professor of Paediatric Immunology
Institute of Child Health
University College London

Risk–benefit assessment

Dr Gwyn Morgan (Co-chair)

Professor Alan Boobis, OBE (Co-chair)
Director
Department of Health Toxicology Unit
Imperial College London

Professor John Ashby

Senior Syngenta Fellow
Syngenta Central Toxicology Laboratory

Dr John Evans

Senior Director, Pathology
Safety Assessment
AstraZeneca

Professor David Harrison

Head, Division of Pathology
University of Edinburgh

Professor Brian Lake

Head of Molecular Sciences Department
BIBRA International Limited

Professor Peter Moldéus

Vice President, Global Safety Assessment
AstraZeneca
Sweden

Professor B. Kevin Park, FMedSci

Head, Department of Pharmacology
University of Liverpool

Dr Jennifer Sims

Global Head of Safety Profiling and Assessment
Project Support
Novartis Pharma

Dr Per Sjöberg

Partner
Eureda KB
Sweden

Post-marketing surveillance

Professor Munir Pirmohamed (Co-chair)

Professor of Clinical Pharmacology and Honorary
Consultant Physician
University of Liverpool

**Professor Janet Darbyshire, OBE, FMedSci
(Co-chair)**
Director
MRC Clinical Trials Unit

Dr Richard Ashcroft
Head of Medical Ethics Unit and Reader
in Biomedical Ethics
Imperial College London

Dr Keith Beard
Consultant Physician and Hospital Prescribing
Adviser
NHS Greater Glasgow

Professor Alison Blenkinsopp
Professor of the Practice of Pharmacy, Department
of Medicines Management
Keele University

Dr Kevin Cheeseman
Global Director of Development Pharmacogenetics
AstraZeneca (UK)

Professor Stephen Evans
Professor of Pharmacoepidemiology
London School of Hygiene and Tropical Medicine

Dr Stephen Inglis
Director, National Institute for Biological Standards
and Control (NIBSC)

Dr Alun McCarthy
Head of Clinical Pharmacogenetics and Psychiatry,
Medical Genetics
GlaxoSmithKline (UK)

Dr Frances Rotblat
Senior Physician
MHRA

Professor Saad Shakir
Director
Drug Safety Research Unit Southampton

Dr Lincoln Tsang
Attorney, Arnold and Porter LLP
Non-executive member of the National Biological
Standards Board, NIBSC

Professor Tom Whalley
Director of HTA Programme
Department of Pharmacology and Therapeutics
University of Liverpool

Dr Louise Wood
Director of GPRD Division
MHRA

Appendix 3 - Glossary and abbreviations

ADR	Adverse Drug Reaction	MRC	Medical Research Council
ALT	Alanine Aminotransferase	NCE	New Chemical Entity
AMRC	Association of Medical Research Charities	NHS	National Health Service
BBSRC	Biology and Biological Sciences Research Council	NICE	National Institute for Health and Clinical Excellence
BHF	British Heart Foundation	NMR	Nuclear Magnetic Resonance
Celecoxib (Celebrex)	A COX-2 inhibitor used to reduce pain and inflammation in osteoarthritis and rheumatoid arthritis	NOAEL	No Observable Adverse Effect Level
COX-2 inhibitor	A class of non-steroidal anti-inflammatory drugs (NSAIDs), thought to have fewer side-effects than traditional NSAIDs	NPfIT	The National Programme for Information Technology coordinated by NHS Connecting for Health
CRUK	Cancer Research UK	OTC	Over the Counter - a medication that is available from a pharmacy without a prescription
DNA	Deoxyribonucleic acid	PCR	Polymerase Chain Reaction
ECG	Electrocardiogram	PEM	Prescription Event Monitoring
EudraCT	A database of all clinical trials commencing in the European Union from May 2004 onwards	PET	Positron Emission Tomography
EudraVigilance	A data processing network and management system for pharmacovigilance in the European Economic Area	Pharmacogenetics	The study of genetic factors that influence an organism's reaction to a drug
FDA	Food and Drug Administration	PoC	Proof of Concept
Genomics	The branch of genetics that studies organisms in terms of their genomes (their full DNA sequences)	Polymorphism	A variation in the DNA that is too common to be due merely to new mutation. A polymorphism must have a frequency of at least 1% in the population
GP	General Practitioner	Proteomics	A branch of biotechnology concerned with analysing the structure, function and interactions of the proteins produced by the genes of a particular cell, tissue or organism, organising the information in databases, and applications of the data
GPRD	General Practice Research Database	R&D	Research and Development
HIV	Human Immunodeficiency Virus	Rofecoxib (Vioxx)	A type of COX-2 inhibitor used in the management of acute pain and osteoarthritis
HMO	Health Maintenance Organisation	SCID-XI	X-linked severe combined immunodeficiency
IT	Information Technology	SNP	Single Nucleotide Polymorphism
KOL	Key Opinion Leader	SSRI	Selective Serotonin Re-uptake Inhibitor
MEMO	The Medicines Monitoring Unit	WHO	World Health Organization
Metabolomics	The study of changes in metabolite profiles as a result of a biological disruption (such as disease or physiological stress).		
MHRA	Medicine and Healthcare Products Regulatory Agency		
MMR	Measles, Mumps and Rubella		
MORI	Market & Opinion Research Institute		

Appendix 4 - References

Chapman, S., Reeve, E., Rajaratnam, G. and Neary, R. (2003)

Setting up an outcomes guarantee for pharmaceuticals: new approach to risk sharing in primary care.

British Medical Journal, 326, 707–709

Elmore, J. G. and Gigerenzer, G. (2005)

Benign breast disease – the risks of communicating risk

New England Journal of Medicine, 353, 297–299

House of Commons Health Committee (2005)

The influence of the pharmaceutical industry

London: The Stationery Office Limited

Kohn, L., Corrigan, J. and Donaldson, M. (eds) (1999)

To err is human: building a safer health system.

Institute of Medicine. Washington DC, National Academy Press

Kola, I. and Landis, J. (2004)

Can the pharmaceutical industry reduce attrition rates?

Nature Reviews: Drug Discovery, 3, 711–715

Miller, M. A. (2002)

Chemical database techniques in drug discovery.

Nature Reviews: Drug Discovery, 1, 220–227

Pirmohamed, M., James, S., Meakin, C., Green, C., Scott, A. K., Walley, T. J., Farrar, K., Park, B. K. and Breckenridge, A. M. (2004)

Adverse drug reactions as a cause of admission to hospital:

Prospective analysis of 18 820 patients

British Medical Journal, 329, 15–19

Raynor D. K. and Knapp, P. (2000)

Do patients see, read and retain the new mandatory medicines information leaflets?

Pharmaceutical Journal, 264, 268–270

Wong, I. C. K. (1999)

Pharmacovigilance resources in the United Kingdom.

Pharmaceutical Journal, 263, 258–288



The Academy of Medical Sciences
10 Carlton House Terrace
London SW1Y 5AH

Tel: 020 7969 5288

Fax: 020 7969 5298

Email: apollo@acmedsci.ac.uk

Web: www.acmedsci.ac.uk

Date of publication: November 2005