

## (2) THE STRUCTURE AND FUNCTIONS OF THE MEDICINES CONTROL AGENCY

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*The Medicines Control Agency plays a vital role in ensuring the timely availability of new medicines of known quality, safety, and efficacy. It is soon to be merged with the Medical Devices Agency (see Pj, 5 October, pp501–4), but its functions and responsibilities will remain largely unchanged*

Ask a health care professional to name half a dozen health care organisations that have a significant impact on the lives of almost everyone in the United Kingdom, few (if any) would select the Medicines Control Agency (MCA). Even if they could name the agency, it is even less likely that they could accurately describe its pivotal role in UK health care.

One reason for this anonymity lies in the fact that the MCA is a regulatory body — and mention of anything to do with the law conjures up images of dry and dusty texts with esoteric wording and complex interpretations. However, doctors, pharmacists and other health care professionals are constantly interacting with and implementing medicines legislation, making their ignorance of the workings and role of the MCA less convincing and justified.

One way to grasp the immense impact that the MCA has on the general population and on the workings of the health care system generally is to consider the issues concerning the supply of medicinal products. For instance:

- 1 Who checks the appearance of and the wording on the packaging of pharmaceutical products dispensed and sold by pharmacists?
- 1 Who is responsible for checking the wording of the patient information leaflet that accompanies all dispensed and purchased products?
- 1 Who issue Product Licence numbers?
- 1 Who determines whether a pharmaceutical product from a wholesaler can be legally supplied against a doctor's prescription?
- 1 Who monitors the activities of pharmaceutical wholesaling companies?

- 1 Who approves a clinical trial protocol before a trial can start in the UK?
- 1 Who is responsible for monitoring adverse drug reactions?
- 1 Who determines whether the safety profile of a marketed medicinal product is sufficiently poor for the indications to be restricted or even to have the product removed from the market?
- 1 Who authorises the activities of pharmaceutical inspectors when they visit manufacturing sites of pharmaceutical companies?
- 1 Who checks that the information given to prescribing GPs and hospital doctors corresponds with the approved indications for each prescribed product?

The answer to each of these questions is the Medicines Control Agency. And just why the MCA is so important to the practice of medicine in the UK is discussed in this article.

### LEGISLATIVE FRAMEWORK

The MCA is an executive agency of the Department of Health. It was created in April 1989 (in succession to the Medicines Division of the Department of Health), established on 11 July 1991, and achieved Trading Fund status on 1 April 1993. The MCA has full financial self-sufficiency: this means that the Agency does not take funds from the government, but is supported by the fees it charges industry and others for the services it provides.

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Ministerial responsibility for the MCA is held by the Secretary of State for Health. The Secretary of State determines the policy and financial framework within which the MCA operates, but does not normally become involved in the day-to-day management of the agency. The Secretary of State is accountable to Parliament for all matters concerning the MCA.

It is the ministers of the Department of Health who are accountable to Parliament on matters relating to human medicines regulation in the UK. The Department of Health, through the MCA, discharges functions on behalf of the other territorial health departments in the UK, eg, the Northern Ireland Department of Health. (Department of Agriculture ministers carry out a similar function for veterinary medicines, which are controlled by the Veterinary Medicines Directorate, based in Weybridge, Surrey.)

The MCA is accountable to the Ministers in the Department of Health who comprise the "licensing authority". The licensing authority is the legislative entity with responsibilities under the Medicines Act 1968 and relevant European Community (EC) directives. The MCA deals with all European legislation that has been transposed into UK law and with which the licensing authority must comply.

It has recently been announced by the UK Department of Health that the MCA and the organisation responsible for the regulation of medical devices, the Medical Devices Agency, will merge to become a single executive agency in April 2003. This will create a single body for both medicines and medical devices, which mirrors the situation in many other European countries and in the United States. One rationale for the creation of the new single entity is that, in the

development of new therapeutic products, there is increasing blurring of the distinction between medical devices and medicinal products. The merged organisation will have a new chairman, and non-executive members will be invited to sit on the new agency's board. It is to be called the Medicines and Healthcare Products Regulatory Agency. Its location has not yet been announced.

**Functions undertaken by the MCA on behalf of the licensing authority** Medicines are controlled by a system of licensing and conditional exemptions from licensing as laid down in UK and European Union legislation. Authorisations to manufacture, market, distribute, sell and supply medicinal products are granted in the UK by the MCA on behalf of the licensing authority (or by the European Commission under the centralised system of approval of marketing authorisations).

The MCA has also been the UK good laboratory practice monitoring authority since April 1997.

The MCA controls clinical trials, advertising and other promotional claims, quality control, manufacture of products that do not have a marketing authorisation, and the supply of imported medicinal products. The safety of medicinal products that have a marketing authorisation is also controlled (pharmacovigilance), and the MCA is required to take action when adverse effects occur with authorised medicinal products.

The MCA provides professional assessors and administrative support for the Medicines Commission and the so-called "section 4 advisory committees" (formed under section 4 of the Medicines Act 1968). The Medicines Commission or one of the advisory committees must be consulted before a decision is taken by the licensing authority to refuse a marketing authorisation, or to revoke, vary or suspend a marketing authorisation on grounds of quality, safety and efficacy.

**Aims and functions of the MCA** The aim of the MCA is to safeguard public health by controlling medicines. The MCA ensures that the medicines sold or supplied in the UK are of an acceptable standard of quality, safety and efficacy. Equally, the MCA has to carry out its responsibilities without unnecessarily impeding the activities of the pharmaceutical industry. A detailed list of the functions of the MCA is given in Panel 1.

The MCA has declared its intention for new medicines to reach the public at the earliest opportunity. It does this by having one of the consistently fastest assessment times in the EU for marketing authorisation applications (MAAs) of new active substances (a mean time of 33 days in 2001).

**The organisation** The MCA is formed of eight divisions, whose staffing levels are shown in Panel 2.

The primary functioning units of the MCA are the board of management and the operations management team. The board of management comprises primarily the direc-

tors of the agency's divisions and provides support and advice to the chief executive in the day-to-day operations of the agency.

The operations management team (formerly called the executive committee) is responsible for the day-to-day operation of the MCA. Its membership is determined by the chief executive and its purpose is to:

- 1 Monitor the performance of the MCA and to deliver the performance requirements of the annual business plan and receive the monthly management accounts
- 1 Monitor corporate targets, including financial targets and business volumes, and to receive the composite quarterly report
- 1 Develop corporate and business plans for consideration by the board
- 1 Review the effectiveness and efficiency of the agency's operations according to a programme of annual priority reviews for each business area
- 1 Recommend priorities for the allocation of resources within the agency
- 1 Support the culture and communication programme and oversee implementation of human resource policies, including the monitoring of training and staff development across the agency
- 1 Approve and be responsible for the agency's standard operating procedures
- 1 Monitor the maintenance of standards and receive reports on quality issues

#### THE LICENSING DIVISION

The licensing division is responsible for the assessment of data submitted in support of marketing authorisation applications (MAAs).

Licensing group 1 deals with:

- 1 Assessment unit 1 for new chemical entities (full and abridged applications) (includes homoeopathics, radiopharmaceuticals and dental and surgical products)
- 1 Assessment unit 2 for biologicals (full and abridged applications)
- 1 Assessment unit 3 for abridged applications
- 1 Assessment unit 4 for abridged applications
- 1 Committee support unit, which supports the Committee on Safety of Medicines and its subcommittees
- 1 Applications from manufacturers to carry out clinical trials in the UK under the clinical trial exemption (CTX) scheme
- 1 Statistics

Licensing group 2 is responsible for:

- 1 Off-site storage of MAAs at Hinchley Wood
- 1 Marketing authorisations for parallel imports
- 1 Registration of MAAs submitted, data entry and licence issue

The biological and biotechnology assessment group deals with the more com-

## Panel 1: Functions of the MCA

- 1 To operate a system of licensing, classification, monitoring and enforcement which ensures that medicines sold or supplied in the UK for human use are of an acceptable standard
- 1 To monitor adverse reactions to medicines and suspected defective medicines, and (where necessary) remove or restrict the availability of such medicines
- 1 To ensure compliance in the UK with statutory obligations relating to the manufacture, distribution, sale, labelling, advertising and promotion of medicines
- 1 To safeguard UK standards for public health protection by representing the UK when regulatory matters are considered by the European Union, the World Health Organization and in other international forums
- 1 To manage, on behalf of the Department of Health, the British Pharmacopoeia and work undertaken by BP staff relating to the European Pharmacopoeia
- 1 To discharge the functions of the UK good laboratory practice monitoring authority

Source: MCA Framework Document, 1997

plex area of registration of biological products and the ever-changing area of biotechnology products.

The logistical management of the receipt of MAAs and the issuance of marketing authorisations is facilitated by a computerised system, PLUS (Product Licence User System).

**The clinical trials unit** The licensing division deals with clinical trials exemption certificates, which are usually issued at the beginning of Phase 2 trials. The clinical trial certificate (CTC) and the clinical trial exemption scheme are used to authorise the first clinical trials in patients for a particular formulation of a product.

A company may start a one-month trial supported by toxicology data to carry out a one-month trial. If the company decides it wants to do a six-month trial instead, it has to send in toxicology data that justify the longer trial. In this case, the company would probably send in the trial data that had been accumulated to date.

This is an example of a variation to the CTX application, of which the MCA receives about 500 per year.

**Advice to companies** Advice is willingly given by the licensing division of the MCA to companies at any stage during the development of a new medicinal product.

In its meetings with companies, the MCA creates an ad hoc team, whose membership depends upon what the company wants advice about. A full team would comprise a manager, a pharmacist, a toxicologist, a medical assessor and a statistician.

**Assessment of the marketing authorisation application** The division manager is responsible for ensuring that the work is done within the agreed time scale and for the overall co-ordination of the assessment. The dossier is received in three main parts (pharmaceutical, toxicological and clinical) and each part is dealt with by the respective assessors separately.

To complete the assessment, there are further meetings of the licensing division team, particularly concerning the production of individual assessment reports for quality, safety and efficacy. From these, an overall assessment report is produced, which summarises the MCA's scientific assessment of the data submitted by the company. It is this that forms the basis for the approval or rejection of the MAA.

**The licensing role in Europe** The MCA is committed to the successful functioning of the European pharmaceutical licensing systems. The licensing division has undertaken work on applications submitted through either the centralised procedure or the mutual recognition procedure.

In the centralised procedure, a rapporteur is appointed to co-ordinate the assessment of the MAA. The MCA is the leading rapporteur (20 per cent of all MAAs) for all centralised MAAs.

Under the mutual recognition procedure for obtaining a marketing authorisation, the principle is that an authorisation is obtained first in one member state (the reference member state, RMS). The MCA is the regulatory authority most commonly used as RMS, primarily because of its highly efficient and rapid assessment.

**Parallel imports** The UK parallel import licensing scheme permits the marketing in the UK of medicinal products that have marketing authorisations in other EU member states. The sole requirement is that the imported product must be equivalent to the authorised UK product. The administrative procedures necessary for maintenance of parallel import marketing authorisations are identical to those for UK-based marketing authorisations.

**Homoeopathic registration scheme** The homoeopathic registration scheme is for use by homoeopathic products that satisfy certain criteria:

- 1 The dilution of the stock contained in the product must be at least 1 in 10,000 of the mother tincture
- 1 The products must be for oral or external use
- 1 No therapeutic claims must be made for the product
- 1 The product name must be the scientific name of the stock

The MCA received 44 applications and issued 34 certificates in 1999/2000. Since the scheme is now five years old, 34 renewal applications have also been processed.

#### THE POST-LICENSING DIVISION

The objective of the post-licensing division is to protect public health by ensuring the quality, safety and efficacy of marketed medicines, including the provision of information to promote safe and effective use. Post-licensing activities are required for a number of reasons:

- 1 There is limited knowledge about safety when a medicine receives a marketing authorisation
- 1 As there is a need to make new medicines available speedily, it may be necessary to restrict the initial conditions of the licence
- 1 The practice of therapeutics evolves over the lifetime of the marketing authorisation
- 1 Wider access may be safely permitted for some medicines
- 1 Communications about medicines and their impact on safe use

The division deals with pharmacovigilance, variations, renewals, legal reclassification of medicinal products, product information and advertising.

**Pharmacovigilance** Pharmacovigilance covers suspected adverse drug reaction (ADR) reports that are submitted via the yellow card scheme, periodic safety update reports, data derived from company-sponsored studies, published literature, signals that may be unrecognised safety hazards, major investigations and, in extreme cases, drug withdrawals. Information may also be received from other regulatory authorities that have recognised a suspected safety issue, and from record linkage databases (eg, GPRD, see below).

**Variations to the terms of the marketing authorisation** Variations to the terms of the marketing authorisation may be undertaken for a wide variety of reasons. It is essential that the marketing authorisation holder keeps the authorisation up to date. There may be a change to the indications for which the product is approved or the manufacturer holding the marketing authorisation may change.

**Renewals** A marketing authorisation is valid for five years, at which stage its safety status must be reviewed and, if deemed acceptable, a renewal is issued. The review focuses on the periodic safety update reports that the marketing authorisation holder has to submit and uses a broad range of sources of evidence on therapeutic evolution.

## Panel 2: Divisions of the MCA

Divisions	Full time equivalents
Directorate (chief executive)	4
Licensing division	169
Post-licensing division	139
Inspection and enforcement division	116
Information management division	32
Executive support division	40
Finance and human resources division	20
GPRD group	16
Total	543

**Changes to legal classification** All new chemical entities are available initially only as prescription-only medicines (POMs). At some later stage in its lifetime, the drug may prove to be sufficiently safe for legal controls on the drug to be relaxed and for it to be made available for sale through community pharmacies.

Equally, the safety profile may change in the other direction, with concerns about the safety of a product previously available without a prescription needing it to be reclassified as a POM.

It is the post-licensing division that deals with these legal reclassifications, in consultation with the Committee on Safety of Medicines and following statutory consultation. The final decision is taken by the Health Minister, following which the POM Order is amended.

**Enquiries** A vast number of enquiries are received each year, ranging from those from health professionals and patients to requests for information from Parliament and the press.

**Patient information** The division also approves the information leaflets that must be issued with all dispensed medicines. It is assisted in this programme by an MCA quality review group, which has model leaflets that have been tested on potential users on which to base decisions.

**Control of advertising** It is essential that medicines are used rationally and that potential users are not misled by advertising of non-POM medicines. The MCA in effect monitors the self-regulation of advertising by the industry.

All advertising must comply with the marketing authorisation and with the summary of product characteristics agreed at the time of approval of the product. Prescription-only medicines cannot be advertised direct to public.

#### INSPECTION AND ENFORCEMENT DIVISION

Pharmaceuticals must be manufactured and distributed to the highest possible standards, and it is a legal requirement that the MCA verifies that these standards have been met.

**The inspections group** The inspections group covers good manufacturing practice (GMP), good distribution practice (GDP), good clinical practice (GCP) and good laboratory practice (GLP). Almost 650 inspections were carried out in 1999/2000, of which about 60 per cent were at manufacturing sites and 40 per cent at wholesaling sites.

All manufacturing facilities are inspected every two years, irrespective of size. Inspection of wholesale premises is carried out every four years. A small number of GMP inspections are also carried out on behalf of the European Medicines Evaluation Agency.

The group also inspects and issues licences to manufacturers and wholesalers of veterinary pharmaceuticals (but excluding veterinary biological products).

The division's licensing office is responsible for issuing and maintaining licences for manufacturers, wholesalers, and importers. Almost 10,000 export certificates were issued in 1999/2000.

The division takes about 3,000 largely randomly chosen samples of both licensed and unlicensed medicinal products for analysis, mainly from community pharmacies.

Examples of unlicensed products that are tested include herbal products. This testing is done to maintain the high quality of medicinal products available in the UK.

The Defective Medicines Reporting Centre (DMRC) receives between 200 and 250 reports each year of potential quality defects, from the public, professional bodies and pharmaceutical companies.

Export certificates may be issued by the inspection and enforcement division on request to help exporters satisfy the import requirements of third countries. These certificates state that statutory manufacturing requirements have been fulfilled by the manufacturer of the particular medicinal product and that the manufacturing premises have been inspected.

The good clinical practice compliance unit assesses compliance with GCP guidelines and regulations. To achieve this, on-site inspections are carried out at pharmaceutical sponsor companies, contract research organisations, investigational sites and other facilities involved in clinical trial research.

**The enforcement group** The enforcement group ensures that there is compliance with medicines regulations. Reports of possible infringements of medicines regulations are received from medicines inspectors, other parts of the MCA, practising doctors and pharmacists, the Royal Pharmaceutical Society of Great Britain and members of the public.

Marketing authorisation holders may infringe the terms of their authorisations. There may also be instances when people try to sell products for which medicinal claims are made that either have not or cannot be proven. The group is particularly vigilant in looking for counterfeit medicines.

**Laboratories and licensing group** The UK GLP monitoring authority was transferred in April 1997 from within the UK Department of Health to the MCA. The GLPMA inspects companies that carry out non-clinical studies in support of marketing authorisation applications.

**Policy, borderline substances and standards** The work of the policy group involves giving advice on the interpretation of the legal position in response to enquiries from both within and outside the agency, possibly by producing agency guidance notes.

The borderline substances section determines whether an active ingredient is a medicine, a cosmetic or a food using an independent statutory review mechanism and a transparent assessment process.

The standards group maintains and audits the division's procedures. Assessment of the division's work is carried out by obtaining feedback from its customers.

**British Pharmacopoeia** Production of the British Pharmacopoeia (BP) is carried out by the secretariat group and the BP laboratory unit.

The pharmacopoeial secretariat group prepares the BP in collaboration with the BP laboratory unit and the BP Commission and its technical committees.

#### EXECUTIVE SUPPORT DIVISION

As its name implies, the executive support division provides the infrastructure and environment in which the agency can effectively and efficiently carry out its activities. It co-ordinates all major policy issues, communications (both internal and external), personnel matters and office support services.

**Information centre services** The information centre is the focal point for the information activity within the agency. It deals with information to the public, income generation using information, training in information resources, internal sources of information and published sources.

There is an extensive library and reference collection, and the MCA subscribes to a vast range of journals. Any press coverage of the activities of the MCA are also copied and distributed throughout the organisation. On-line databases are regularly scanned, a process which has been revolutionised by the wide availability of CD-ROM technology.

Requests for information come from a wide range of external locations. There is a central enquiry point, which receives about 350 telephone calls each week. Written requests for information are dealt with at the rate of almost 50 per week. Parliamentary questions and ministerial correspondence are also channelled through the information centre.

A further activity is the production of the Medicines Act Information Letter (MAIL).

The EuroDirect subscription service is also based here, which provides draft and finalised EU documents.

**Fees policy and central support** The fees policy and litigation co-ordination unit is responsible for the development and ongoing review of the fees that are charged by the MCA for the services it provides.

Many of the activities essential to the running of the MCA are contracted out to external suppliers (eg, reprographics). The executive support division is also responsible for the premises and other office services provided.

**European support, policy co-ordination and personnel** The European and other international support unit co-ordinates all major European and international issues that affect the licensing of medicinal products in the UK.

Policy co-ordination by the executive support division may be necessary when a number of MCA divisions have to provide input into policy advice to Ministers, other parts of the Department of Health and other government departments and agencies.

The personnel unit deals with all recruitment and promotion issues, induction training for all new members of staff, and gives advice on personnel matters to MCA managers and staff.

**Corporate services** The disparate corporate services group comprises personnel matters, facilities and estate management, the building manager, health and safety co-ordination and the control of the telephone system.

The personnel unit operates within a competence development framework, which is intended to improve personal effectiveness, ensure that there is effective interpersonal skills, and that all staff are delivering results and providing a quality service.

The unit deals with personnel and development strategy, ensures that there are equal opportunities for all staff, and manages recruitment and selection and employee relations.

#### FINANCE AND HUMAN RESOURCES DIVISION

The self-funding status of the MCA is managed through the finance and human resources division. The division operates to ensure that all staff understand the requirements of good financial control, the cost of resources, how much income can be obtained from each activity and the efficiency of working practices in each part of the MCA.

It also aims to ensure that financial aspects are closely allied to all planning of activities, that the financial competencies are strengthened across the agency, and that everyone has the financial information they need to make sensible decisions.

It sets budgets and reports the annual accounts and deals with ways of controlling income and costs. Almost 60 per cent of the costs are allocated to staff costs and these and staff numbers are tightly controlled.

### GENERAL PRACTICE RESEARCH DATABASE

The General Practice Research Database (GPRD) is the most recently formed division within the MCA. The database was acquired in April 1999 from the Department of Health's statistics division and had been previously operated by the Office for National Statistics. It is the largest computerised database of anonymised longitudinal patient records from general medical practice in the world. It currently holds about 35 million patient years of data.

The data have an immense range of potential uses in such areas as clinical epidemiology, drug safety, drug use, health outcomes, health service planning, pharmacovigilance, pharmacoconomics and prescribing analysis.

Those who wish to use the database must pay a fee, a requirement that also applies to the other divisions within the MCA. Users include academics, the Department of Health, the NHS, the Office for National Statistics, regulatory authorities and the pharmaceutical industry.

The database is operated as a separate function and entity within the MCA, completely separate from the agency's regulatory functions and responsibilities. It is run on a not-for-profit basis and is also self-financing. This ensures compliance with the terms under which it was donated to the Department of Health. The manager reports directly to the MCA's chief executive.

The database is not "complete". Data are continually being added from about 400

general practices around the UK who are paid a fee for the patient records that they supply. The GPRD is always keen to increase the number of contributing practices, but already currently receives data from practices that cover about 5 per cent of the UK population.

### INFORMATION MANAGEMENT DIVISION

The information management division was established in March 2000 to develop and implement an information strategy, to develop and manage existing information technology systems and to manage IT systems. The creation of the division was in recognition of the vital business and unique importance of the information that is held by the MCA. Its use and release for the full benefit of the agency itself and for external stakeholders is an essential business requirement. The existing business process systems are:

PLUS	Product Licence User System
ADROIT	Adverse Drug Reaction Online Information Tracking
BLIS	Business Licensing Information Services (for inspections)
ECS	Export Certificate System

The information management division is also responsible for subscription-based links for industry to access PLUS and ADROIT. This is done through RAMA (Remote Access to Marketing Information) and AEGIS (ADROIT Electronically Generated Information Service).

### Information management strategy group

The information management strategy group is a newly formed group that is investigating ways in which internal efficiency and effectiveness can be improved.

Management systems that are being reviewed include finance, personnel, business process and information systems. There has also been a trend to identify new external revenue streams and to investigate finance initiatives.

The other groups that exist within the information management division are the PLUS management and development group and the ADROIT management and development group.

**IT services** As is inevitable within such a large computer-based organisation, the role of IT services is crucial. IT services is responsible for the general maintenance and management of the IT throughout the MCA. It supports and develops various systems that are essential for the successful functioning of the agency's work.

The computer system was upgraded in 1997, and all the regional offices and Hinchley Wood are also connected to the main system.

The major databases used by the MCA are PLUS, ADROIT and BLIS. There are at least 500 personal computers in the Market Towers premises in central London which operate with Windows NT Workstation 4, using Word 97, Excel 97, PowerPoint 97, Outlook 97 and Explorer 3. IT Services also runs the MCA's internet website.