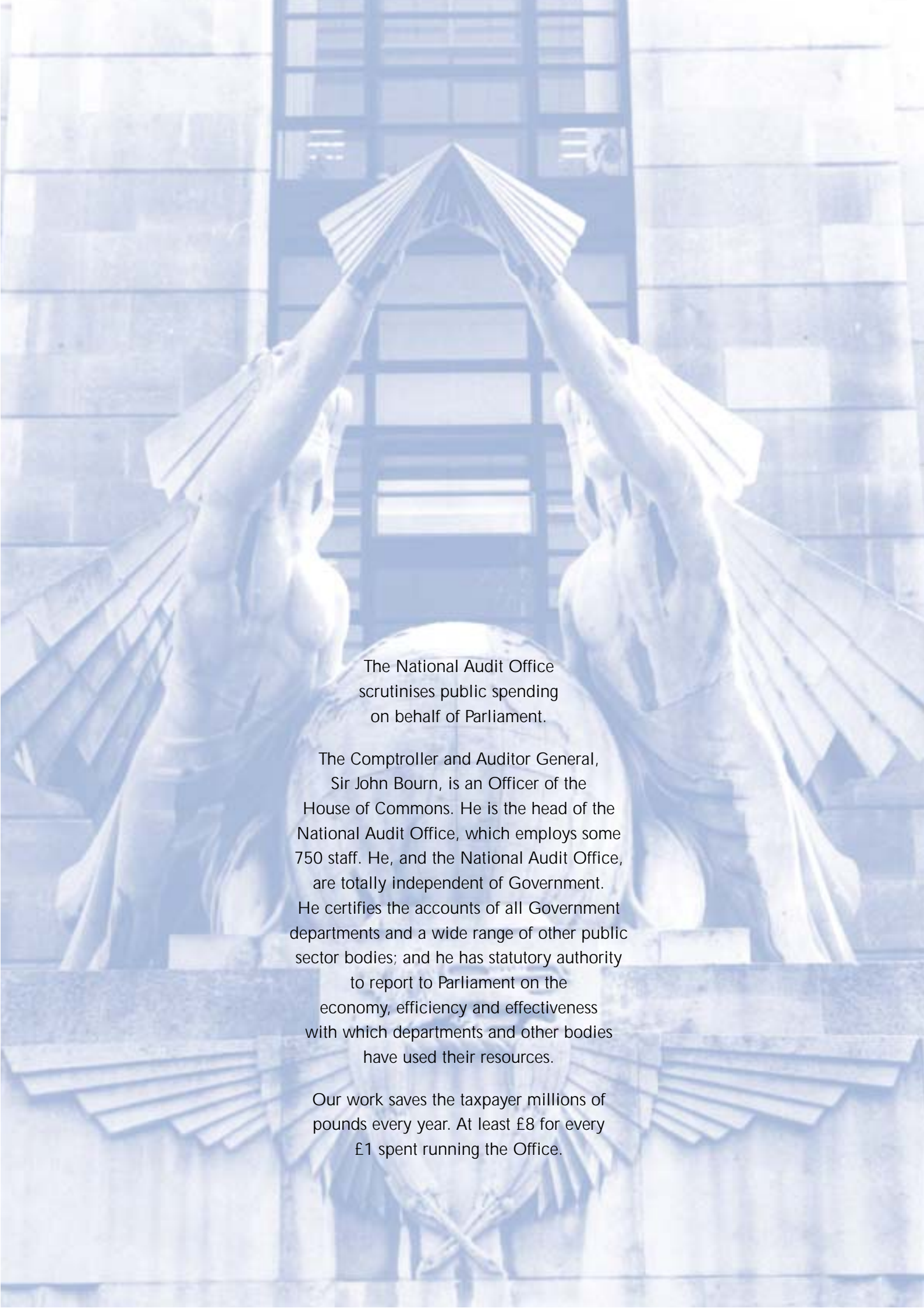


# Safety, quality, efficacy: regulating medicines in the UK

REPORT BY THE COMPTROLLER AND AUDITOR GENERAL  
HC 255 Session 2002-2003: 16 January 2003





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# Safety, quality, efficacy: regulating medicines in the UK



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This report has been prepared under Section 6 of the National Audit Act 1983 for presentation to the House of Commons in accordance with Section 9 of the Act.

*John Bourn* National Audit Office  
Comptroller and Auditor General 8 January 2003

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# executive summary

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- 1 Since 1989, the Medicines Control Agency (the Agency) has been responsible for protecting public health by ensuring the safety, quality and efficacy of well over a billion prescriptions and medicines sold over the counter in the UK each year. This role is rooted in the 1968 Medicines Act which was a response to the 1960s thalidomide tragedy and it involves licensing, regulation and surveillance of medicine manufacture, supply, promotion and provision. The Agency is an authoritative source of information on medicines for the UK and provides advice and information to a number of overseas governments and regulators.
- 2 The Agency's work supports the UK Licensing Authority for human medicines, a role generally discharged by the Secretary of State for Health on behalf of all interested UK Ministers. The Secretary of State is also advised by statutory expert committees established under the Medicines Act. A Ministerial Advisory Board oversees the performance of the Agency. As an Executive Agency of the Department of Health and a Trading Fund, the Agency's day-to-day management is the responsibility of a Chief Executive and Management Board.
- 3 The Agency's workload is on the increase, except in applications for innovative chemicals, where applications for marketing authorisations by the pharmaceutical industry have slowed down. The advent of products derived from biotechnology and gene therapy may represent a much larger portion of Agency workload in the future. European legislation introducing regulation to herbal medicines for the first time is being negotiated and legislation already passed will tighten the regulation of clinical trials in humans from May 2004. The licensing of new medicines is becoming increasingly centralised in Europe, as markets in the Member States become more similar, and discussions are ongoing about whether all innovative medicines should be required to go through a central licensing procedure.



- 4 The Agency is to merge in April 2003 with the Medical Devices Agency, which is responsible for ensuring the safety, quality and performance of medical devices, to form the Medicines and Healthcare products Regulatory Agency. Although the functions of the two agencies will not change materially, there will be a new Board, including non-executive directors and a new post of Agency Chair, whose remit will include representing the Agency in public.



## Protecting public health

- 5 The Agency has a good record in ensuring that licensed medicines for sale or supply in the UK have a favourable balance of risks and benefits when used as directed. Twelve licensed medicines have had to be removed from the market in the last five years because of safety concerns, but this compares well with more than 200 new marketing authorisations granted in the UK through national and European procedures during that period, and the four thousand different medicines already on the market. The Agency's licensing decisions also accord well with the views of independent experts in medicines safety in the UK and abroad. Through regulatory action (for example reducing the size of packs of paracetamol tablets to encourage a reduction in the number of tablets sold at one time without prescription) the Agency has, moreover, contributed to improving the safe use of medicines.
- 6 The quality of medicines in the UK is also generally high. This is testament to the Agency's rigorous licensing and inspection regime for laboratories, manufacturing plants and wholesale warehouses, which is internationally recognised. The Agency has also achieved some success in prosecuting those selling poor quality or illegal medicines and is currently targeting illegal sales over the internet.
- 7 The Agency has taken the lead internationally in developing the science of medicines safety surveillance or *pharmacovigilance*, which is still evolving. Voluntary reporting by health professionals of suspected adverse drug reactions is a key element of this work and the Agency continues with efforts to encourage better reporting, including extending the scheme to pharmacists, nurses and others.
- 8 The public will themselves be able to report suspected adverse reactions via NHS Direct from February 2003. This may help improve data on groups of medicines (e.g. herbals) and patients (e.g. children) that are not well covered by the current system. The Agency has developed a strategy for developing a more proactive approach to safety monitoring work and is taking it forward, although full implementation will require additional resources, new commitments from industry and acceptance at a European level.





## Communication and external relationships

- 9 While few medicines need to be withdrawn from the market for safety reasons, the Agency has a range of other regulatory options for ensuring they are used safely and effectively, including provision of additional information, warnings on labels and leaflets and direct communication with prescribers and pharmacists. However, the Agency does not routinely monitor the effectiveness of these warnings in changing prescribing habits and there is some evidence that safety messages do not always get through to those who need them.
- 10 Evidence from doctors, pharmacists and patients suggests that the information provided to patients on medicines is often confusing and inadequate. Moves to widen the availability of medicines without prescription make improving patient information leaflets and labels an even greater priority and the Agency is contributing to a European-level review of the relevant regulations.
- 11 The role of the Medicines Control Agency is not well understood by the wider public, and even many health professionals. This contrasts with the United States Food and Drug Administration which maintains a high profile and targets safety information directly to consumers and patients. To fulfil its role of protecting a public increasingly taking control of its own healthcare and using the internet to obtain information, the Agency has recognised the need to be more outward-looking and begun to produce more tailored information for the public. The new post of Agency Chair provides the opportunity to take this public communication work further.
- 12 To help deliver the government's pledge of a safer NHS for patients, the Department of Health (the Department) and the Agency are developing guidance to improve the labelling and packaging of medicines in hospitals, including reducing the scope for confusion between similarly packaged medicines. These factors are significant contributors to medication error. There is also scope for the Agency to work with others to raise the profile of medicines safety, beginning at the earliest stages of professional training of healthcare staff. Existing local and regional networks, building in particular on the enhanced role of the pharmacist both in the community and the hospital, could also contribute more to disseminating safety information.
- 13 The Agency consults regularly with patient groups and other stakeholders but we found there was scope to improve the transparency of these consultations, and to review the level of support provided for the lay membership of the Medicines Act bodies. The Agency's role requires it to keep in close contact with other bodies. It has a concordat with the National Institute of Clinical Excellence, a part of whose role is to appraise the clinical and cost effectiveness of medicines, as well as with the National Patient Safety Agency.





## Providing a service to industry

- 14 Since its creation, the Agency has achieved major improvements in the quality of service to companies wishing to license medicines. The time to market for innovative products is now much faster, with benefits for both patients and industry. The Agency has achieved this without direct costs to the taxpayer. With a decline in the number of new applications for innovative medicines and increasing centralisation of regulatory work in Europe, though, the Agency's clients have new priorities. They are looking to regulators for advice and guidance and efficient processing of changes to licences throughout the lifecycle of medicines, and they are willing to pay for these services.
- 15 Recognising the need to remain competitive, the Agency is addressing these concerns through client surveys and quality improvement measures. It is also reviewing the fee structures to ensure they reflect the real costs of the work done. Ultimately, however, the level and structure of fees and the Agency's powers to charge for additional services are a matter of policy for Ministers.
- 16 In deriving all its funding from industry fees, the Agency differs from some of its overseas counterparts, who have a proportion of direct governmental funding. The Agency is also unusual in having a stated objective to facilitate the development of the UK pharmaceutical industry. This is a matter of concern to some stakeholders, regarding the Agency's independence, although there are various safeguards in place to prevent conflicts of interest. As part of establishing the new Agency, the Department will review the way in which the relationship between the new Agency and industry is reflected in its objectives.

## The future Agency

- 18 The creation of the new Medicines and Healthcare products Regulatory Agency provides the opportunity to build on the undoubted strengths of the Agency, which continues to be a world leader in terms of its scientific expertise and regulatory experience. In the management of resources, the Agency has already taken action to address weaknesses in financial management and human resources support. It has also put in place improved corporate governance and risk management arrangements to meet Treasury requirements on all government departments.
- 19 Most importantly, the new Agency will be faced with the challenges and opportunities of shaping and working within a new European regulatory system, which may come into being in the next three to five years. All stakeholders agree that a strong UK medicines regulatory agency is needed to protect the public health although much more licensing work may be carried out centrally in the future. Preserving a strong Agency, and retaining and enhancing the expertise within it, may involve the Agency and Department in some key decisions about its priorities. As the Agency's role evolves in future the Department may need to consider the financial sustainability of the current funding arrangements.

## Structure of the report and methodology

- 20 Against this background we looked at the way the Agency regulates medicines for sale or supply in the UK. The report, which aims to provide a helpful analysis on which the new merged Agency can build, examines:
- the background and accountability arrangements of the Medicines Control Agency, and the strategic threats facing it: Part 1;
  - how well the Agency has addressed the first part of its Mission Statement to protect public health, through ensuring the safety, quality and efficacy of medicines in the UK: Part 2;
  - how well the Agency has tackled the second part of its Mission Statement to protect public health through communicating information about medicines: Part 3; and
  - the level of service the Agency provides to the pharmaceutical industry: Part 4.
- 21 Our methodology involved detailed examination of documentation and interviews with Agency staff, consultation with a wide range of stakeholders, surveys of doctors, the public and patients and consultation with an expert panel. Appendix 2 sets out our methodology in more detail and Appendix 4 details the expert input.



# Recommendations

The Agency ensures a high standard of medicines safety and quality in the UK and is a source of good practice for many nations in medicines regulation. We found much good practice and some innovative plans for the future. More detailed recommendations are at Appendix 3, and the main areas where the Agency and its successor can build on this record are as follows:

## On protecting public health by regulating medicines

The Agency should:

- (a) identify resources and work with others to fully implement and deliver its excellence in pharmacovigilance strategy, which is designed to make safety monitoring less reactive.

The Department and the Agency should:

- (b) ensure transparency in the arrangements for preventing conflicts of interest in the Medicines Act bodies that advise Ministers.

## On protecting public health by communicating information on medicines

The Agency should:

- (c) continue to work to identify what improvements to medicines labelling and information leaflets can be made in the UK within existing legislation, building on new guidelines for industry and involving the public;
- (d) build on actions already taken to ensure that the Drug Alert distribution system for recall of defective medicines across the UK reaches all appropriate health professionals, especially in the light of widened prescribing powers;
- (e) continue to inform the public giving higher profile to the risks of purchasing Prescription-only medicines on the internet and publicise its work in this area, subject to the need to avoid jeopardising the Agency's covert investigation activities;
- (f) consider whether its public profile is sufficient to enable it to fulfil effectively that part of its mission involving the provision of information that contributes to the safe and effective use of medicines and consider in what ways this profile can be strengthened;
- (g) build on its existing regional networks, and work with others, such as hospital and community pharmacists and consultants, to disseminate key information on medicines safety more effectively to health professionals including GPs.

The Department and the Agency should:

- (h) work with Royal Colleges and other professional organisations to integrate a greater knowledge of medicines regulation and surveillance into health professionals' training.



## On providing a service to the pharmaceutical industry

The Agency should:

- (i) continue its client survey work across all services to industry and publish details of how it has responded to feedback.

## On the management of the Agency's own resources and performance

The Department and the Agency should:

- (j) ensure where necessary that the Department's and the Agency's objectives are better integrated;
- (k) identify clearly for stakeholders and managers the Agency's key performance objectives, ensuring that they reflect the full breadth of its functions;
- (l) examine the scope to adopt performance indicators which measure progress towards outcomes, rather than simply outputs;
- (m) ensure, when setting objectives for the new Agency that, in achieving the dual objectives of protecting the public and providing a service to industry, potential conflicts of interest are minimised and effectively managed.

The Agency should:

- (n) review the strategic plan to ensure that the Agency can continue effectively to protect UK public health within the changing European regulatory environment;
- (o) implement a permanent cost and time recording system to allow continuous review of its costs against income streams.



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NP

# Part 1

## The role of the Medicines Control Agency is complex and the environment in which it works is changing

- 1.1 In 2001, nearly 600 million prescriptions for medicines were dispensed in the UK, and some 700 million packages of non-prescription medicines were supplied. Since 1989, when it took over from the former Medicines Division of the Department of Health, the Medicines Control Agency (the Agency) has been responsible for ensuring the safety, quality and efficacy of these medicines (Figure 1). The Agency's mission statement is:

*To promote and safeguard public health through ensuring appropriate standards of safety, quality and efficacy for all medicines on the UK market. Also, to apply relevant controls and provide information which will contribute to safe and effective use of medicines.*

Its work covers the majority of the activities involved in the life cycle of a drug, from discovery to marketing and periodic renewal of licences (Figure 2 overleaf).

### 1 Aims and Objectives of the Agency

**Aim:** To safeguard public health by controlling medicines.

**Objectives:**

- To protect public health by ensuring that medicines sold or supplied in the UK for human use are of an acceptable standard of safety, quality and efficacy;
- To discharge its responsibilities efficiently and effectively, without causing unnecessary impediments to the activities of the industry, whilst ensuring that fees are no higher than is necessary;
- To contribute effectively to the protection of UK public health interests through implementation of UK and European licensing arrangements and in relation to the evolving EU licensing responsibilities;
- To advise the Secretary of State on policy relating to the functioning of the established regulatory system to contribute to policy on its development and to contribute to the Department's consideration of pharmaceuticals policy as a whole;
- To aim to meet high level performance targets set annually by the Secretary of State.

*Source: Medicines Control Agency Framework Document*

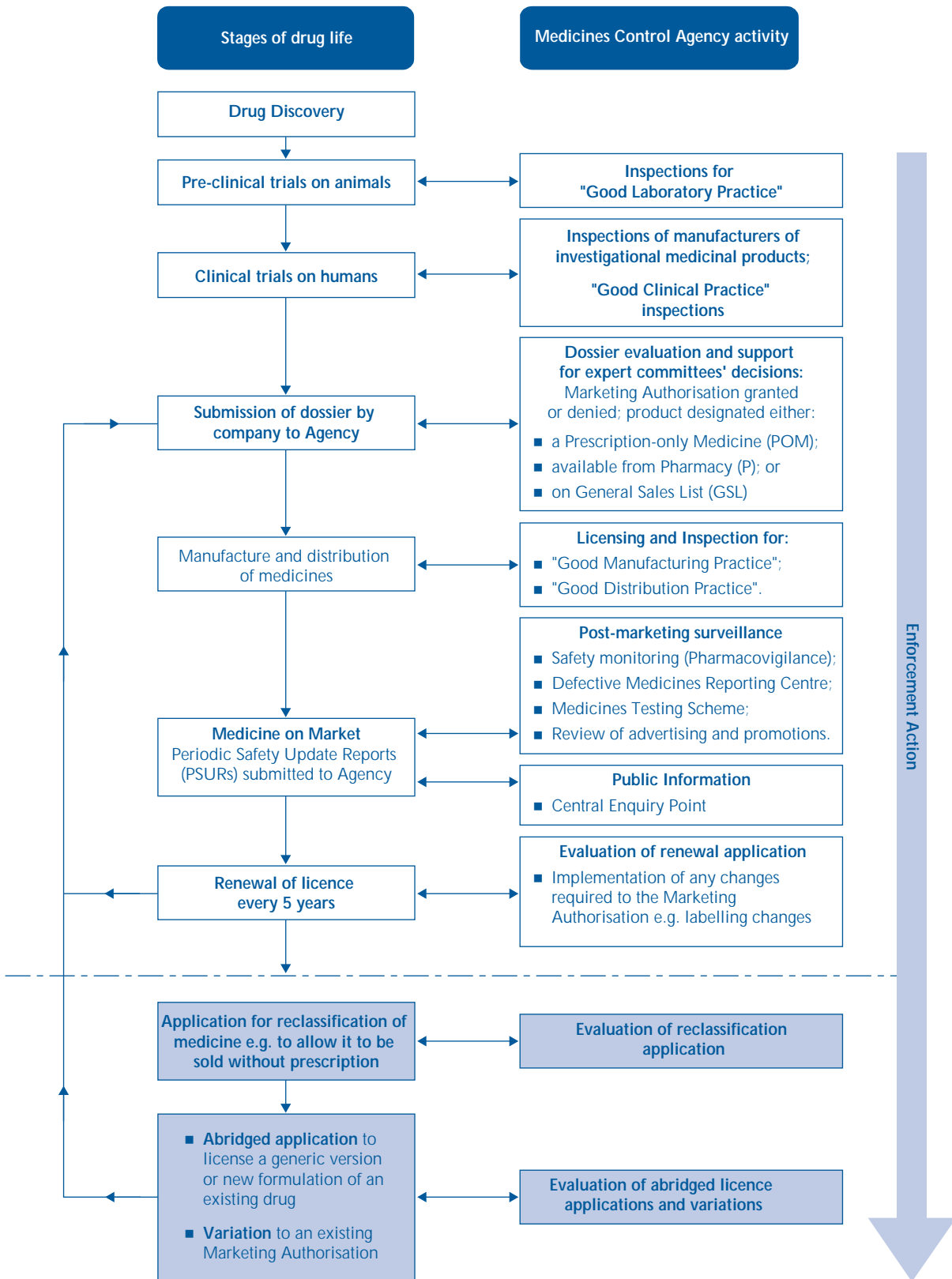
- 1.2 The Agency is not responsible for assessing the relative cost-effectiveness of different medicinal products or treatments. That task is the responsibility of the National Institute for Clinical Excellence, in England and Wales, and of the Scottish Medicines Consortium in Scotland. Nor is the Agency involved in setting prices for medicines in the UK. The prices of branded prescription medicines supplied to the NHS are indirectly controlled through the Pharmaceutical Price Regulation Scheme, which regulates the profits that companies can make on these medicines. A maximum price scheme for the main generic medicines sold to community pharmacies was introduced in August 2000. The Pricing and Supply Branch of the Department of Health administer both schemes.

### The Agency has enforcement powers under the 1968 Medicines Act

- 1.3 The Agency carries out enforcement activity where there are breaches of the law in relation to sale, supply, manufacture and promotion of medicines. Its officers investigate illegal activities based on allegations from within the Agency, the public or other agencies, and some examples are shown in Figure 3 overleaf. Their enforcement powers under the 1968 Medicines Act and supporting legislation include the right to enter any premises to inspect, to take samples or to require production of any books or documents, and the Agency can prosecute offenders, usually through a Crown Court action. Officers work closely with enforcement authorities throughout the UK, Europe and the rest of the world on international issues.



2 Medicines Control Agency activities and the lifecycle of a medicinal product



Source: National Audit Office

## The Agency also manages two key medicines information resources

1.4 On behalf of the Department of Health, the Agency also manages the publication of the British Pharmacopoeia.<sup>1</sup> In 1999, the Agency assumed management of the General Practice Research Database from the Department of Health. The database contains anonymised patient data on health-related events, prescribing, treatment and outcomes collected from general practice records on more than 3 million patients in the UK, starting in 1987. It forms the largest database of longitudinal patient data of its kind in the world and is used by researchers in industry and academia and by government departments, including medicines regulatory authorities.

## Accountability to Ministers

1.5 The Agency carries out its regulatory task on behalf of the UK Licensing Authority for human medicines which consists of Ministers of Health, Environment, Food and Rural Affairs and Ministers in Northern Ireland and Wales. In practice, the Secretary of State for Health generally acts on their behalf and is responsible for the control of medicines for human use in the UK.

1.6 Day-to-day activities of the Agency are the responsibility of the Chief Executive, who acts as Accounting Officer, and the Management Board. Oversight is formalised by means of a Ministerial Advisory Board, composed of representatives from the Department of Health, the pharmaceutical industry, the NHS and devolved regional administrations (Figure 4).

## The Agency will merge with the Medical Devices Agency in April 2003

1.7 In June 2002, the Secretary of State for Health announced that the Medicines Control Agency would merge with the Medical Devices Agency in April 2003, forming a new Agency, to be called the Medicines and Healthcare products Regulatory Agency. The core activities of the two agencies will not be materially affected. Subject to Parliamentary approval, the new Agency will be a trading fund, as the Medicines Control Agency is now. The new Agency will have a Board of executives and non-executives; its Chair will report directly to Ministers.

### 3 Medicines Control Agency enforcement work

#### Examples of illegal activities resulting in enforcement action

- Sale of prescription-only medicines over the internet
- Sale of unlicensed medicines with harmful or non herbal ingredients
- Sale of counterfeit medicines
- Sale of contaminated/adulterated medicines
- Illegally misleading promotion of medicines

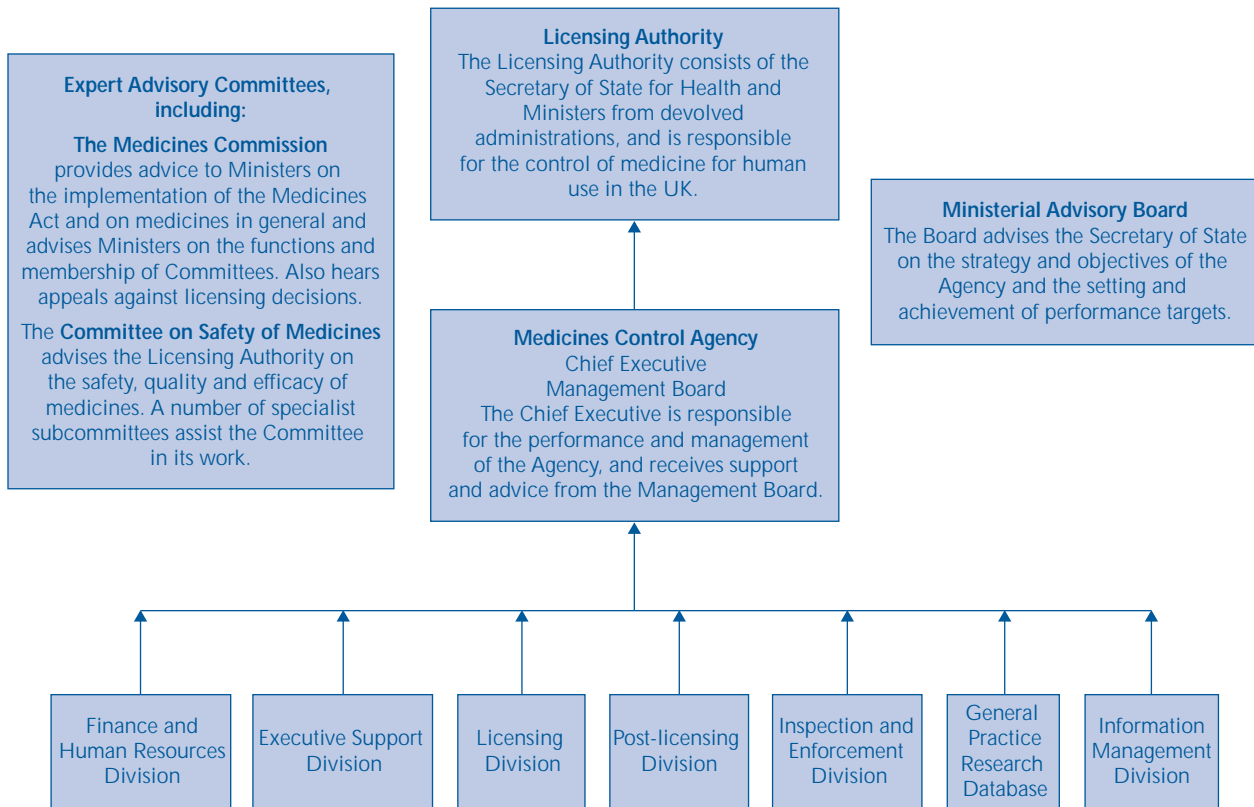
#### UK bodies with whom the Agency works collaboratively on enforcement issues

- National Criminal Intelligence Service
- Police Forces
- HM Customs and Excise
- Prescription Pricing Authority
- Association of Port Health Officers
- Trading Standards and Environmental Health Units
- Royal Pharmaceutical Society of Great Britain
- General Medical Council
- Immigration Authorities
- Industry trade associations & individual companies
- Home Office
- Department of Trade and Industry
- Veterinary Medicines Directorate
- Scottish Executive
- Northern Ireland Office
- Welsh Assembly
- Department of Health NHS Counter Fraud Service
- Prescription Medicines Code of Practice Authority

Source: National Audit Office

<sup>1</sup> The definitive compendium of specifications for medicines in the UK and some Commonwealth countries. The term 'BP' used in the labelling of a medicine indicates it has been prepared according to these specifications.

#### 4 The Medicines Control Agency and the Medicines Act bodies



Source: National Audit Office

### The Agency's and Department's objectives are not sufficiently integrated and Agency performance measures do not fully reflect its aims and activities or assist business planning

1.8 The Agency is responsible for advising Ministers on the regulation of human medicines. As part of this function, it advises Ministers on how regulatory issues can contribute to the achievement of their wider policy aims. The Agency does this, for example, through providing information and briefing but more specifically, by contributing to the achievement of medicines-related objectives such as those set out in the NHS Plan for England (Figure 5). While the objectives of the Department and the Agency overlap only to a limited extent, it is important that they work together closely in areas such as those overleaf in Figure 5.

1.9 The Agency has developed a set of performance measures which are *relevant*, *measurable* and *timed*. Aspects such as the time taken to process applications and the level of agreement between the Agency and expert committees are within the control of the Agency, and can be measured numerically. Other targets for achievement of business improvements have clear timings attached.

1.10 Reported information tends to focus on targets where measurement is easiest, such as the speed of assessment of applications or the time taken to enter suspected adverse drug reaction reports on the computer system. While these output measures show very strong performance (almost without exception 100 per cent achieved), they can divert management attention (and funds) away from the more difficult-to-measure areas where there is room for improvement, such as the effectiveness of safety information aimed at protecting public health.

1.11 None of the activities in Figure 5 are reflected in the Agency's corporate objectives, or the performance measures against which it reports externally. There are no reported objectives or performance measures for providing effective medicines information to the public and others, or for support for the development of



## 5 NHS Plan objectives to which the Agency contributes

Selected NHS Plan Taskforce objective	Relevant Agency work currently underway
Improved public access to medicines	Reclassification of medicines from prescription-only to pharmacy or general sale list, extension of prescribing powers
Improve children's health services and reduce inequalities	Paediatric working group, on the extent and effects of "off-label", or unlicensed, prescribing to children
Improve mental health in primary care and access to services	Improved labelling and patient leaflets to support prescription of medicines called selective serotonin re-uptake inhibitors for depression
Improve clinical quality across primary and secondary care	Publication of drug safety information for clinicians and monitoring of its effectiveness in changing prescribing habits  Working group on improving the safety of medicines packaging and labelling in hospitals
Provide more and better information for patients	Working group on improving patient information leaflets and disease awareness guidelines
Help older people to stay healthy	Working group on improving patient information leaflets
Increase smoking cessation facilities, especially for manual groups	Help doctors prescribe anti-smoking therapies confidently, through effective safety information  Wider availability of Nicotine Replacement Therapy
Teenage pregnancy	Emergency Contraception availability over the counter
Suicide prevention	Restrictions on pack sizes of analgesics

Source: National Audit Office analysis

European medicines regulation. No explicit link is made with the Agency's work in managing the General Practice Research Database and the British Pharmacopoeia. There is also a lack of performance measurement in the areas where the Agency faces key threats and opportunities, for example, benchmarking activities against other European regulators.

1.12 Although the Agency is dedicated to protecting the public health, the information it reports on its performance at that task is not well designed for the public, or health professionals, to interpret. Reported performance measures focus almost solely on the *outputs* achieved (e.g. number of inspections of UK manufacturing licence holders carried out) rather than the *outcomes* for public health.

1.13 The Agency has worked to develop outcome measures but there are difficulties in identifying appropriate targets for good performance. For example, it will never be possible to anticipate all side effects of licensed products. However, there is potential to improve outcome measures by relating outputs of the licensing and surveillance processes to each other. For example where serious unexpected adverse drug reactions occur it would be possible to consider whether they should have been anticipated during the assessment of the safety, quality and efficacy of the product in question.

1.14 The Agency's performance information is also not always useful for industry as a stakeholder. The main measure of the quality of service is the speed of completion of

licence application assessments, which has now been reduced to a near minimum consistent with a proper evaluation of all the scientific evidence. Pharmaceutical company representatives we interviewed expressed a desire for a level of support and advice during and after the application process greater than that currently provided by the Agency.

## The regulation of medicines is becoming driven increasingly from Europe

### The Agency operates within an overarching system of EU medicines regulation

1.15 In 1993 the European Medicines Evaluation Agency was established by the European Union to co-ordinate cross-European regulatory work and in 1995 a set of new regulations and directives established three routes by which a medicinal product can come to market in the UK:

- the **national procedure**, whereby a company may apply to the Medicines Control Agency for a licence to market a product in the UK only;
- the **centralised procedure**, in which companies apply to the European Medicines Evaluation Agency for an authorisation to market the product across the European Union. This procedure is compulsory for

products derived from biotechnology, and optional for other high technology or innovative products. Experts from one member state are nominated to carry out the assessment, and those of other member states have the opportunity to contribute to the final decision, which is then binding on all member states.

- the **mutual recognition procedure**, which begins with the company filing an application dossier with the regulatory agency of a member state of their choice. This "reference member state" carries out an assessment and may grant a national marketing authorisation. It then shares the assessment with other "concerned member states", who may comment on or object to the authorisation proposed for their own territory. Any unresolved objections are subject to arbitration by the European Committee on Proprietary Medicinal Products (known as CPMP). Once this is complete, a national marketing authorisation in each concerned member state is granted.

- 1.16 In 2000, the European Commission began a process of consultation on wide ranging changes to the regulatory system, partly in response to the likely expansion of the European Union. Among other changes, the proposals envisaged further development of the centralised procedure so that all new pharmaceutical products would be required to go through that route. Member States and the European Parliament are still discussing these proposals.

## The Agency is required to regulate an increasing range of products as a result of EU Directives

- 1.17 The European Union regulatory environment works alongside the UK's national regulatory environment, and EU Directives must be transposed into UK law. Three European Directives have recently had an impact on the range of products the Agency is expected to regulate.

### (a) Homoeopathic medicines

- 1.18 EU Directives in 1992 and 2001 set out requirements for each national regulatory authority to implement a simplified registration scheme for homoeopathic medicines. The Agency implemented a scheme in 1994 that required any homoeopathic products developed since then and intended for sale on the UK market to be registered. So far, 356 homoeopathic medicines have been registered with the scheme. The Agency has found no evidence of significant safety risks from the approximately 3,000 older homoeopathic products that received licences "of right" as they were already on the market when the 1968 Medicines Act was passed. However, some have been withdrawn from the market because of problems complying with the evolving EU quality standards.

- 1.19 The Agency plans to introduce in 2002-03 a new 'national rules' scheme for products that did not meet the eligibility criteria of the original registration scheme. At this early stage the Agency is not able to estimate how many applications might be made to the new scheme.

### (b) Herbal medicines

- 1.20 There is no estimate of the number of herbal medicines sold in the UK. A 1999 market research report<sup>2</sup> estimated that the value of herbal medicine sales in the UK was some £50 million a year and growing. Some 500 herbal medicines are licensed but an unknown number of others are exempt from licensing under the Medicines Act 1968, and can be sold as over-the-counter products as long as they make no claims on the packaging or in the form of a brand name, and are entirely herbal. Or, under the 'herbalists exemption', they can be sold in personal consultations between herbalist and patient. Some herbal medicines have been banned or their availability restricted on safety grounds.
- 1.21 An EU Directive is currently being negotiated and the Agency has consulted herbals manufacturers and other interested groups on its proposed requirements for a simplified compulsory registration scheme. This would cover any product that has been used as a traditional remedy and would be intended to protect patients by bringing these products within the regulatory framework, allowing them to make limited efficacy claims.

### (c) Clinical trials of medicines

- 1.22 Clinical trials are currently regulated on a voluntary basis, and the Agency carries out inspections where requested. From 1st May 2004 an EU Directive will require, for the first time in the UK, formal authorisation of Healthy Volunteer studies carried out for the purpose of assessing clinical efficacy and safety. This will involve inspection of sites involved in clinical trials work and audit of the investigational medicinal products used in clinical trials. The benefits of this include better administration of clinical trials and safer use of medicines under development.

## The Agency faces increased competition within Europe

- 1.23 The Agency already faces competitive threats from other European regulators who can also bid for a share of the reducing volume of new active substance licensing work under the EU mutual recognition arrangements. More centralisation of licensing work and the expansion of the European Union are likely to mean less work to share between more regulators in both the centralised and mutual recognition streams.

1.24 The Agency has identified that:

- a potential loss of business in new active substance applications would affect income strongly, as this work attracts the highest fees and brings continuing income from follow-up work;
- loss of this high-profile scientific work coming into the Agency could make it less attractive as an employer for highly-qualified scientists;
- loss of expertise could diminish the Agency's ability to protect UK public health through safety monitoring and risk benefit assessment;
- loss of scientific expertise could also damage the Agency's reputation and lead to further loss of business.

1.25 The Agency is looking to improve the quality of the services it provides to industry in order to attract more business under the competitive mutual recognition stream. It also aims to maintain a strong presence in European centralised work, and considers that the changes could bring opportunities to build on its reputation as a European leader, for example through the expanded inspection regime required by the Clinical Trials Directive.

## Volumes of work for the Medicines Control Agency are unpredictable, but generally increasing

1.26 The number of new active substance applications submitted to the Agency and its overseas equivalents has decreased over the last seven years, reflecting a reduction in the number of major new discoveries ready to be marketed. In other areas the number of applications, particularly through the European system, is increasing<sup>3</sup>, including:

- abridged licences, where the product uses an active substance that has already been approved. These increases reflect in part the increasing use of generic medicines in the NHS;
- parallel import licences, which allow the importation from elsewhere in the European Union of medicines which are equivalent to medicines on the UK market. A doubling in parallel import licence applications over the last two years has come about because of medicine price differentials between the member states of the European Union;
- variations to existing marketing authorisations, such as a change in use, dosage or pharmaceutical form. The Agency can also require a variation to introduce additional safety precautions;

- renewals of marketing authorisations, which are granted for a period of five years. This process helps ensure that the licence reflects current knowledge about the balance of risks and benefits of the product.

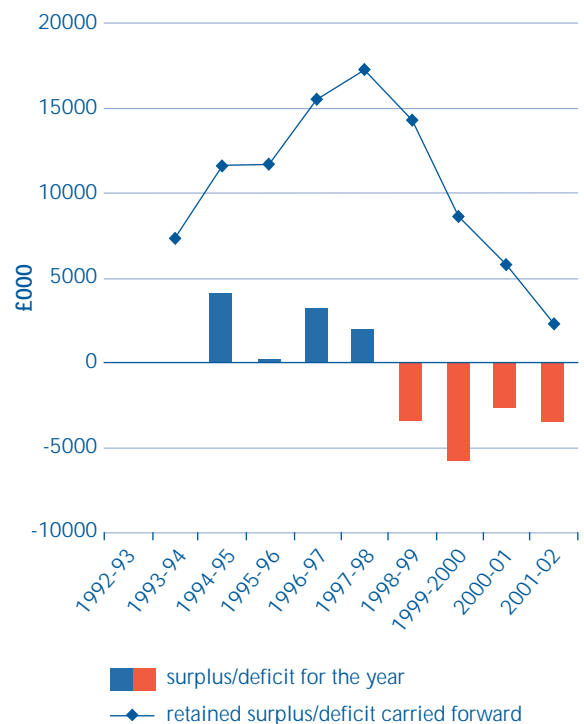
## The Agency is seeking to improve its financial and operational management, by tackling financial pressures, human resources issues and IT

### (a) Financial Management

1.27 The Government established the Agency as a financially self-sufficient Trading Fund in 1993, fully funded through fees charged to industry. In 2001-02 income amounted to £40 million. The Agency is required to "break even, taking one year with the next, and to set its fee levels to achieve this". It may hold reasonable cash reserves, but by 1998, had accumulated a retained surplus of some £17 million.

1.28 In 1998 Ministers approved a reduction of 12.5 per cent in fees across the board to begin eliminating the surplus, by generating a series of operating deficits. By 2001-02 the retained surplus had been reduced to less than £2.5 million (Figure 6).

### 6 Medicines Control Agency annual and cumulative surplus/deficit position



Source: National Audit Office analysis

1.29 In addition to the fees reductions, the Agency has had to fund investment in the General Practice Research Database (paragraph 1.4). The Database is regarded as a valuable resource by both academia and industry and the Agency's post-licensing team are themselves among clients who use it for innovative research. A legal dispute between a user and the Agency over access to the Database led to the Agency making a settlement of £1 million, and income estimates had to be revised downwards. The £6 million the Agency invested into developing the Database into a modern research tool is expected to be recouped by 2007-08, rather than by 2003-4. Nevertheless, the Agency has expanded the customer base and continues to support the enhancement of the Database and explore new uses for the data.

1.30 The Agency has increasingly taken on additional work, for example in leading the UK position on medicines within Europe, for which there is no associated fee income. Industry clients are pressing the Agency for advice about their applications and the regulatory process generally, which also does not yet attract fees.

1.31 The fact that not all activities have a related income stream causes resource allocation problems. Moreover, although the Agency has a limited time-recording system it is not fully used and cannot provide comprehensive Agency-wide costing data to inform fully the annual process of setting its fees. To date, adjustments in fees have generally been made on the basis of an assessment of the overall financial situation, rather than a reflection of the actual change in associated costs.

1.32 Internal auditors and the National Audit Office as external auditors have also highlighted weaknesses in financial control including a lack of controls over spending and a failure to focus on rising levels of outstanding fees. By 2000-01, year-end debtors had risen to more than £4 million, or 13 per cent of turnover.

1.33 In response, by 2002, the finance team, under new leadership, had implemented a range of improvements to financial management in the Agency including:

- an improved "zero-based" budgeting procedure to help to identify and eliminate unnecessary expenditure;
- a new purchase ordering system to provide more control over expenditure;
- more active pursuit of outstanding fees to bring down the level of bad debts; and
- additional compliance checks on the turnover statements provided by companies in support of claims for fee discounts.

## (b) Human resources management

1.34 Like its overseas counterparts, the Agency faces strong competition in recruiting and retaining the best scientists and experts. While industry can offer financial rewards and the university sector can offer professional and academic recognition, regulatory work has not historically offered these benefits. This means that for some posts there are difficulties in attracting the best candidates.

1.35 As part of its Culture and Communications Change Programme, the Board has set up three high-level working groups to identify and implement programmes for change, focusing on management and leadership; personal development and performance management; and communications. Activities during 2002 include management development training for operational managers and seminars for senior staff; a best practice guideline for internal communications; revised performance management/personal development arrangements; the introduction of new centrally co-ordinated recruitment procedures; and recruitment of an experienced permanent Head of Human Resources.

## (c) Information Technology

1.36 The Agency has identified the need for major investment in IT in order to help it evolve and remain competitive. It has planned a project, likely to cost some £50 million over 10 years, to fully integrate licensing and post-licensing systems and modernise financial and other support systems. In December 2002, following Departmental approval, the Agency signed a contract with Accenture to design, build and operate the new systems, and work on the project has now started.

1.37 We have provided the Agency with a more detailed management report on performance measurement, human resource and information technology issues. A copy of the Executive Summary is at Appendix 11.



# Part 2

## Protecting public health by regulating medicines

2.1 To meet key elements of its Mission Statement to ensure the safety, quality and efficacy of medicines on the UK market, the Medicines Control Agency carries out a range of functions which we examine in this part:

- authorisation of medicines for sale and supply;
- inspecting the manufacture and distribution of medicines;
- monitoring suspected adverse drug reactions, taking action as necessary;
- taking action to respond to safety concerns;
- reviewing medicines advertising and promotional material.

### Authorisation of medicines for sale and supply

The Agency has a good record in ensuring that medicines authorised for sale in the UK are safe

2.2 A pharmaceutical company wishing to market a medicine must apply to the Agency for a *marketing authorisation*. The Agency then assesses the evidence on safety, as well as quality and efficacy. It makes a recommendation to the Licensing Authority as to whether authorisation should be granted. The process also involves, in some cases, seeking advice from the expert Medicines Act advisory bodies which were described in Figure 4. The Agency has in place systems for quality assurance, peer review and audit of its assessment process for innovative medicines, generics and biological products.

#### 7 Twelve medicines licensed by the Agency were withdrawn on the grounds of public safety, compared with over 200 new licences granted in the same period

Year	Number of medicines withdrawn because of safety concerns	Drug names	Prescribed for
1997-98	4 (2 were of the same class of medicine)	Troglitazone (Romazin) Pemoline (Volital) Dexfenfluramine, Fenfluramine	Type II diabetes Attention deficit hyperactivity disorder Obesity (appetite suppressant)
1998-99	2	Sertindole (Serdolect) Mibefradil (Posicor)	Psychosis Hypertension
1999-00	3 (2 were of the same class of medicine)	Pulmonary surfactant (Alec) Amfepramone, Phentermine	Neonatal respiratory distress Obesity (appetite suppressant)
2000-01	2	Cisapride (Prepulsid) Droperidol (Droleptan)	Gastrointestinal problems Schizophrenia
2001-02	2	Cerivastatin (Iipobay)* Kava-Kava*	Hypercholesterolaemia Herbal product used for anxiety

\*indicates where a company made a decision to withdraw the medicine voluntarily.

Source: Medicines Control Agency

## 8 Levels of agreement or "concordance" between the Agency's and others' decisions

	2001-02
Percentage of decisions where there was agreement between the assessment of the Medicines Control Agency and the opinion of the Committee on Safety of Medicines, where the decision was referred to the Committee *	96 per cent
Percentage of decisions where there was agreement between the Medicines Control Agency and the EU regulator	97.5 per cent

\* decisions referred to the Committee include all new decisions on whether to license medicines and some decisions on changes to existing licences.

Source: Medicines Control Agency

- 2.3 One measure of the effectiveness of the Agency's authorisation procedure is the number of medicines that are subsequently withdrawn from the UK market, in relation to those approved. This has remained consistently low over time (Figure 7 previous page), indicating a high level of consistency and reliability in the assessments, although the medicines that were withdrawn were prescribed for common conditions that affect a significant number of people.
- 2.4 A further effectiveness indicator for the market authorisation process is the high proportion of cases where the Committee on Safety of Medicines' opinion agrees with the Agency's assessment in cases referred to the Committee. The extent of agreement between the Agency and other EU regulators on applications reviewed under mutual recognition is also high (Figure 8).

### Inspecting the manufacture and distribution of medicines

#### Rigorous inspections have contributed to the high quality of authorised medicines

- 2.5 The Agency operates a licensing system for manufacturing plants and wholesale distribution warehouses to ensure that these aspects of the medicines supply chain meet optimum standards and deliver high quality medicines to the market. Sites and companies are inspected for compliance with published standards and guidelines covering all stages of the medicine life-cycle (Figure 2).
- 2.6 Registration of the inspection regime to the international quality standard ISO 9002 has resulted in a well-developed system of internal quality control and the quality of the Agency's inspection work is internationally recognised. The Governments of New Zealand and Australia place reliance on it under mutual recognition arrangements, and the Agency's inspectors are regularly called upon to do international training.

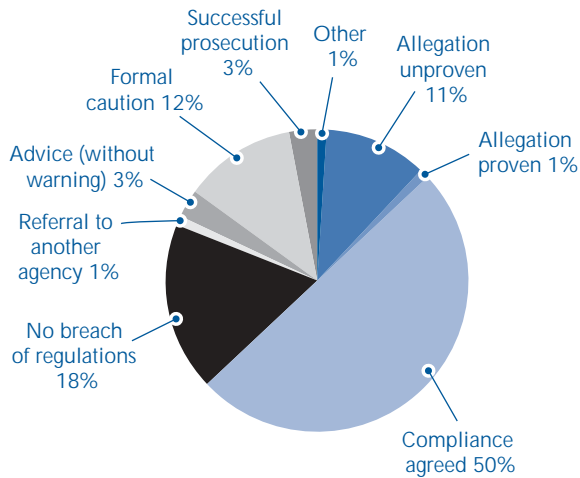
#### The Agency has met its target to inspect manufacturing plants but is under pressure to maintain the frequency of other inspections

- 2.7 The Agency meets its formal performance target to inspect all UK manufacturing sites every two years. It also meets European targets for the inspection of sites manufacturing products with a European licence, set by the European Medicines Evaluation Agency. Overseas sites manufacturing products for the UK market are currently inspected once every three years, in line with European standards.
- 2.8 As some staff retired and others resigned, inspections of pre-clinical testing of new products have been under pressure. In 2001-02 about a third of sites were not inspected within the 27-month aspirational target. Following the appointment of additional inspectors the Agency does not anticipate continuing problems.

#### The Agency is successful in maintaining standards through investigations, sanctions and follow-up inspections

- 2.9 The Agency carries out proactive work not only to ensure that manufacturing and distribution standards are high but also to ensure compliance with licensing requirements, the Medicines Act and related legislation. The Agency can modify, suspend or revoke manufacturers' and wholesale dealers' licences in the event of serious deficiencies being found during an inspection. Following testing and other investigative work, where problems are found the Agency may use a range of sanctions including a warning letter, formal caution or criminal proceedings. Where possible, the Agency agrees steps that will lead to compliance with standards and this was achieved in half of the 179 cases handled in 2001-02 (Figure 9).
- 2.10 The Agency carries out follow-up investigations to determine whether previous enforcement activities have resulted in long term compliance. This is generally done on a case-by-case basis, but the Agency also carries out more systematic follow-up work. An example of effective action is shown in Figure 10.

**9** Most enforcement work results in compliance with standards, though 15 per cent of cases end in formal caution or successful prosecution



Source: Medicines Control Agency

2.11 Recently the Agency's enforcement activities have increasingly focused on illegal unlicensed products. Its work in 2001-02 on pharmaceutical substances sold illegally as traditional Chinese medicines resulted in 1,005 seizures, with an estimated street value of £25,000. The Agency found extensive non-compliance, and an absence of formal quality control procedures in the manufacturing, preparation, processing, assembling and packaging of these products, and this has led to five prosecutions so far, as well as seven formal cautions. Further legal proceedings are expected in 2003 and following years.

A number of areas are currently excluded from independent inspection and may present risks to public health

2.12 A number of aspects of medicine development and production in the UK are currently not subject to mandatory regulation. **Figure 11** shows the different types of sites and processes that are currently unregulated or which are only voluntarily regulated. Some are expected to come under mandatory regulation in due course, but several areas will remain outside the scope of the Agency's routine inspection work for the foreseeable future.

2.13 It is not part of the Agency's remit to inspect ward-based activities in hospitals. Under the 1968 Medicines Act, exemptions allow doctors, pharmacists and nurses to undertake sterile preparation activities without statutory inspection, although these are subject to professional

**10** Effective enforcement action on illegal ingredients in skin-lightening creams

- In 2000, the Agency investigated 75 sites that were thought to be supplying skin-lightening creams illegally containing pharmaceutical ingredients, in the form of cortico-steroids.
- The Agency found that 62 retail outlets were indeed contravening the Medicines Act and they issued formal warnings. The 62 outlets also signed letters of compliance, agreeing to cease trading in these products.
- In 2001, the enforcement team re-visited 29 of the 62 sites, and tested a number of products seized. They found high levels of compliance, and none of the samples tested were found to contain any pharmaceutical ingredients, indicating that the previous warnings and education in this area had been effective.

Source: Medicines Control Agency

regulation. Whilst hospital pharmacies generally have appropriate quality assurance procedures over this work, there are concerns that some preparation work is still being done on wards, where the risks of contamination of the medicine are much greater. In their December 2001 report, the Audit Commission recommended that Trusts should ensure that ward-based preparation is stopped<sup>4</sup>. The Department encourages Trusts to ensure that this work is carried out in hospital pharmacies where possible, but considers that this may not always be possible (e.g. in intensive therapy units).

- 2.14 Some hospital pharmacies are specifically licensed for manufacture of medicines and inspected by the Agency, but many are not. The inspection of unlicensed hospital pharmacies is not part of the Agency's remit, although at the request of Ministers it carried out a limited number of voluntary inspections, to assess risks and levels of compliance. This led to the Department instituting an internal programme of inspections by NHS pharmaceutical experts, but it has no plans at present to commission further inspection work from the Agency.

The Agency has not assessed the effect of reducing the level of its off the shelf medicine testing

- 2.15 In addition to ensuring that manufacture of medicines is of high quality, the Agency operates a Medicines Testing Scheme to assess the quality of medicines found on the UK market. Samples are taken from community pharmacists, wholesalers and manufacturers. The scheme is designed to detect cases where:

- the content of active ingredient is different from the specified level;

## 11 Some aspects of medicine development, production or administration are not currently subject to statutory Medicines Control Agency inspection

### Unregulated or voluntarily regulated area

### Future prospect of regulation?

#### Development

##### Clinical Trials

Compliance with EU Directive 2001/20/EC will become mandatory from Spring 2004. The new key requirements of the Directive on those sites carrying out clinical trials will be:

- Formal authorisation of all healthy human volunteer studies
- Manufacturing licences for Investigational Medicinal Products
- Compliance with Good Manufacturing Practice
- Supply of Investigational Medicinal Products for testing at no cost to the patient

The key requirements on EU regulators will be:

- To assess compliance with the Directive
- To meet an EU performance target (probably 60 days) for review of information
- To exchange information between member states

Clinical laboratories (clinical analytical laboratories doing support work for clinical trials. They analyse samples to detect various medical parameters or levels of the investigational medicines in the volunteers)

These sites do not fall within the Good Laboratory Practice Monitoring Authority's remit currently. There are plans to incorporate them into the Clinical Trials Directive inspection programme.

The Agency are considering developing ISO 9002 quality standards for these laboratories.

#### Manufacture

##### Manufacture of Investigational New Products

Regulation to become statutory in 2003.

##### Manufacture of Active Pharmaceutical Ingredients

Regulation to remain voluntary until European legislation (2001 Review) is adopted.

##### Manufacture of non-active ingredients used in final product manufacture

Non-active ingredients are not subject to regulatory inspection but the manufacturers' systems for assessing the quality of such materials are covered by the Agency's routine inspections.

#### Preparation by healthcare professionals

##### Hospital pharmacies in the NHS or private hospitals/clinics (also carry out some limited manufacture)

Hospital pharmacies that hold manufacturer's licences are inspected. The Agency has been asked to inspect a number of unlicensed pharmacies at Ministers' request. Subsequently, the Department issued a "Controls Assurance Standard" for the Safe and Secure Handling of Medicines, against which Trusts are assessed by internal auditors annually.

##### Ward-based sterile preparation by doctors or other professionals

Exempt from regulation under the Medicines Act.

##### Non orthodox practitioners

These include practitioners who hold a manufacturer's licence to mix or assemble unlicensed medicines, including homoeopathic medicines, and supply them following a consultation, under an exemption in the Medicines Act. The Agency is empowered to inspect the premises and processes used.

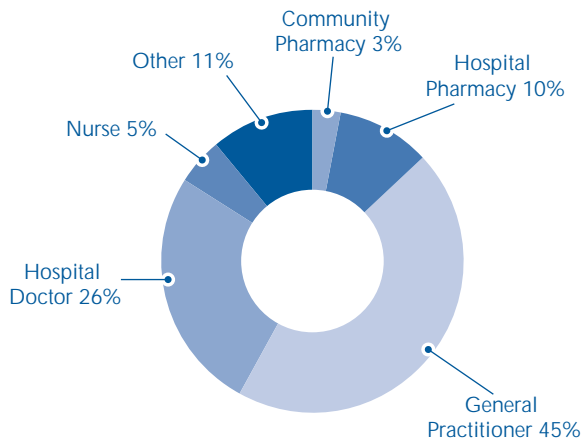
- the information on the label is incorrect or does not comply with regulatory requirements;
- the analytical method is not suitable; or
- the product specification is inappropriate for the product.

2.16 The Agency aims to test around 3,000 samples under the Medicines Testing Scheme each year, although this figure is not based on a systematic assessment of the level of risk to public health. This pre-planned testing work is not given as high a priority as work arising from

enforcement operations and inspections, which is done where a specific risk to public health is suspected, and is more complex and time-consuming. Because higher priority site inspection and enforcement work is on the increase, the number of pre-planned samples tested decreased to around 2,500 in 2001-02. The Agency has not assessed the costs and benefits of maintaining any particular level of testing, but aims to increase the number of laboratory staff to achieve 3,000 samples a year again in future.



## 12 Most Yellow Card reports come from general practitioners



### NOTE:

The total number of adverse drug reactions reported in the UK in 2001-02 was 19,254.

Source: Medicines Control Agency

## Monitoring suspected adverse reactions to medicines in clinical use and taking action as necessary

### Arrangements for identifying safety risks compare well with the rest of the world

2.17 The thalidomide tragedy in the 1960s, in which an estimated ten thousand babies in Europe suffered malformations after their mothers were prescribed the drug to reduce morning sickness, focused attention on the potential for previously unidentified safety risks from medicines. In response to this, the Medicines Control Agency's predecessor body in the Department of Health was one of the first national authorities to set up a monitoring system.

2.18 Since 1964, the "Yellow Card Scheme" has been collecting information on suspected adverse reactions to medicines in the UK from health professionals, principally General Practitioners (Figure 12). In 2001-02, there were some 19,000 such reports, of which 57 per cent were serious and 3 per cent fatal, or less than one adverse reaction for every 10,000 prescription medicines dispensed.

2.19 Similar arrangements are in place in most developed countries although the groups of people who can make reports differ from country to country (Figure 13). Drug companies have a legal obligation to report serious adverse reactions to the Agency.

2.20 The Yellow Card Scheme (Figure 14) is the cornerstone of the Agency's work on medicines safety monitoring, or *pharmacovigilance*, and the Agency has taken a leading role in the development of this discipline worldwide. For example, in the 1990s the Agency developed a medical terminology for use in regulatory affairs, including pharmacovigilance and adverse drug reaction recording. This terminology has been adopted as the international standard, and its use aids comparison and consistency. The Agency has also provided advice to several countries on its leading-edge approach to the analysis of adverse reaction data. This makes use of a specially-designed computer system, the Adverse Drug Reaction Online Information Tracking database. It will be providing formal training to other countries in the future.

2.21 The Agency's pharmacovigilance team continuously reviews its adverse drug reactions database for "signals" or disproportionate increases in the number of reactions connected with use of a particular drug. Most attention is focused on newer medicines, where unexpected reactions are more likely to arise and the safety profile cannot be fully established prior to licensing. In 2001-02, some 384 signals were reviewed and further research on these included:

## 13 The groups providing reports of adverse drug reactions are different from country to country

Who reports reactions?	Drug companies	Doctors	Nurses	Pharmacists	Coroners	Dentists	Patients
UK	Compulsory	Voluntary	From October 2002	Voluntary	Voluntary	Voluntary	Via NHS Direct from Feb 2003
France	Compulsory	Compulsory	Compulsory	Compulsory	Compulsory	Compulsory	No
Sweden	Compulsory	Compulsory	No	No	Compulsory	Compulsory	No
Netherlands	Compulsory	Voluntary	No	Voluntary	Voluntary	No	No
USA	Compulsory	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary
Canada	Compulsory	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary

Source: National Audit Office

14 The Yellow Card used by health professionals to report suspected adverse drug reactions


In Confidence


**SUSPECTED ADVERSE DRUG REACTIONS**

If you are suspicious that an adverse reaction may be related to a drug or combination of drugs please complete this Yellow Card. Please report all adverse reactions for black triangle (▼) drugs and only serious adverse reactions for established drugs. For additional reporting advice please see page 10 of the BNF or the MCA website [www.open.gov.uk/mca/mcathome.htm](http://www.open.gov.uk/mca/mcathome.htm). Do not be put off reporting because some details are not known.

<b>PATIENT DETAILS</b>		Patient Initials: _____	Sex: M / F	Weight if known (kg): _____	
Age (at time of reaction): _____		Identification (Your Practice / Hospital Ref.):*			
<b>SUSPECTED DRUG(S)</b>					
Give brand name of drug and batch Number if known					
_____	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____
<b>SUSPECTED REACTIONS:</b>					<b>Outcome</b>
Please describe the reaction(s) and any treatment given:					Recovered <input type="checkbox"/>
Date reaction(s) started: _____ Date reaction(s) stopped: _____					Recovering <input type="checkbox"/>
Do you consider the reaction to be serious? Yes / No					Continuing <input type="checkbox"/>
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):					Other <input type="checkbox"/>
Patient died due to reaction <input type="checkbox"/>	Involved or prolonged inpatient hospitalisation			<input type="checkbox"/>	
Life threatening <input type="checkbox"/>	Involved persistent or significant disability or incapacity			<input type="checkbox"/>	
Congenital abnormality <input type="checkbox"/>	Medically significant; please give details:				

\* This is to enable you to identify the patient in any future correspondence concerning this report.  
Please attach additional pages if necessary.

**OTHER DRUGS (including self-medication & herbal remedies)**

Did the patient take any other drugs in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug (Brand, if known)	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

**Additional relevant information** e.g. medical history, test results, known allergies, rechallenge (if performed), suspected drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the date of the last menstrual period.

<b>REPORTER DETAILS</b>		<b>CLINICIAN (if not the reporter)</b>	
Name and Professional Address: _____		Name and Professional Address: _____	
Post code: _____	Tel No: _____	Post code: _____	Speciality: _____
Speciality: _____	Date: _____	If you would like information about other adverse reactions associated with the suspected drug, please tick this box <input type="checkbox"/>	

Send to Medicines Control Agency, CSM FREEPOST, LONDON SW8 5NR or if you are in one of the following NHS regions:  
 (a) CSM Mersey, FREEPOST, Liverpool L3 3AB  
 (b) CSM West Midlands, FREEPOST SW2991, Birmingham B18 7BR  
 (c) CSM Northern, FREEPOST 1085, Newcastle upon Tyne NE1 1BR  
 (d) CSM Wales, FREEPOST, Cardiff CF4 1ZZ

**NOTE:**

Yellow Cards are included in copies of the British National Formulary; the Association of the British Pharmaceutical Industry's compendium of data sheets and Summaries of Product Characteristics; the OTC Directory; the Nurses Prescribing Formulary; the Monthly Index of Medical Specialities; and can be printed out from the Agency's website or completed on-line at [www.mca.gov.uk](http://www.mca.gov.uk).

Source: Medicines Control Agency

- assessing the data available on causality and assessing the risk to public health;
- identifying the groups of patients taking the drug and whether there were any special health factors in these groups which could have caused the reported reaction;
- identifying whether the drug was commonly prescribed with another drug, in case there could be a possible drug interaction at work;
- looking for corroborative information from other sources in the UK and abroad. Some 40,000 adverse drug reaction reports were received from abroad in 2001-02; and
- consulting the Committee on Safety of Medicines for expert advice on the balance between risk and benefit and its public health significance.

2.22 All voluntary reporting systems suffer from under-reporting. The proportion of suspected adverse drug reactions which are reported is very variable, and it has been estimated that only around 10-25 per cent of reactions experienced by patients are reported. However, a recent study<sup>5</sup> has shown that the reporting rate may rise to around 50 per cent for serious reactions for new medicines. The Agency considers that the level of reporting by some groups, for example hospital doctors, is particularly low. Our survey highlighted some of the reasons doctors do not participate (Figure 15).

2.23 Since the inception of the Yellow Card Scheme the Agency has taken action to increase participation by:

- extending the scheme to allow reporting by coroners in 1969; hospital pharmacists in 1997; community pharmacists in 1999; and nurses, midwives and health visitors in 2002;
- setting up hospital-based Regional Reporting Centres for the West Midlands, Northern and Yorkshire, Wales and Mersey regions to receive reports and encourage participation by providing feedback to health professionals in their regions. A further Centre was set up in Scotland in October 2002;

- adding Yellow Cards to GPs' prescription pads, to copies of the British National Formulary and the Monthly Index of Medical Specialists;
- advertising the scheme in articles in medical and pharmaceutical journals;
- introducing limited electronic reporting arrangements for some general practitioners; and
- launching an electronic on-line form for all healthcare professionals.

2.24 In addition, the Agency has taken specific steps to further promote adverse drug reaction reporting through:

- a scheme identifying new medicines with a black triangle symbol on the patient information leaflet to encourage prescribers specifically to report all suspected adverse reactions with these medicines;
- setting up special reporting schemes for certain groups of patients, for example, those suffering from HIV and AIDS, where health professionals are specifically requested to report any drug reactions or interactions; and
- introducing an updated, simplified, anonymised Yellow Card in 2000 to avoid the potential negative effect on numbers of reports of new guidance on patient confidentiality.

2.25 Doctors in our survey were divided on the question of whether making the reporting of adverse reactions compulsory would help, and only half said they thought it would. The Government has no plans to introduce compulsory reporting.

2.26 The National Patient Safety Agency also has an interest in the safe use of medicines flowing out of the Department's April 2001 action plan, *Building a safer NHS for patients*. Their role includes the collection and analysis of information from NHS staff and patients on adverse incidents, including medicines-related incidents. This role has similarities with the work of the Medicines Control Agency under its Yellow Card Scheme in terms of collecting reports and

## 15 The most common reasons given by GPs and hospital doctors for not reporting adverse effects of medicines

- recently tried to report online but found I couldn't so didn't bother
- not my responsibility to report
- too busy
- it is not easy to find Yellow Card when necessary
- too junior to fill in a card
- it never comes to mind at the right time
- uncertain of the threshold for serious reactions
- not really sure what should be reported
- it takes a long time to fill out the form
- reporting generates too much extra work
- the system is not convenient

Source: National Audit Office survey of doctors

communicating risks, and there is a potential risk that confusion about reporting may affect both systems. The two agencies have agreed a joint working protocol.

## Patient reporting is to be rolled out in response to calls from patient groups

2.27 The Medical Devices Agency has since 2001 accepted electronic reports from consumers and others on adverse incidents arising from the use of regulated medical devices. These include items as diverse as contact lenses and condoms, heart valves and hospital beds, resuscitators, surgical instruments and wheelchairs. But the Medicines Control Agency, in common with other European regulators, has not had arrangements for reports from the public, because of concerns over their quality. From February 2003, however, the Agency is to roll out patient reporting via NHS Direct across England.

2.28 The results of our surveys of doctors and the public indicate that the move to introduce patient reporting is likely to be welcomed. Two thirds of doctors supported the reporting of adverse reactions by patients, saying it would either definitely or probably be helpful. And 60 per cent of the public we asked said they would consider using a telephone hotline or other method to report adverse reactions if they experienced them. Of those who actually reported having experienced an adverse reaction with a medicine, 72 per cent said they would do so. Most of the patient groups and other stakeholders we consulted considered that the extension of reporting rights to patients will enhance the monitoring of medicines, and also give additional coverage of non-prescription medicines where there is currently very little reporting.

## Unlicensed herbal medicines are not well covered by monitoring of adverse reactions

2.29 Herbal medicines, the majority of which are currently unlicensed, are usually purchased without the advice or involvement of a conventional doctor, pharmacist or other professional with access to the Yellow Card scheme. As a result, there is relatively little data on adverse reactions to these medicines. In 1996 the Agency wrote to all doctors and pharmacists inviting reports of suspected adverse reactions to any herbal medicines (licensed or unlicensed) and requesting samples for testing where available. Although the proportion of reports relating to herbal medicines doubled, it remains small at less than half of 1 per cent of all reports received.

2.30 Some herbal medicines have potential for serious side-effects. Preparations containing Kava-Kava were voluntarily withdrawn from the market in 2001 after concerns over liver toxicity. In December 2002, on the advice of the Committee on Safety of Medicines and the Medicines Commission, Ministers took action to further protect public health by prohibiting the use of Kava-Kava in unlicensed herbal remedies.

2.31 There is also evidence that some herbal medicines can interact with conventional medicines. One example is St John's Wort, which can reduce the effectiveness of a range of medicines from oral contraceptives to heart medication. The Agency has now made it compulsory for licensed products containing St John's Wort to include warnings about possible interactions on packaging labels. The inclusion of similar warnings on unlicensed products has been brought in through a voluntary agreement between the Agency and the herbals industry.

2.32 Our survey of the public showed that 13 per cent used herbal remedies at least once a month, with 10 per cent using them at least weekly. But 17 per cent of all those who had used herbal remedies said they would not tell their doctor that they were using them if prescribed a conventional medicine. Herbal medicines represent one area where patient reporting via NHS Direct may help fill an important gap in the Agency's drug safety data.

## Legitimate but unlicensed use of medicines in children is a cause for concern

2.33 The Agency is also concerned at the extent to which doctors in the UK use medicines outside their normal licensed uses. Many medicines are not specifically licensed for use in children, mainly because of a lack of relevant clinical trials by pharmaceutical companies during development. Research<sup>6</sup> has shown that up to 90 per cent of medicines prescribed to children in hospitals are not actually licensed for such use and there is a perception that side-effects in children are not always captured by the Yellow Card scheme.

2.34 In 2000 the Committee on Safety of Medicines set up a paediatric working group to advise it on the unlicensed use of medicines in children and how this might be minimised. The group aimed to improve the availability of medicines licensed for children and the monitoring of adverse drug reactions in children, using the existing regulatory framework, rather than introducing new regulations. The Agency is also involved in an initiative in this area at European level.



2.35 The "Orange Card" reporting scheme, run by the British Paediatric Surveillance Unit, part of the Royal College of Paediatrics and Child Health, is designed for surveillance of certain rare conditions in childhood. In June 2002 the Agency commissioned a study to monitor the incidence and nature of suspected adverse drug reactions with a fatal outcome in children under 16.

### The quality and quantity of safety information from companies to regulatory authorities in Europe could be improved

2.36 One of the conditions of drug licences issued in the UK or elsewhere in the EU is that pharmaceutical companies must report to the Agency any serious adverse reactions they are made aware of, within 15 days. In addition, companies must provide a summary of world-wide safety data for their product every six months for the first two years of a drug's life, and then annually until the end of the initial five year licence period. After this reports are submitted every five years. In April 2002, the European Medicines Evaluation Agency reported that not all companies holding centralised authorisations were complying with these regulations and they planned to take steps against offenders.

2.37 The Agency's regular inspections of company facilities can look for evidence that pharmacovigilance systems are in place, but Agency inspectors have not in the past routinely tested these systems for any evidence of under-reporting. Recognising this gap in their regulatory role, the Agency has now begun developing a programme of specific pharmacovigilance system checking work and the first inspection was carried out in 2002.

### The Agency prioritises its review of safety information

2.38 The Agency's pharmacovigilance group has access to a wide range of safety data from the UK and overseas. With large volumes of information, and insufficient resources to examine all of it fully, the Agency prioritises the material to optimise public health benefit. Adverse drug reaction reports coming from overseas are given lower priority, as are drug company safety reports on medicines where another European regulator has taken the lead in the licence assessment.

2.39 This approach to joint working with European regulators is sensible, as with nearly 600 of these company safety reports every year, the Agency must rely on its European partners to share information coming out of their regulatory work promptly. However, a new pharmacovigilance database designed to enable electronic data sharing across Europe has yet to be populated with data by most countries, including the UK. The Agency expect to be able to submit data in 2003.

2.40 The Agency has recently begun researching safety issues using the General Practice Research Database. Like other licence-holders of the database, the Agency has to pay a fee for using it and additional charges for commissioning any research from its scientific staff. Recent studies have shown that the database can make an important contribution to safety monitoring and, with more resource, the Agency could make fuller use of it.

2.41 Some overseas regulators direct resources towards commissioning external research into pharmacovigilance issues. For example, the US Center for Drug Evaluation and Research at the Food and Drug Administration has contracts with seven universities for research into medicines usage and co-prescribing, among other topics. The Swedish Medical Products Agency takes a different approach and is seeking to obtain company sponsorship for independent studies which it would oversee. As well as providing an additional source of safety information, the overseas agencies told us that their links with academia were important in maintaining a strong scientific base. The Medicines Control Agency does not maintain formal links with academia, though it has informal links through the Committee on Safety of Medicines and has the power to commission external studies.

### The Agency has developed a strategy to improve pharmacovigilance and is now in the process of implementing it

2.42 Recognising the need for safety monitoring to evolve, the Agency's post-licensing division had by July 2001 developed a conceptual strategy for achieving "excellence in pharmacovigilance". Full implementation of the strategy will need additional resources at the Agency, new commitments from industry and adoption at a European level. The Agency has recruited scientific staff to key posts and is taking the lead in European discussions.

### Taking action to respond to safety concerns

#### Action by the Agency can help mitigate the risks from wider access to medicines

2.43 The Department of Health set out the aim of making more medicines more widely available to patients in the 2000 NHS Plan. In April 2002, following work with key stakeholders and changes to the law, the Agency introduced a revised procedure for companies to apply for reclassification of medicines from prescription-only to non-prescription status. Of seven successful applications since the introduction of the new procedure, two moved medicines from prescription-only to make them available in pharmacies and five

## 16 Restrictions on sales of paracetamol tablets have reduced the number of overdoses

- Paracetamol is the UK's most widely used painkiller with an estimated 30 million packs sold each year. It is safe and effective when used as recommended, but is also the most common method of self-poisoning through overdose, accounting for half of all cases of liver failure. Paracetamol is fatal in relatively small doses - possibly as few as 20 tablets. In 1997 it was estimated that paracetamol overdoses accounted for 40,000 hospital referrals a year and between 100 and 150 deaths. From the 1980s, the rise in sales and increasing availability of the drug were paralleled by increasing misuse. Doctors also suspect that some fatal overdoses were unintentional.
- In September 1998, following advice from the Medicines Control Agency, regulations on the sale of paracetamol and salicylates (aspirin) were introduced such that:
  - pharmacies can sell up to 32 tablets per sale only. (They may still sell up to 100 tablets in certain cases where a patient needs continuing pain relief). Sales of more than 100 tablets require a prescription;
  - other retail outlets can sell a maximum of 16 tablets (the previous limit was 24);
  - specific warnings on the prevention of accidental paracetamol overdose must be printed on packets and leaflets.
- At the same time, nearly all tablets became available only in blister packs. These restrictions were not applied to effervescent forms, granules, powders, suppositories and liquids, which are seldom implicated in overdose. The Government aimed to reduce the number of related deaths by 10 per cent.
- A study by the Centre for Suicide Research at Warneford Hospital in Oxford of data from the Office of National Statistics, five liver units and seven general hospitals between September 1996 and September 1999 showed that:
  - deaths from paracetamol poisoning fell by a fifth and from salicylates by a half; two thirds fewer liver transplants were performed on patients poisoned by paracetamol; and non-fatal self-poisonings with paracetamol fell by 11 per cent;
  - the average number of paracetamol tablets taken in an overdose fell by seven per cent;
  - there was a 17 per cent drop in incidents involving 32 or more pills.
- These results were borne out nationally and there is also evidence that the drop in overdoses was not matched by an increase in other forms of self-harm. Both the Agency and the Centre continue to monitor hospital admissions, liver transplants and deaths from overdoses.

Source: Medicines Control Agency

allowed medicines that had previously been available only in pharmacies to go on general sale. The Agency has consulted on each, including to assess safety risks.

2.44 In the past, the Agency has been able to use regulatory methods to mitigate the risks of increasing access to medicines. **Figure 16** sets out how reducing the size of packs of paracetamol had a direct effect on the number of accidental and deliberate poisonings.

### Purchase of medicines via the internet poses a new challenge for the Agency

2.45 One per cent of the public we surveyed had purchased prescription-only medicines over the internet, saying this was the easiest way to obtain the medicine and that it cost less than through a prescription. It is, however, illegal to supply prescription-only medicines to UK consumers over the internet or through mail order, irrespective of whether an online consultation has been carried out. The most common medicines purchased this way in the UK are listed in **Figure 17**.

## 17 Top ten Prescription-only Medicines marketed over the internet in the UK

1	Xenical	Obesity
2	Proscar	Prostate disorders
3	Propecia	Hair loss
4	Viagra	Erectile dysfunction
5	Uprima	Erectile dysfunction
6	Reductil	Appetite suppressant
7	Zyban	Anti-smoking
8	Relenza	Influenza
9	Phentermine	Obesity
10	Meridia	Obesity

Source: Medicines Control Agency monitoring data

2.46 Purchasing prescription-only medicines without a prescription carries potentially serious risks:

- self-diagnosis may be incorrect;
- the medicine purchased may not be appropriate to treat the condition;
- side-effects from the medicine may be serious, including exacerbating other existing conditions, and there may be adverse interactions with other medicines being taken; and
- the quality and safety of the medicine is not assured.

2.47 The problem of illegal internet selling requires international co-operation. None of the EU regulators we visited had yet made substantial headway in tackling it, and all recognised that it would be very difficult to achieve full compliance with medicines legislation. The Medicines Control Agency has been monitoring the problem for two years, and has made this area of enforcement activity a priority in 2002-03. Work will focus on commonly purchased prescription-only medicines from UK-based websites, whilst sites based overseas will be referred to the appropriate national regulatory authorities. In the meantime, the Agency is taking enforcement action on illegal internet sales of prescription-only medicines through the closure of web sites and prosecution.

## Reviewing medicines advertising and promotional material

A combination of statutory and self-regulation covers advertisements for medicines

2.48 Direct advertising of prescription-only medicines to the public is illegal in the UK and the rest of the European Union. Advertising of medicines available over the counter is, however, allowed. And advertising of prescription medicines to doctors or others qualified to prescribe or supply them is also legal. The control of medicines advertising in the UK is based on a long-established system of self-regulation underpinned by statutory powers administered by the Agency. The three main bodies involved in the self-regulatory system are the Prescription Medicines Code of Practice Authority, the Proprietary Association of Great Britain and the Advertising Standards Authority, of which the first two administer Codes of Practice.

2.49 The Proprietary Association of Great Britain, the trade association of companies selling non-prescription medicines, examines all advertisements submitted by its members and consults with the Agency. When advertising prescription-only medicines to health professionals, companies are required to comply with the Association of the British Pharmaceutical Industry Code of Practice. The Prescription Medicines Code of Practice Authority, run at arm's length by the Association of the British Pharmaceutical Industry, handles complaints against the Code, publishing its rulings, and may require advertisements to be withdrawn.

2.50 While the Agency has the power to require sight of advertisements in advance, it usually exercises this power only where:

- the product is a newly licensed and intensively monitored medicine;
- the product has been reclassified to make it available without prescription for the first time; or
- the product's previous advertising has breached the regulations.

2.51 The Agency's Advertising Unit carries out monitoring of prescription-only medicine advertising in medical journals, concentrating particularly on newly launched products. It also investigates complaints about advertising from any source, including health professionals and the public. In 2001-02, 50 advertisements were amended or withdrawn after scrutiny by the Agency, and a further 81 potential breaches were identified through complaints, following which action was taken. Examination at any stage by the Agency does not preclude it from taking later action if it subsequently decides there has been a breach of regulations, and this was the case in October 2002 when it requested the withdrawal of an advertisement for an oral contraceptive, which had also been examined by the Prescription Medicines Code of Practice Authority.









# Part 3

## Protecting public health by providing information on medicines

3.1 As part of its mission statement, the Agency aims to *provide information which will contribute to the safe and effective use of medicines*. There is no specific funding allocation for this work, which is covered, along with all the Agency's activities, out of fees paid by drug companies. This part of the report looks at how effectively the Agency communicates important safety information on specific medicines through:

- regulating the leaflets and labels provided with medicines;
- issuing quality alerts; and
- issuing safety warnings or precautions as necessary.

3.2 This part of the report also looks at the ways in which the Agency communicates more widely with the public, interest groups and health professionals, to contribute to the safe use of medicines.

### Regulation of medicines leaflets and labels

#### Medicine leaflets are often confusing and inadequate

3.3 The information which must be included in the patient information leaflets prepared by licence holders and supplied with licensed medicines is governed by European legislation. The Agency regulates it and examines all changes to labels and leaflets. It may also insist on additional information or warnings being added before granting or renewing a licence. Whilst there are some good practice examples of clear and useful leaflets, particularly among over-the-counter medicines, most stakeholders agree that they are often confusing and are disregarded by patients.

3.4 This was reflected in our public survey which showed that only around 30 per cent of people read all the information in the leaflet. Some 8-12 per cent never read any of it. Some 40 per cent felt that too little

information was provided, and 20 per cent would like to see more information on the likelihood of the listed side effects. In our sample of doctors, half of respondents reported that their patients had difficulty interpreting the information on medicine leaflets.

3.5 In the United States, the Food and Drug Administration have introduced new simplified "drug facts" sheets for over-the-counter medicines which provide shorter, more targeted information about medicines in an easier-to-read format. In the UK, an example of good practice is led by Doctor Online, a peer-reviewed patient information service run as part of the internet facility NHS Net at [www.doctoronline.nhs.uk](http://www.doctoronline.nhs.uk). The service has developed a set of simplified information sheets for medicines commonly used in hospitals that doctors can obtain online and an example is included at Appendix 10. However, the Agency has not been involved in developing these documents.

3.6 In May 2002, the European Commission's High Level Group on Innovation and Provision of Medicines called for a review of legislation on patient information leaflets taking into account the views of users as well as regulators and industry. The Agency is working with these groups to take forward their concerns as part of the review.

#### The Agency is leading work to reduce medication error by improving labelling and packaging of medicines in hospitals

3.7 The Department of Health's plans for improving safety in the NHS are set out in the 2001 report, *Building a safer NHS for patients*. Among the proposals, the report set a target for reducing by 40 per cent the number of serious errors in the use of prescribed medicines by the end of 2005. Research has shown that labelling can be involved in up to 25 per cent of medication errors<sup>7</sup>. The Committee on Safety of Medicines established a sub-group to advise Ministers on the role that medicines packaging and labelling might play in minimising the risk of such errors. The sub-group published in April 2002 a set of principles to be applied by the

<sup>7</sup> *Joint Commission: preventing adverse events in behavioural healthcare: a systems approach to sentinel events*. Oakbrook Terrace, IL: Joint Commission on accreditation of healthcare organizations. Quoted in *Building a safer NHS for patients*, Department of Health.

pharmaceutical industry. **Figure 18** describes one group of medicines where changes to wording and product design are expected to help save lives.

- 3.8 The Agency has since led a working group involving the pharmaceutical industry, healthcare professionals and lay representatives to develop best practice guidance for labelling. This group examined the scope for changes to the packaging of medicines used in hospitals and elsewhere, many of which appear almost identical apart from a different name or dosage (**Figure 19**).

## Issuing defective medicine alerts

### Drug Alerts about defective medicines do not reach all who should receive the information

- 3.9 There are around 100 confirmed reports of UK drug defects each year and around 140 from the EU. If a quality defect poses a risk to patients the Agency issues a drug alert. There were 28 UK and 4 EU alerts in 2001-02. These are sent by fax to key contacts in the wider NHS, community pharmacies, dispensing doctors, private hospitals and pharmaceutical wholesalers. Drug Alerts are not sent to doctors generally or to the general public, unless there is a major public health risk requiring a recall.
- 3.10 The creation of Primary Care Trusts, an exercise which was completed in April 2002, made it difficult for the Agency to identify an effective cascade mechanism to reach community pharmacists via these new bodies. It was only in September 2002 that the Agency agreed with the Department of Health that it could use the Department's electronic link to disseminate drug alerts to community pharmacists. The new cascade procedure was first used on 10th October 2002.
- 3.11 Arrangements are in place to distribute alerts via email or fax to regional pharmacy contacts in NHS Hospitals, the National Care Standards Commission, Pharmaceutical Advisers and Directors of Public Health in Primary Care Trusts. Recipients are asked to distribute alerts to a range of healthcare professionals, including community pharmacists, general practitioners and nurses. It is the recipients' responsibility to ensure appropriate distribution within their own organisation. The Agency has begun testing the operation of the system through Drug Alert effectiveness surveys, of which the first was carried out in December 2002.
- 3.12 In the case of medicines available on general sale, communication of information on defective medicines, though rarely required, is more difficult. Manufacturers and marketing authorisation holders are required to contact all retail outlets stocking the suspect batch of medicine but, as these non-pharmacy outlets are not included in the Drug Alert fax cascade system, they rely on newspaper advertisements, as with many other non-pharmaceutical products.

### 18 Changes to the labelling and packaging of vinca alkaloids used in chemotherapy to help prevent fatal errors

- In 1981, the Medicines Control Agency approved the drug vincristine for use in chemotherapy. The Agency required warnings to be included in the drug's packaging to state that it was "not for intrathecal use", i.e. not for injection into the spine.
- In 2000, the expert report on the NHS, *An organisation with a memory*, identified the elimination of accidental deaths from maladministered spinal injections as a key area for improvement by the end of 2001. There had been at least 13 such deaths over 15 years.
- In February 2001 an 18-year old chemotherapy patient in a Nottingham hospital died after he was wrongly given an injection of vincristine into his spine, when it should have been injected into a vein. The external enquiry into the incident concluded that poor design of the medicine's packaging was a contributory factor to the error.
- Following the enquiry, the Medicines Control Agency referred to the Committee on Safety of Medicines for advice. The Committee considered the labelling of this whole group of medicines, the vinca alkaloids, and recommended that to avoid any risk of confusion, labels should state clearly the approved route of administration **only**, i.e. "for intravenous use only". The Agency has taken steps to ensure that companies comply with this labelling change.
- The Department of Health has developed guidance on the safe administration of intrathecal chemotherapy and a training pack for staff.
- The Department also sought tenders in March 2002 from manufacturers who could design devices for spinal procedures to eliminate the risks of error.

### 19 Similar packaging of medicines in hospitals can contribute to safety risks



Packaging of sodium chloride, water and lignocaine.

Source: *BMI, Vol322:p308. Reproduced from 'Building a safer NHS for patients', Department of Health*

## 20 Regulatory actions other than withdrawal of a marketing authorisation

Type of regulatory action	Number of actions in 2001-02
Variations to marketing authorisations to require the inclusion of additional warnings or restrictions on labels and leaflets	515
Automatic addition of a drug to the list of intensively monitored "black triangle" medicines	78
Articles on drug safety in the Agency publication <i>Current Problems in Pharmacovigilance</i> , sent free to all healthcare practitioners who can report adverse reactions	26
"Dear Doctor" letters containing amended prescribing advice sent by pharmaceutical companies with the approval of the Agency	9
Refusal to renew a marketing authorisation at the five-yearly renewal date	Nil

Source: Medicines Control Agency

## Issuing safety warnings

To communicate concerns over the safety of medicines, the Agency has a range of options, but there are concerns over their effectiveness

3.13 Whilst the number of medicines which have their marketing authorisation withdrawn from the UK market is low, a large number of other types of regulatory action are taken routinely each year by the Agency to address ongoing safety concerns (Figure 20).

3.14 Despite the range of methods of communication, safety warnings are not always effective. Cisapride is a treatment for acid regurgitation (heartburn) which can interact on rare occasions with certain medicines affecting the heart. Warnings issued over a number of years did not get through to prescribers effectively, and the drug was eventually withdrawn (Figure 21).

3.15 In the area of "over-the-counter" medicines also there are concerns that safety warnings could be more effective. In April 2002 the Committee on Safety of Medicines issued a warning that medicines containing aspirin should not be given to children under 15 because of the risk of a rare and potentially fatal condition known as Reye's syndrome. There were already warnings in place that children under 12 should not be given these products.

3.16 The Committee announced the extension to 12- to 15-year-olds via the public media, through an article in its bulletin to health professionals, including pharmacists,

## 21 The withdrawal of Cisapride and the difficulties of publicising safety warnings

- Cisapride (chemical name preprulsid) is a treatment for acid regurgitation (heartburn) and related disorders of the upper gut. It was first licensed in December 1988.
- Cisapride can cause heart problems such as prolonged heartbeat or abnormal heart rhythms in rare cases. This is most likely to occur when the drug is used at the same time as other medicines that affect the heart or medicines that slow the breakdown of cisapride, thus increasing its level in the blood.
- The Agency required information about such side-effects and drug interactions to be included in labels and leaflets on licensing and to be regularly updated as new information (such as new interacting medicines) emerged.
- The Agency and the Committee on Safety of Medicines informed UK doctors and pharmacists of the risks to patients through the safety bulletin *Current Problems in Pharmacovigilance* in 1995, 1996, 1997 and 1998, giving information on how to use cisapride safely. Despite these warnings, prescribing and dispensing of cisapride to patients at risk of heart problems or those taking interacting medication continued. Between 1996-7 and 1997-8, co-prescribing of cisapride with potentially interacting medicines only fell from 11.9 per cent to 10.7 per cent.
- Between 1995 and 2000, 70 cases of serious adverse reactions with cisapride were reported in the UK.
- The Committee on Safety of Medicines reviewed the benefits and risks of cisapride in 2000 and concluded that the balance between risk and benefit was not favourable. Licences for cisapride were therefore suspended and the drug was withdrawn from the UK market. The Committee took into account the fact that repeated warnings on how to use the drug safely had not been effective in changing UK prescribing and dispensing practice.

and by requiring warnings to be printed on all new packages and leaflets. It also released the announcement in advance to groups closely associated with the issue. Despite this, the pharmacy trade association, the National Pharmaceutical Association, told us it was disappointed not to receive advance notification, as it would have wished to alert its members directly. The Agency pointed out that with a large number of interested parties it was necessary to limit discussions in advance of the announcement to those most closely involved, which included pharmacist representatives. In October the Committee simplified its advice, and the Agency used a press release and press briefing, in particular to the pharmaceutical press, to draw attention to the changes, which resulted in widespread coverage.

3.17 The Agency has not, however, examined data on usage in the case of aspirin, and does not know if consumers' behaviour has been affected. It does not have a high-level performance measure for the effectiveness generally of regulatory action and does not yet routinely measure understanding of, and compliance with, the safety advice given to patients and health professionals. Although the Agency continues to monitor the level of reported adverse reactions where there is a specific safety concern over a

medicine, several stakeholders felt that there was scope to make more proactive use of resources such as the General Practice Research Database (for prescribed medicines) in developing this work. The Agency believes this may require additional resources.

3.18 The Agency's actions on Zyban, an aid to smoking cessation, does provide a good practice example, however. Safety monitoring by the Agency had established that adverse reactions (including potentially fatal seizures) occurred around the time, between 2 to 4 days into treatment, when dosage was doubled. The Agency issued advice to doctors to change dosage regimes, and then actively monitored the incidence of reported adverse reactions. This monitoring confirmed that the rate of adverse reactions had fallen, **Figure 22 below**, and that further regulatory action was not necessary.

### Health professionals would like to see improvements in dissemination of the Agency's drug safety information

3.19 Data<sup>8</sup> from 1999 showed that readership among doctors of the Agency's main drug safety publication *Current Problems in Pharmacovigilance* had fallen to 27 per cent. In response, in 2000, the Agency sent out its own questionnaire to a random sample of 10,000 general practitioners, hospital doctors and community and

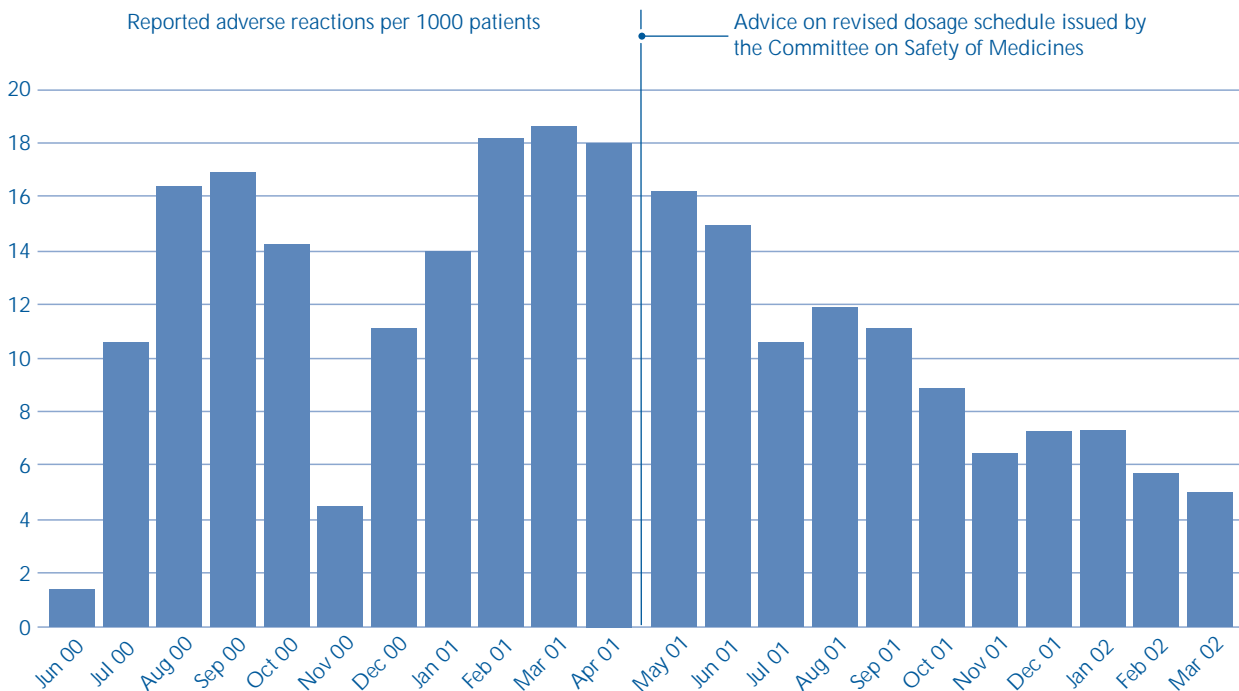
hospital pharmacists receiving the publication, to assess its usefulness and find ways in which information could be put across to health professionals more effectively.

3.20 The Agency's survey results backed up concerns about readership levels. The response rate overall was only 14 per cent, and most of these respondents said they merely skimmed the publication. Doctors' representatives we talked to said time pressure and the problem of "information overload" was partly to blame. Hospital pharmacists were the only group of whom a majority said they regularly read the whole issue.

3.21 Despite the low readership rates, the Agency's survey showed that when health professionals do read *Current Problems* it makes a valuable difference. Half of general practitioners responding said they had changed their practice as a result of reading a particular issue of the bulletin, along with a slightly smaller proportion of pharmacists. More than 60 per cent of all respondents said they had changed the advice they gave to patients after reading it.

3.22 Most doctors in our survey were generally satisfied with the safety information provided by the Agency. However, a few considered that safety alerts are often too late or the information comes only after the issue has been reported in the newspapers. Doctors made a number of suggestions for improved dissemination, **Figure 23**.

## 22 Monitoring adverse reactions to the smoking cessation drug Zyban confirmed that safety messages had got through to the public following press publicity and a subsequent safety campaign



Source: Medicines Control Agency

8 Based on an attitude survey carried out by the independent *Drug and Therapeutics Bulletin* among its own readers in 1999.



3.23 The Agency acknowledges that improvements could be made to the safety information it provides to doctors, and have devised a strategic approach for information management in the future, including provision of information in "layers" so that the user can access as much or as little as needed, with information provided via the internet. Delivery of a tailored medicines support and information system for healthcare professionals is made more difficult by the fact that integrated information systems for the NHS are not yet in place.

## Communicating more widely about medicines

### The Agency has not actively sought to develop a relationship with the public

3.24 The Agency receives up to 350 telephone calls and around 100 written enquiries each week from the public and others about medicines. However, any public statements about medicines safety have generally been made by the Chair of the Committee on Safety of Medicines rather than the Agency and, as a consequence, there is a low level of recognition among the public, and even among health professionals, of the latter's role.

3.25 The Agency considers that the public's main source of advice on medicines is the doctor or the pharmacist and this was borne out by our survey. But increasingly consumers are seeking information on health matters directly, for example using the internet, where unofficial information about medicines may not always be reliable. Five per cent of our survey respondents said they would use the internet if they wanted to know more about a medicine they were using.

3.26 Among the overseas regulators we visited, the Food and Drug Administration (Center for Drug Evaluation and Research) in the United States had devoted most resources to communication directly with the public. This partly reflects a different approach to information provision in an environment where, unlike in Europe, direct advertising of prescription-only medicines to the public is allowed. As well as the internet, methods the US regulator used included:

- Public meetings on important safety issues;
- Surveys of the public;
- Poster advertisements (**Figure 24**); and
- General awareness campaigns.

### 23 Doctors' suggested improvements in the dissemination of safety information

#### Comment/suggestion

Safety alerts should be sent through email or available on the internet

Safety alerts should be better targeted towards doctors likely to use the specific medicine

Safety information should be easier to read (e.g. with simpler bullet points)

Safety information should be provided more frequently

*Source: National Audit Office survey of general practitioners and hospital doctors*

### 24 Public advertisements by the US Food and Drug Administration



*Source United States Food and Drug Administration*

- 3.27 The World Health Organisation's Uppsala Monitoring Centre in Sweden has organised a series of meetings between drug safety experts from around the world to discuss improving the communication of drug safety information. The conclusions were set out in a book<sup>9</sup> published in May 2002, which recommended that regulators, as well as industry, should contribute more to: a climate of openness about medicines; empowering consumers through information about their medicines; informing the public more effectively about the risk/benefit balance; and improving education about medicines.
- 3.28 The Agency recognises that there is scope to put safety messages across more effectively by improving the quality of information it provides. In the light of experience gained from the publicity surrounding recent medicines safety issues, for example on the third generation oral contraceptive and the MMR vaccine, in 2002 it revised procedures for public communications with the aim of providing more balanced and tailored information to the public.
- 3.29 The Agency has also developed a source of information on herbal medicines and potential adverse interactions for use by the public as part of its website, although this has not been advertised to the public generally.
- 3.30 In a MORI poll of the public, conducted on behalf of the independent Science Media Centre in April 2002, some 61 per cent of people questioned expected science to guarantee a medicine was safe, although in reality any medicine involves a balance between risks and benefits. The creation of the new merged agency - the Medicines and Healthcare products Regulatory Agency - with a new Agency Chair who is expected to maintain a much higher public profile, brings the opportunity to explore new methods of disseminating safety and other information on medicines to the public. It also brings the opportunity to raise awareness of the Agency's work more generally and improve the quality of public debate about medicines safety, although to do so may require a more explicit allocation of funding to this activity.

### Consumer and patient groups would like to see stronger lay representation in medicines decision-making

- 3.31 All medicines carry the risk of side-effects. Whether these are acceptable depends on the severity of the condition they are designed to treat and the individual circumstances of the patient. The public is also becoming increasingly aware, through reporting in the media, of the risks involved in taking medicines for more minor conditions, as well as vaccines. Consumer and patient groups told us they were concerned that the Agency and the Committee on Safety of Medicines does not routinely involve patient groups in decision-making where a difficult risk/benefit balance is involved, or seek their views explicitly. For example, they

cited the Food and Drug Administration in the United States, which regularly holds public meetings on drug safety issues. They would like to see a similar approach in the UK.

- 3.32 The Committee on Safety of Medicines is responsible for providing expert advice and monitoring decisions about medicines safety, e.g. on whether to withdraw a marketing authorisation or increase the warnings attached to a particular medicine. Its members are expert physicians, toxicologists, pharmacists and pharmacologists from a range of disciplines in the UK. The Medicines Commission is a broader-based committee, which is required to include at least one member with wide and recent experience of the pharmaceutical industry. It hears appeals by applicants on licensing decisions and advises Ministers on these and on medicines policy generally.
- 3.33 The committees have two and one lay representatives respectively. However, lay members are not always included on working groups of the Committee on Safety of Medicines. In view of the highly technical nature and large volume of the information discussed by the Committees, the consumer groups we spoke to considered that there was scope to review the level of support to lay members, to ensure it enables them to contribute effectively to decision-making.

### Greater openness in consultations could improve policy-making

- 3.34 The Consumers' Association told us they welcomed the opportunities offered by the Agency to respond to consultation requests on policy issues, and frequently do so. But they were concerned that the Agency did not publish in full the results of such consultation exercises or provide feedback to those organisations that responded. This concern was shared by the National Pharmaceutical Association, the national body of Britain's community pharmacy owners.

### Better links with the health professions could improve the safe and effective use of medicines

- 3.35 Doctors' representatives we consulted told us that although many doctors were familiar with the Committee on Safety of Medicines as the source of urgent safety alerts, fewer were aware of the Agency's role as protector of public health or source of information on medicines. One reason may be that, whilst medical students receive technical tuition on the potential for adverse reactions and interactions with medicines, their undergraduate education does not cover the arrangements in place for licensing and monitoring medicines or a discussion of the role of the Agency. Only some doctors, such as those who go on to study clinical pharmacology at the

postgraduate level, would be likely to cover this aspect in their training. The Agency recognises that recognition and understanding of its work among health professionals could be improved.

- 3.36 In response, the Agency has occasionally provided speakers for courses organised by the Royal Colleges that provide postgraduate medical training. But health professionals we consulted believed that there is further scope for information on the role of the Agency, and in particular on the importance of reporting adverse reactions to medicines, to be more fully integrated into both undergraduate and postgraduate syllabuses.

### Local networks could be used to greater effect to get safety messages across to health professionals

- 3.37 The Agency has four regional monitoring centres, which promote the collection of adverse drug reaction reports and disseminate safety information at a local level, and a fifth has recently been set up. Other regulators we visited overseas had a greater local presence to give them direct access to health professionals. For example, in France a network of 32 regional centres, based in hospitals and funded by the regulatory agency, provides important links with doctors on the ground. In the UK, the Medical Devices Agency has a network of Medical Devices Liaison Officers in all Acute and Primary Care Trusts.

- 3.38 The Department of Health's September 2000 report, *Pharmacy in the future*, set out the Government's aims to integrate pharmacy services better with other healthcare professions and ensure that pharmacists have a greater role in increasing the benefits patients get out of medicines.

- 3.39 Pharmacists can help filter information and avoid the problems of "information overload" which doctors told us affected their ability to absorb important advice on medicines. Some doctors already see pharmacists in this role - seven per cent of respondents to our survey cited the pharmacist as their normal source of safety information. One hospital doctor commented:

*"I think pharmacists need to ensure that doctors are fully aware of drug problems. These problems could be advertised at monthly medical meetings by a person designated in the trust to inform colleagues of drug problems, on the basis of evidence and inform us about what can be done."*

- 3.40 There are some good practice examples of pharmacists taking a very active role in promoting and monitoring medicines safety. Working with doctors, such professionals can improve patient outcomes by, for example, the management of multiple prescribing or identifying potential drug interactions. In April 2002, the Royal Free Hampstead NHS Trust appointed the first

ever consultant pharmacist for patients with HIV, who was charged with monitoring and reducing the risks and maximising the benefits of the medicines available to these patients. As an illustration of good practice in this area abroad, in the Netherlands health system, community pharmacists regularly make presentations to local doctors on the main medicines safety news and summarise prescribing advice.

- 3.41 Resources for such work are an important consideration. The Audit Commission's report on medicines management noted in 2001 that generally there were financial constraints which prevented them from devoting enough time to clinical as opposed to administrative or simply dispensing activities<sup>10</sup>. The report also noted, however, that productivity of pharmacists varied significantly across hospitals and that NHS Trusts could take action to improve, including introducing more automated prescribing arrangements. This would free time for hospital pharmacists to take on a greater clinical role.

### The Agency is legally constrained from sharing some types of information

- 3.42 The National Institute for Clinical Excellence is the independent organisation responsible for providing national guidance on treatments and care for those using the NHS in England and Wales. Part of this work involves appraising alternative technologies and treatments based on evidence of both clinical and cost-effectiveness. This role is distinct from that of the Medicines Control Agency, which regulates the safety, quality and efficacy of medicines. It is outside the remit of the Agency to comment on which medicines are *most* efficacious or cost-effective for the NHS.

- 3.43 Nevertheless, decisions on whether medicines have the desired effects and whether they are cost-effective rely on similar data and information. In July 2002, the House of Commons Health Committee recommended closer working relationships and communication between the Medicines Control Agency and the Institute to improve the quality and quantity of information available to the Institute for making its assessments on new drug therapies.

- 3.44 The Government has agreed to explore the possibility of a closer working relationship between the Agency and the Institute. Although the two organisations have had an agreed protocol on working together since August 2000, there are legal constraints under the Medicines Act on the information the Agency can disclose, designed to protect commercial confidentiality. The Agency is discussing with industry what information must remain confidential at least until the completion of licensing procedures and is to review the Medicines Act in the light of the 2001 Freedom of Information Act. The increasing use of the centralised European procedure for licensing medicines may also restrict the scope for sharing information with the Institute.







# Part 4

## Providing a service to the pharmaceutical industry

4.1 The aim of the regulatory system and the Agency is to protect public health, but in doing so it also provides a service to the pharmaceutical industry by licensing new medicines and developments of existing ones. Services provided to the industry also include licensing of manufacturers and wholesale dealers, and the provision of export certificates to facilitate the export trade. In addition, Ministers have set an objective that the Agency should avoid creating "unnecessary impediments" for the pharmaceutical industry. This part of the report examines how well the Agency has provided these services and balanced this with its overriding aim of protecting public health.

### Industry's need for expeditious licensing of new active substances has been met without reducing quality of the approval process

- 4.2 In 1987, Ministers in the then Department of Health and Social Security commissioned a study of its Medicines Division to recommend efficiency improvements in the light of increasing volumes of regulatory work. The resulting report<sup>11</sup> described unnecessarily slow review times for licensing applications (up to two years for new active substances).
- 4.3 The report recommended that the full cost of the Division should be charged to industry, with a fee structure that related directly to the cost of carrying out different types of work. It also saw a need to improve the level of informal communication with industry. The Medicines Control Agency was created in 1989 to give effect to these recommendations.
- 4.4 Since its establishment, the Agency has consistently reduced the time it takes to assess licence applications for major new active substances, despite a growing number of applications in the 1990s (**Figure 25 overleaf**). In 2001-02 it spent on average 33 working days assessing new drug applications, though this measure does not represent the actual elapsed time,

because it excludes the time the Agency spent awaiting answers to follow-up queries it raised with the applicant company. The Agency more than met the European Union targets of 55 and 70 days for assessing mutual recognition and centralised applications respectively.

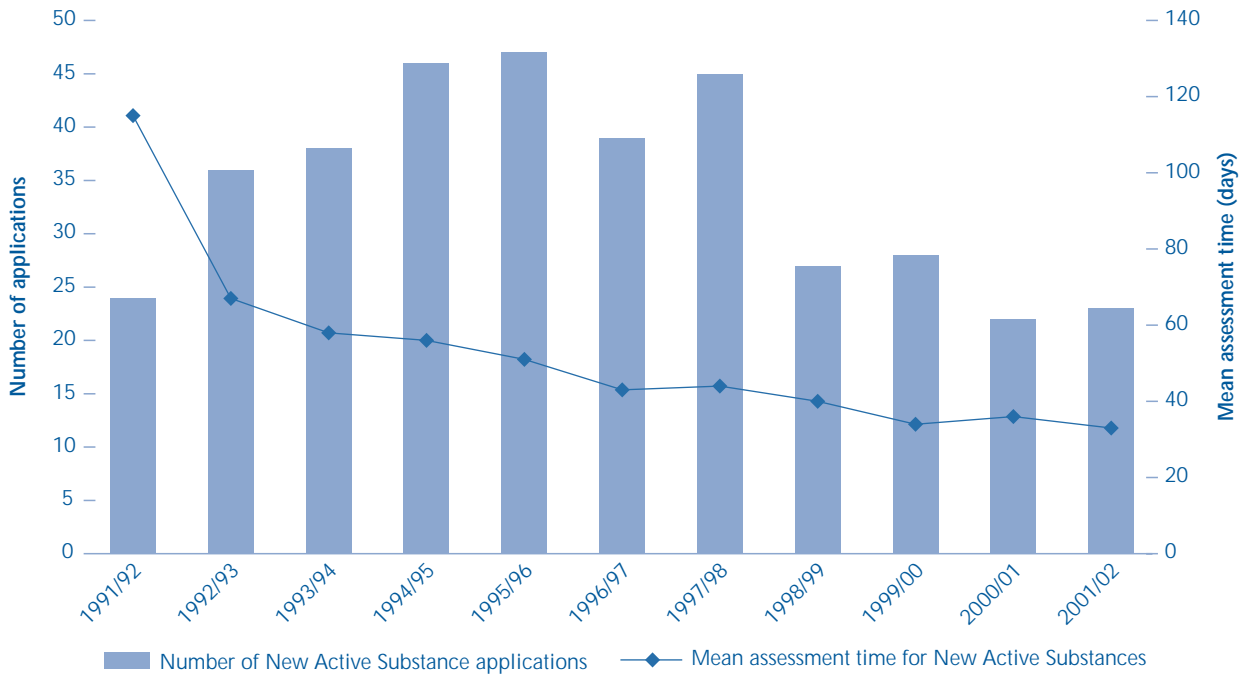
- 4.5 The reductions in assessment times have largely been the result of efficiency gains resulting from business reorganisation, investment in updated technology and revised working practices. The Agency has also introduced more quality measures in its licensing work. However, the Agency considers that it is now approaching the minimum average assessment time consistent with a proper evaluation of all the scientific evidence, and has no target to reduce assessment time further.

### Industry has faced delays in post-licensing work

- 4.6 Since its creation in 1989, the Agency has reorganised to focus on business streams, and improved the flow of work. The Agency has found it difficult, however, to keep up with increasing volumes of post-licensing business, which covers variations and renewals of existing licences, and the industry's concern over the level of service has been reflected in survey feedback. The Agency told us the problems arose because it had had difficulty recruiting staff, particularly for renewals work.
- 4.7 Progress against targets for variations work has been helped by the introduction of a simplified European regulation, which the UK was the first in Europe to implement. But large backlogs of renewal work had built up by 1999-2000 with some 1,400 unprocessed applications over 90 days old, compared with a monthly incoming workload of around 200. Although companies can still market their product while renewals or variations are under assessment, delays can lead to uncertainty and affect their business planning. The Agency recognises these problems and has taken action to redesign business processes. To monitor progress on both renewals and variations, it has continued to survey pharmaceutical industry client representatives.

11 *Study of control of medicines*, Dr NJB Evans, PW Cunliffe, 1988

## 25 The Agency has consistently reduced assessment times for major new drugs



### NOTE:

Includes centralised, mutual recognition and national applications

Source: National Audit Office analysis of Agency data

## The Agency's service has not always met industry's wider needs

- 4.8 Laboratory service companies have had concerns about levels of service in the Agency's inspection work. The British Association of Research Quality Assurance, representing internal auditors of many of the Agency's Good Laboratory Practice and Good Clinical Practice clients, told us that some of its members were concerned that the declining frequency of inspections left them unable to demonstrate to their own clients that they had met appropriate quality standards. When it became apparent that some inspection frequencies were declining, the Agency recruited new staff and has reduced the backlog.
- 4.9 As a means of improving service, the Agency is now extending client survey work to the majority of its business areas. Industry representatives we consulted welcomed these efforts to improve performance and measure client satisfaction. This process of feedback should also help companies improve the standard of their applications and reduce the need for follow-up questions. But in the industry's view, the Agency needed to do more to demonstrate the efficiency and consistency of its assessment processes through transparent quality assurance and performance reporting arrangements.

4.10 As well as delivering improvements to the direct work of licensing and monitoring since 1989, the Agency has made efforts to contribute in various ways to an improved regulatory environment by:

- working with industry on revised guidelines for reclassifying medicines to allow sale without prescription where this is safe;
- putting the UK government case in Europe that the option for companies to apply for a licence through the mutual recognition process should be retained. This is also the position of UK industry;
- working with European agencies towards closer IT integration. Electronic filing of applications is already underway and electronic reporting of adverse drug reactions by electronic means will be possible for all countries during the course of 2003; and
- being influential in establishing the current European medicines regulatory regime and maintaining an important position in the European field. The UK currently holds the Chair of the European Medicines Evaluation Agency Management Board.

4.11 Industry representatives we spoke to felt there was scope for the Agency to do more to promote the UK position in Europe and that more resources should be devoted to providing high-level representation on European expert committees. They would like to see European agencies generally taking a more integrated approach to regulation, with different agencies concentrating on their particular strengths, and relying more on each other's work.

## The Agency may be at risk of not providing services that industry within Europe requires

4.12 With an increasingly global pharmaceutical market, most new medicines will be sold in more than one European country. It therefore makes sense for companies either to apply to the European Medicines Evaluation Agency for a centralised European marketing authorisation, or to achieve mutual recognition of a licence obtained in one member state. Historically, the UK has been among a handful of countries with well-established and well-respected regulatory expertise. The Medicines Control Agency has as a result received a larger share of applications under the mutual recognition arrangements than would be expected.

4.13 In recent years, however, competition from other European regulators has increased. The two main reasons for this, put to us by industry in the UK and regulators abroad, were:

- that industry is increasingly looking to consult with regulatory agencies for advice before submitting applications. While the Swedish Medical Products Agency has focused on encouraging dialogue with companies, and charges for its advice, the Medicines Control Agency has not been able to charge a fee for advice to industry. As a result, it has found it difficult to devote resources to this work. The Agency is considering what changes to its powers may be needed to allow it to charge fees for this work; and
- the fees charged by the Medicines Control Agency for new active substances are the highest national fees in Europe.

4.14 The high level of UK licence fees partly reflects the fact that the Medicines Control Agency is financed entirely by fee income, whilst some other regulators have partial state funding. It also reflects the fact that UK headline fees are designed to cover a broader range of work throughout the life of a product than is the case in some other countries. For example, the Netherlands Medicines Evaluation Board Agency is not responsible

for inspection and enforcement activities. The Agency is acutely aware that it needs to remain competitive to retain its share of both centralised and mutual recognition business in Europe. However, the level and structure of fees charged by the Agency is a policy decision for Ministers.

## The Agency has worked with potentially conflicting dual objectives to help industry and protect public health

4.15 Since its creation, the Agency has been required in its Framework Document to avoid creating "unnecessary impediments" to the pharmaceutical industry. In line with this, the Agency has recently been closely involved in efforts to improve the regulatory environment for industry through the work of the Pharmaceutical Industry Competitiveness Task Force, set up by the Government in March 2000. This role has, however, been articulated in the Agency's 2001 Corporate Plan in a more active way than its original remit not to create impediments. The remit has been re-expressed as being "to facilitate the development of a successful UK pharmaceutical industry for the benefit of the wider interest of the UK economy".

4.16 Stakeholders from the consumer and patient groups we consulted were concerned that the relationship between the Agency and the industry it regulates may be too close. This perception is reinforced by the fact that the Agency is fully funded by fees from industry, which is not the case in some other countries (Figure 27).

### 27 Funding arrangements abroad differ from those of the Agency

Regulator	Percentage of funding derived from industry fees
Canadian Therapeutic Products Directorate	66 per cent
US Center for Drug Evaluation and Research	52 per cent
French Agence Française de Sécurité Sanitaire des Produits de Santé	50 per cent
Swedish Medical Products Agency	95 per cent
Netherlands Medicines Evaluation Board Agency	100 per cent
UK Medicines Control Agency	100 per cent

Source: National Audit Office

There are high level controls in place to avoid conflict of interest but the objective to facilitate industry is being reviewed

- 4.17 The Agency's remit towards industry, like its fee levels and structure, is a matter for Ministers. There are, however, safeguards in place to manage conflicts of interest that could arise from industry funding the costs of the Agency.
- 4.18 The Committee on Safety of Medicines provides one safeguard, because any complex decision on a medicine must be referred to this body. Membership of the Committee is on the basis of scientific expertise and includes some members who may previously have been involved in research in industry, although no member is currently employed in the pharmaceutical industry. The high degree of concordance between the Agency's views and the Committee's (paragraph 2.4), is consistent with the view that the Agency is taking an objective position.
- 4.19 The existence of the Medicines Commission, which hears appeals by applicants against proposed adverse decisions, is a further safeguard. The legislation for the Commission specifies at least one member with "wide and recent" industry experience, however.

- 4.20 All members of the Committee and the Commission, including those with industry interests, must formally declare and register them for publication annually. Interests must also be declared where necessary at meetings, and members may be required not to participate in some or all of the proceedings.
- 4.21 Moreover, the Agency has taken steps through its internal organisation to avoid conflicts of interest. Work to license a drug is kept separate from the subsequent monitoring of its safety and any adverse reactions. In the light of the forthcoming merger of the Medicines Control Agency and the Medical Devices Agency the Department is to review the way in which the relationship between the new Agency and industry is to be reflected in its objectives.



# Appendix 1

## Chronology of medicines control in the UK

- 1864** First ever edition of the British Pharmacopoeia is published.
- 1925** The Therapeutic Substances Act introduces a licensing system for biological products such as vaccines, insulin and surgical sutures.
- 1948** Creation of the National Health Service.
- The Committee on Classification of Proprietary Medicinal Products is set up to consider the practicality and desirability of limiting or prohibiting the prescribing of certain medicines already on the market.
- 1963** The Committee on Safety of Drugs is set up in the wake of the thalidomide tragedy. Its membership includes independent experts in the fields of medicine, pharmacy, toxicology, pharmacology and statistics. The pharmaceutical industry agrees to submit data on products to the Committee and abide by its advice on safety.
- 1964** Introduction of the Yellow Card Scheme for spontaneous reporting of suspected adverse drug reactions.
- 1965** A European Economic Community Directive sets out the legal basis for control of medicines introduced in its member states.
- 1968** The Medicines Act, which provides for a comprehensive system of licensing affecting manufacture, sale, supply and importation of medicinal products into the UK, receives Royal Assent.
- 1971** Implementation of the Medicines Act provisions and creation of the Committee on Safety of Medicines.
- 1972** Medicines Division of the Department of Health is set up to control the licensing of medicines in the UK.
- 1973** UK joins the European Economic Community.
- 1989** Medicines Control Agency is established by the reorganisation of the Medicines Division.
- 1991** Medicines Control Agency becomes an Executive Agency of the Department of Health.
- 1993** Medicines Control Agency achieves Trading Fund status.
- 1995** Creation of the European Medicines Evaluation Agency and the setting up of the system of centralised and decentralised application routes.
- 1995** UK legislation is brought into line with the European legislation relating to marketing authorisations, labelling and leaflets, through the Marketing Authorisations Regulations.
- June 2002** Merger of the Medicines Control Agency and the Medical Devices Agency is announced. The merger will take effect from 1 April 2003.

# Appendix 2

## Study Methodology

### Work at the Medicines Control Agency

We reviewed a wide range of performance data and management information, reports by other auditors and business planning documents. Where possible, we shadowed selected Agency staff at internal meetings and inspection visits to laboratories.

### Work with Agency stakeholders

We interviewed key stakeholders representing:

- **industry** (Association of British Pharmaceutical Industry Regulatory Affairs Group; British Association of Research Quality Assurance; Proprietary Association of Great Britain)
- **patients/consumers** (Consumers' Association; Macmillan Cancer Relief; National Patient Safety Agency)
- **healthcare professionals** (British Medical Association; National Pharmaceutical Association; Royal Pharmaceutical Society of Great Britain)
- **European Commission** (European Medicines Evaluation Agency)

### Survey-based work

In August 2002, we commissioned DOCTORS.net.uk which obtained the views of a sample of 1220 hospital and General Practice doctors through an electronic survey. We sought doctors' views on:

- The Yellow Card Scheme and adverse reaction reporting generally;

- The quality of information provided to healthcare professionals by the Agency; and
- The quality of patient information leaflets.

We commissioned Ipsos UK's *Capibus* service to carry out a representative public omnibus survey of 2000 members of the public aged 15 years or over who used either prescription or over-the-counter medicines or both. We sought their views on:

- Adverse reaction reporting;
- Herbal medicines;
- Patient information leaflets and packaging of medicines;
- Medical information sources; and
- Buying medicines over the internet.

### High-level benchmarking

We compared the Agency with equivalent medicines regulatory authorities through visits to:

- L'Agence Française de Sécurité Sanitaire des Produits de Santé (France);
- The Medicines Evaluation Board Agency (The Netherlands);
- The Medical Products Agency (Sweden);
- The Drugs and Therapeutics Division (Canada); and
- The Center for Drug Evaluation at the Food and Drug Administration (USA).

These comparisons are set out in more detail at Appendix 9.

# Appendix 3

## Additional detailed recommendations

### On managing its own resources and performance

- The Agency should ensure that on its merger it maintains the skills and resources needed to manage effectively the risks to delivering its IT strategy.

### On protecting the public

The Agency should:

- carry out an assessment of what level of Medicines Testing Scheme sampling is required to protect public health, whether above or below the current level, and what resources are required to achieve it;
- implement the national rules scheme for homoeopathics, drawing on lessons learned from the existing homoeopathic schemes and on experiences overseas;
- carry out an assessment of the risks to public health from the absence of fully effective arrangements for distributing safety alerts for medicines on general sale to the public, and work with industry and retailers to manage these risks;
- make optimum use of the General Practice Research Database and other methods to measure routinely the effectiveness of its regulatory actions and publish the results;
- identify areas where outsourcing of certain research to academia could supplement or enhance its own pharmacovigilance activities, and develop links to facilitate this.

The Department should:

- keep under review the areas of medicines development and production which are not currently regulated and develop strategies as necessary to manage any risks to public health.

### On protecting the public by communicating information about medicines

The Agency should:

- maintain, for example on the internet, a comprehensive public list of medicines that are licensed, including herbal and homoeopathic products;
- publish the responses to external consultations and indicate how it has responded to the points raised;
- consult with health professionals about the best way of presenting medicines information and tailoring it to their needs, and build this into their information strategy;
- continue to work closely with the National Patient Safety Agency to ensure that their respective adverse event reporting systems complement each other effectively and avoid any confusion for health professionals. Information sharing arrangements should be formalised as soon as possible.

The Department and the Agency should:

- ensure that the Agency Board and Medicines Act bodies reflect the interests of the public, through properly resourced lay representation.

### On providing a service to industry

- The Agency should consider international benchmarking (both qualitative and quantitative) of its activities to learn from best practice overseas and demonstrate its competitiveness to industry.

# Appendix 4

## Expert advice

### We are grateful to the panel of experts who advised us during our study. They were:

Professor Alasdair Breckenridge	University of Liverpool Department of Pharmacology and Therapeutics, and Chair of Committee on Safety of Medicines
Mr Peter Cardy	Chief Executive, MacMillan Cancer Relief
Professor Joe Collier	Professor of Medicines Policy, St George's Hospital Medical School, member of Medicines Commission, and editor of the Drug and Therapeutics Bulletin
Dr Peter Fellows	Chair of General Practitioners Prescribing Committee, British Medical Association
Ms Georgina Fletcher-Cooke	Department of Health
Dr Trevor Jones	Director General, Association of the British Pharmaceutical Industry
Mrs Sheila Kelly	Executive Director, Proprietary Association of Great Britain
Professor David H Lawson	Chair of Scottish Medicines Consortium and former Chairman of Medicines Commission
Miss Ann Lewis	Secretary and Registrar, Royal Pharmaceutical Society of Great Britain
Mr Thomas Lönngren	European Medicines Evaluation Agency
Ms Colette McCreedy	Director of Pharmacy Practice, National Pharmaceutical Association
Ms Sue Osborn and Ms Susan Williams	Joint Chief Executives, National Patient Safety Association
Mr Simon Robbins	Chief Executive, Surrey and Sussex Health Authority
Dr Kerr Wilson	Chief Executive, Pesticides Safety Directorate
Mr Roy Alder (observer)	Board Member, Medicines Control Agency

### We are grateful, too, to the following people or organisations whom we consulted:

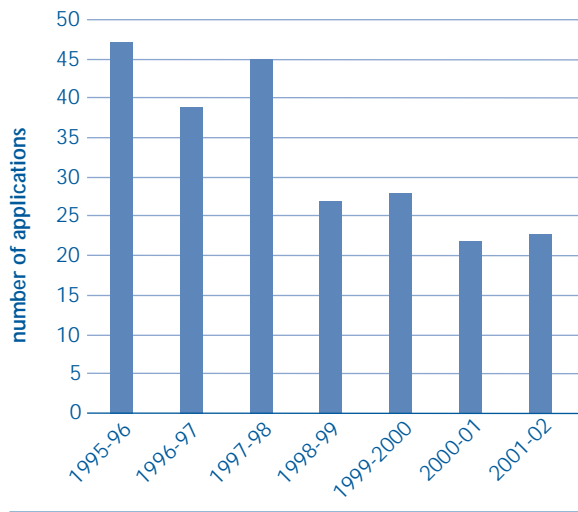
Professor Parveen Kumar	Chair of the Medicines Commission and Professor of Clinical Medical Education at St Bartholomew's and the Royal London School of Medicine
Helen Barnett	Lay member of the Committee on Safety of Medicines
Dr Patricia Wilkie	Lay member of the Committee on Safety of Medicines
Dr Saad Shakir	Director, Drug Safety Research Unit, University of Southampton
Representatives of the pharmaceutical industry, brought together by the Association of the British Pharmaceutical Industry	
The Consumers' Association	
The Centre for Medicines Research International	



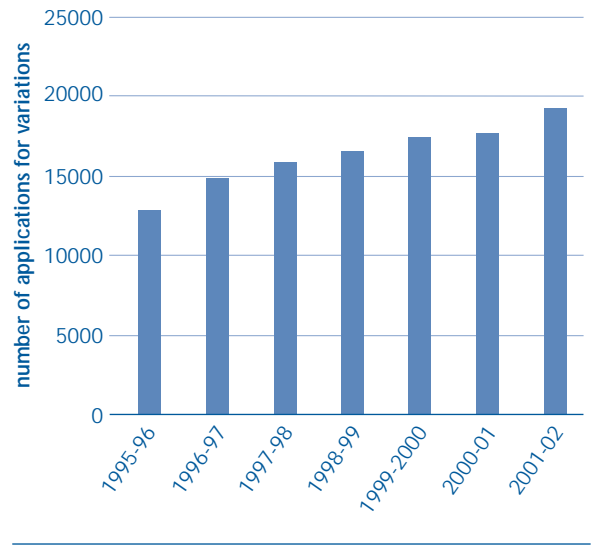
# Appendix 5

## Trends in workload levels

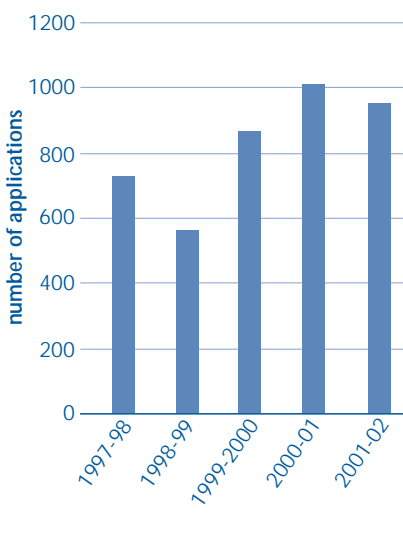
**Trends in the volume of new active substance applications**



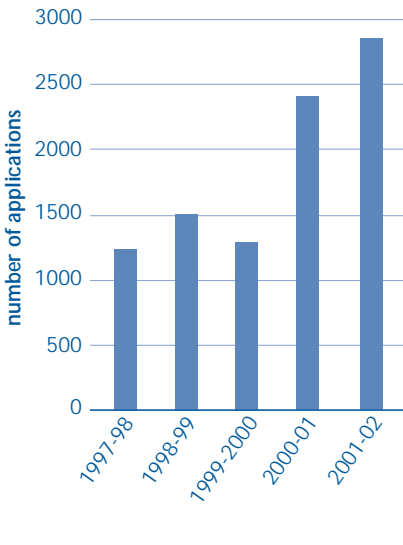
**Trends in the volume of variations to licences**



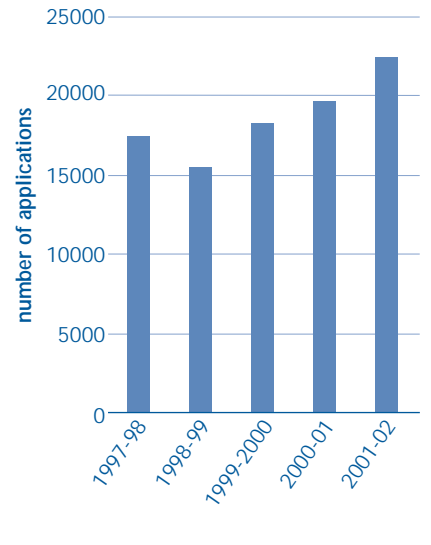
**Trends in the volume of abridged licence applications**



**Trends in the volume of applications for parallel import licences**



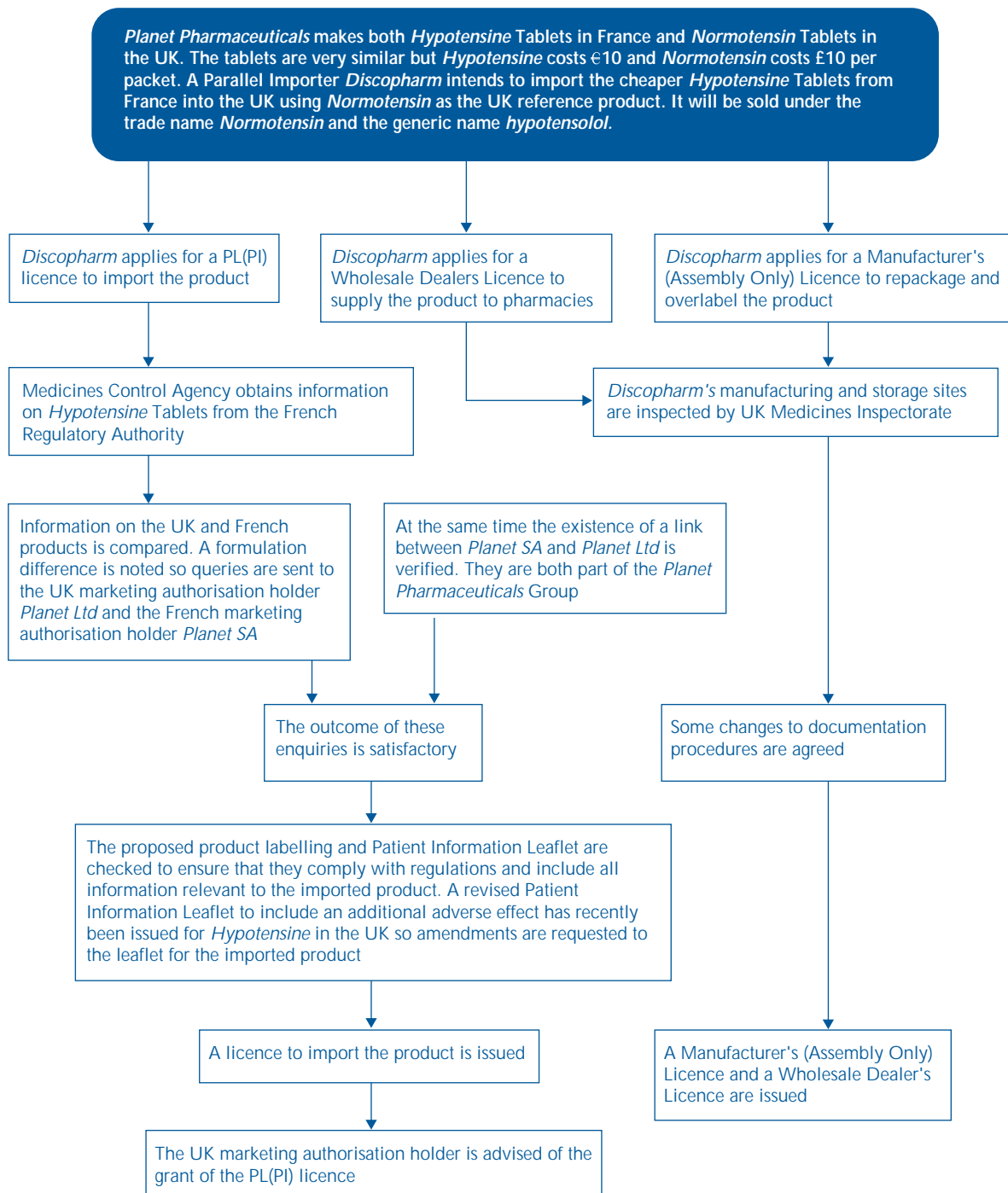
**Trends in the volume of applications for licence renewal**



Source: Medicines Control Agency

# Appendix 6

## Parallel import licensing



### NOTE

All names in italics are fictitious.

Source: Medicines Control Agency

# Appendix 7

## Agency performance targets

High-level target		Performance 2001/02
Safety and Quality	1.1 To assess the quality of the Agency's professional decision-making	96% concordance
	1.2 To enter the following ADR reports onto the ADROIT database:	
	a) Fatal: 100% within 3 working days; 90% within 1 working day	100%; 99%
	b) Serious: 100% within 7 working days; 95% within 3 working days	100%
	c) Others: 100% within 10 working days, 90% within 7 working days	100%
	1.3 To inspect all licensed manufacturers at least once every 26 months and within an average of no more than 24 months	100%
Standards of Service	2.1 To complete new active substance applications within 70 days for centralised applications and 55 for Mutual Recognition	100%
	2.2 To ensure effective, timely and reliable advice and briefing is provided for Ministers	Achieved
Financial control	3.1 Achieve efficiency gains of at least 3% in each year	Achieved
Focus on People	4.1 To develop a Human Resources Strategy	New target 2002/03
	4.2 To achieve a re-accreditation under 'Investors in People'	Internal assessment undertaken

Operating target		Performance 2001/02
Safety and Quality	1.1 a) To monitor all newly introduced medicines intensively for at least two years, followed by risk/benefit review with appropriate amendments to licence prior to removal from intensive surveillance	100%
	1.1 b) To monitor safety profiles of established medicines to identify signals of potential drug hazards requiring investigation and action (weekly)	100%
Standards of Service	2.1 To assess abridged licence applications for Licensing Authority determination: 100% in 100 days	100%
	2.2 a) To assess abridged licence applications for committee advice: 100% in 126 days	100%
	b) To assess clinical trial exemptions: 100% within 63 days	100%
	2.3 To assess variation applications:	
	a) Type I, 100% within 30 days;	100%;
	b) Type II, 100% within 90 days	99%
	2.4 Electronic government targets:	
	a) access to regulatory information on medicines; capability 96%, take up 83%	100%; 96%
	b) anonymised single patient prints; capability 100%, take up 24%	100%; 28%
Financial control	3.1 To pay interest and dividends on capital equivalent to 6% on net assets employed at current values	Achieved
	3.2 To operate within an external financial control limit total of £7.1 million	Achieved
	3.3 To fully review allocation of costs to fees	Scoping study completed
	3.4 To provide monthly management accounts to within 15 days of month end	Achieved
	3.5 To introduce Agency-wide purchase ordering system by Summer 2001	Introduction achieved

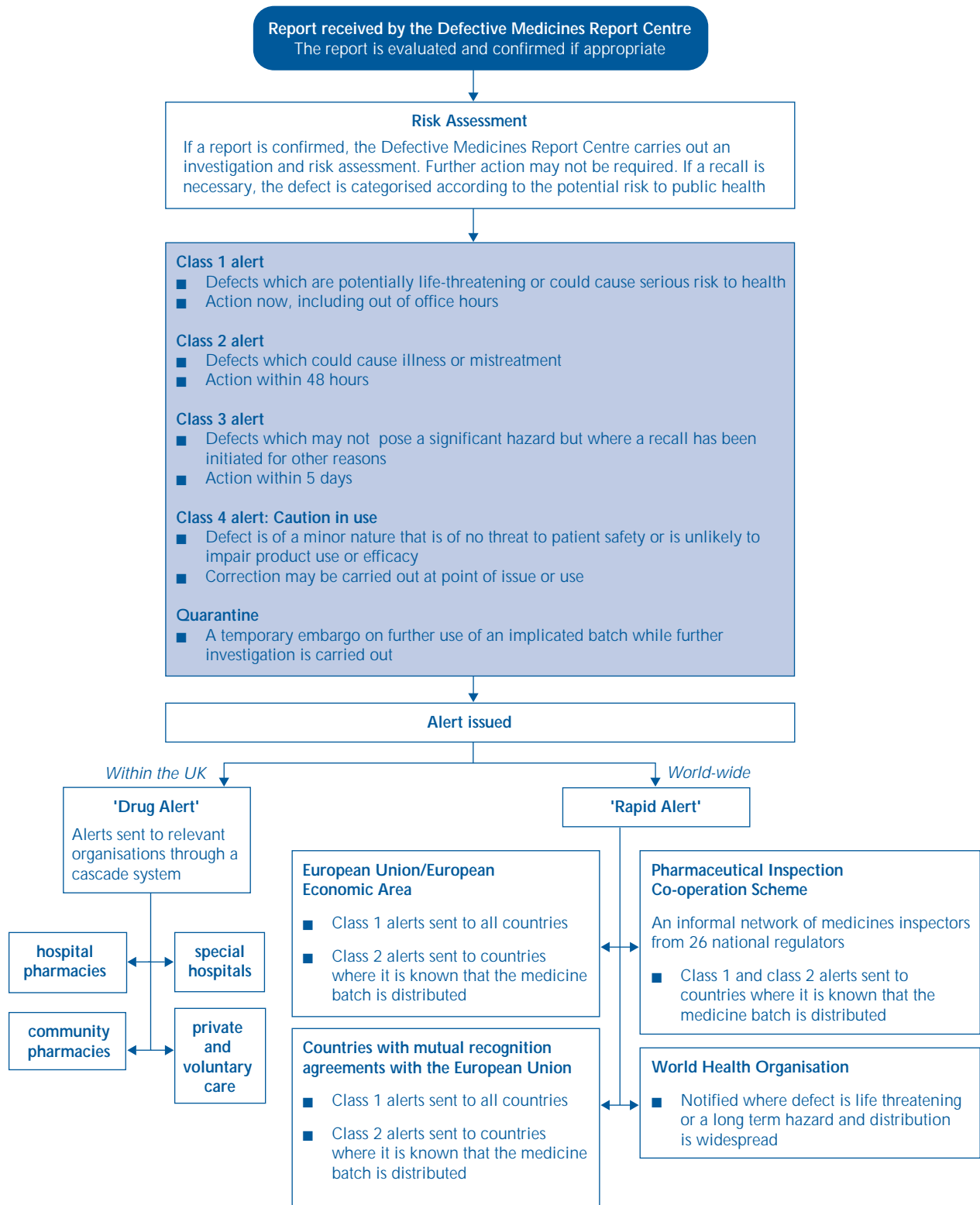
Operating target		Performance 2001/02
Financial Control	3.6 To carry out full review of the fees strategy	Scoping study completed
	3.7 To answer ministerial, official and open government correspondence within 20 days	Achieved
	3.8 To produce quarterly financial accounts	Achieved
Focus on People	4.1 To introduce 360-degree feedback	MCA Board completed
	4.2 To set up training in diversity by June 2001	
	4.3 To carry out further MORI poll and produce results by end 2001	Achieved
	4.4 To produce action plan for Employer of Choice programme by October 2001	Achieved
	4.5 To design and implement management and leadership training programme	New target 2002/03
	4.6 To design and implement a revised performance management and personal development process	New target 2002/03
	4.7 To develop a plan for effective recruitment, development and retention of high quality staff	New target 2002/03

Source: Medicines Control Agency



# Appendix 8

## Defective Drug Alert system



Country	United States of America	Canada	France	Sweden	Netherlands	United Kingdom
<b>Medicines Regulator</b>	Center for Drug Evaluation and Research (CDER)	Therapeutic Products Directorate (TPD); Market Health Products Directorate (MHPD); Health Products and Food Branch Inspectorate (HPFB-I)	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)	Medical Products Agency (MPA)	Medicines Evaluation Board Agency (MEB)	Medicines Control Agency (MCA)
<b>Accountability arrangements</b>	Part of the Food and Drug Administration (FDA), which is an agency of the Department of Health and Human Services	Not an independent agency, but part of the Health Products and Food Branch of Health Canada. Provincial/ Territorial governments have responsibility for the distribution and reimbursement of medicines	A Government agency under the Ministry of Health	A Government agency under Ministry of Health and Social Affairs	An independent Agency reporting to the Minister for Health. It supports the Medicines Evaluation Board	An Executive Agency of the Department of Health
<b>Legally, the licensing authority is:</b>	The Food and Drug Administration	Health Canada	The Director General of the Agency	The Director General of the Agency	The Medicines Evaluation Board	A body of Health and Agriculture Ministers
<b>Areas of activity</b>	Pharmaceutical drugs. Other parts of the FDA regulate food, medical devices, biologics, animal feed and drugs, cosmetics. Inspection and enforcement also carried out	Pharmaceutical drugs, medical devices, disinfectants. Inspection and enforcement also carried out	Pharmaceutical drugs, homoeopathic medicines, herbal medicines, medical devices, cosmetics, blood, cell therapy and gene therapy products. Inspection and enforcement also carried out	Pharmaceutical drugs, homoeopathic medicines, herbal medicines, medical devices, cosmetics, narcotics, alcohol used for technical purposes. Inspection and enforcement also carried out	Pharmaceutical drugs, homoeopathic medicines. The Agency has no responsibility for inspection and enforcement	Pharmaceutical drugs, voluntary homoeopathic registration scheme. Inspection and enforcement also carried out
<b>Approximate number of staff</b>	1870	570	930	300	100	550
<b>Level of non-governmental funding</b>	52 per cent of income comes from industry	Around 66 per cent of funding comes from industry	Around 50 per cent of funding comes from industry	Around 95 per cent of funding comes from industry	100 per cent of funds come from industry	100 per cent of funds come from industry

# Appendix 9

## International comparisons

# Appendix 10

## A simplified drug information sheet

### Frequently Asked Questions

#### Paroxetine

*Always read the information sheet that comes with your medicine*

##### **What does the medicine do?**

It treats mental depression by helping to maintain levels of serotonin.

##### **Is it habit forming?**

No.

##### **How long does it take to work?**

It works within one to four weeks.

##### **How do I take it?**

It comes in tablet form. Swallow the tablets with liquid.

##### **When do I take it?**

Take the medicine at the same time each day.

##### **What happens if I forget a dose?**

Take the forgotten dose when you remember it, if you do so within two hours. If you remember after this time, wait for the next scheduled dose. Do not double dose.

##### **What should I do if I take an overdose?**

You may experience vomiting, severe drowsiness and heart rhythm disturbances. Dial 999 for medical help.

##### **What should I do if I have a reaction?**

You should experience no allergic reactions to this medicine.

##### **Phone your doctor or pharmacist when convenient if you experience:**

Weakness, sweating, nausea, dry mouth, dizziness, problems urinating or vomiting.

##### **Tell your doctor or pharmacist at your next visit if you experience:**

Other discomforts.

##### **Can I still drive and operate equipment?**

Wait to see how the medicine affects you.

##### **Can I go outside when the sun is shining?**

Yes.

##### **Can I still drink alcohol?**

Avoid alcohol as this contributes to depression.

##### **Can I stop taking the medicine?**

Discuss this with your pharmacist or doctor first.

##### **Can I take other medicines?**

Discuss this with your pharmacist or doctor first.

Notes:

# Appendix 11

## NAO Management report to the Agency

We prepared a management report for the Agency to provide more detailed conclusions on a number of areas. The executive summary of the management report is reproduced here.

### Findings

- 1 The Agency has developed performance indicators related to its fee-based outputs and has also attempted to demonstrate the quality of its public health protection work in a "balanced scorecard" style performance statement. The performance indicators and targets included have been agreed with Ministers. However, the performance measurement arrangements are not yet providing the sort of focused, balanced and appropriate information required by all stakeholders, and have not been well integrated with business planning.
- 2 The Agency has been at pains to develop performance measures and targets which are capable of accurate measurements and are attributable to the work of the Agency. However, there is scope to improve the relevance of the information they provide to give the reader more information about the Agency's success against its objectives, even if this involves sharing some outcome measures with other parts of the Department. There is also scope to draw on best practice guidance in constructing measures which are reliable and avoid creating perverse incentives.
- 3 One of the early Executive Agencies, the Medicines Control Agency has also operated as a self-sufficient Trading Fund for nine years. A recent Cabinet Office/Treasury review found that a number of agencies have tended to become detached from their parent Departments and need to reconnect at a strategic level. By following the recommendations of this review, the new merged Agency could contribute to improved policy-making and delivery through strengthened relationships with the Department.
- 4 The Agency has taken important steps to improve all aspects of its Human Resources management function, which was previously weak. At a time of change and external threats to the Agency, a clear focus on people management is a key priority.
- 5 After identifying the need for a major upgrade of its IT provision, the Agency managed a complex procurement project effectively. They sought professional advice and put in place new arrangements for managing risks. After a procurement exercise, the Agency have now signed a contract with Accenture to design, build and operate the new systems, on which work begins in January 2003. As the Agency moves to implementation, continuity in strong risk management arrangements will be needed to ensure a successful outcome.

### Action points for the Agency and Department of Health

- The Agency could look to published best practice when developing performance measurement systems as part of the merged Agency. They should aim to put in place as soon as possible systems that meet the needs of stakeholders as well as helping drive improvements in performance.
- The Agency should consider seeking independent validation of its performance information, which could be provided by the Department's internal auditors or another independent body.
- The Agency and Department should take into account the recommendations of the joint Cabinet Office/Treasury review of agencies when putting in place arrangements for the governance of the merged Agency.
- The Agency and Department should continue to focus on managing uncertainty and communicating a vision of the future agency to staff to help address current and future problems of staff recruitment and retention.
- The Agency and Department should continue to ensure risk management arrangements for the Information Management Strategy remain a priority in the merged Agency.



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# Glossary of terms

Abridged application	An application to market a medicine which does not involve a new active substance, but is a new form of an existing one
Adverse drug reaction	Any unwanted effect from taking a medicine. Monitoring concentrates on serious and/or unexpected reactions
Ayurvedic medicine	A traditional Indian medicine, classified as a herbal medicine and currently not required to be licensed
Black triangle drug	A drug which is intensively monitored by the Medicines Control Agency and for which health professionals are encouraged particularly to report adverse drug reactions. The black triangle symbol appears on labels and leaflets
British Pharmacopoeia (BP)	The set of published standards for the composition and quality of medicinal substances. It also incorporates the European standards of the Pharmacopée Européenne (Ph Eur)
Centralised procedure	The procedure by which a new drug obtains a Europe-wide marketing authorisation through application centrally to the European Medicines Evaluation Agency. It is the compulsory route for biotechnology products
Clinical trial	Testing of a new drug on humans before marketing. It may involve either healthy volunteers or patients
Committee on Safety of Medicines	An expert committee set up under the Medicines Act 1968 to provide advice on medicines safety to Ministers
Efficacy	The extent to which a medicine has the beneficial effect intended
European Medicines Evaluation Agency	The central body responsible for evaluating applications for Europe-wide marketing authorisations and coordinating European medicines regulation
Generic medicine	An unbranded version of an original medicine made under a different name, after patent restrictions have expired. The active ingredient is chemically identical
Good Laboratory/ Manufacturing/ Distribution practice	The quality standards against which Agency inspectors assess company activities in the different stages of development, manufacture and distribution of medicines
Healthy volunteer study	A study of a medicinal product in healthy people who volunteer to allow an investigator to test how the product is handled by the normal human body. The tests usually measure absorption, distribution, metabolism and excretion of the medicine. They may also measure its concentration in the blood after different doses. At the same time investigators measure safety by looking for adverse reactions to the drug
Herbal medicine	A medicine whose constituents are entirely derived from plants
Homoeopathic medicine	A medicine containing highly diluted active ingredients which would in a healthy person produce the symptoms being treated

Investigational Medicinal Product	A medicinal product undergoing development or trial, but not yet on the market
Licensing Authority	The body legally responsible for granting a medicine licence or marketing authorisation
Marketing authorisation	A licence to market a medicine, granted in the UK by the Licensing Authority or in Europe by the European Medicines Evaluation Agency
Medicine (or drug)	A product for the treatment or prevention of disease; for administration to make medical diagnosis; or for restoring, correcting or modifying physiological functions in human beings. <i>Medicine</i> and <i>drug</i> are used synonymously in this report
Medicines Commission	A statutory Committee established under the Medicines Act to advise the Licensing Authority (the Secretary of State) on medicines issues generally
Mutual recognition procedure	The decentralised procedure by which a marketing authorisation obtained in one EU country is recognised by the others, allowing marketing of the medicine across the EU
New Active Substance	An active ingredient in a medicine that has not previously been licensed in any form
Non-interventional trial	A study conducted with a licensed medicine where the prescription of the medicine to the patient and the therapeutic strategy accords with normal medical practice and no additional tests are carried out on the patient. Epidemiological methods are used for the analysis of the data
Paediatric	Relating to the medical treatment of children
Parallel import	A product produced for sale in one EU country but imported by a wholesaler into another EU country where its cost price is higher, usually to make a profit
Periodic safety update report	A report of the available data on safety of a medicine required to be prepared by the marketing authorisation holder at intervals
Pharmacovigilance	The science of medicines safety monitoring
Rapporteur	The national delegation tasked with evaluating a marketing authorisation application through the European centralised procedure
Reference member state	The EU country through which a pharmaceutical company seeks an initial marketing authorisation as part of the mutual recognition procedure
Signal	An alert from any source that indicates a medicine may be associated with a previously unrecognised hazard, or that a known hazard may be quantitatively or qualitatively different from what is already known (e.g. more frequent or more serious)
Trading Fund	A financially self-standing government entity with the power to charge commercially for its services
Traditional Chinese Medicine	A herbal medicine (see above) made according to traditional Chinese medical theories and methods