BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol. 2004 Dec; 58(6): 571–574.
doi: 10.1111/j.1365-2125.2004.02196.x

PMCID: PMC1884637
PMID: 15563354

The changing scene of the regulation of medicines in the UK. Paper from The Use of Medicines: Regulation & Clinical Pharmacology in the 21st Century Symposium – December 2003

Alasdair Breckenridge

Abstract

The Medicines and Healthcare products Regulatory Agency was established in April 2003 by the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). This paper describes the scientific and organizational basis for the merger and describes the various challenges facing this new Agency.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) was established in April 2003 by the merger of the Medicines Control Agency (MCA) which had responsibility for regulating medicines in the UK and the Medical Devices Agency (MDA) which had a similar responsibility for medical devices. The MCA and the MDA were world class regulatory agencies in their own spheres. Leaders in Europe and internationally, they were known for their high professional standards and their innovative performance in regulatory affairs. It is important in creating the MHRA that this reputation for excellence is maintained.

In considering the role of the MHRA it is worth recalling the definition of a medicine and a medical device:

> A medicine is a substance or combination of substances presented for treating or preventing disease, making a medical diagnosis or restoring, correcting or modifying physiological functions in human beings.
> A medical device is a product, other than a medicine, used for patients in healthcare or in the alleviation of injury or handicap. This definition of a medical device covers a large range of products ranging in complexity through a walking stick, a syringe, an anaesthetic machine, to a magnetic resonance scanner. There are over 25 000 different types of medical device in every day use in the UK.

MCA

The MCA had a budget of some £50M, with 95% of its income from licensing fees. It operated as a trading fund, i.e. under a flexible financing framework which covered costs and receipts, capital expenditure, borrowing and net cash flow. MCA employed some 600 staff, comprising scientists with backgrounds largely in medicine or pharmacy, as well as support staff. Its regulatory activities extended across licensing of medicines, post-licensing safety assessment, inspection and enforcement of regulations, control of medicines advertising and supervision of the production of the British Pharmacopoeia.

MDA

The budget of the MDA was £13M with 95% of its income from the Department of Health. It employed 150 staff, consisting of scientists most of whom came from an engineering background, a few nurses and doctors, and support staff. Its regulatory activities were predominantly the post-licensing regulation of the safety of medical devices, the inspection and enforcement of regulations and standards relating to devices.

The responsibility for the licensing of medical devices across Europe lies with Notified Bodies of which there are currently seven in the UK. The MDA had the role of supervising the activities of these Notified Bodies which are autonomous commercial organizations.

MHRA

Thus the MHRA will have a budget of some £63M arising from fees income and from the Department of Health and will function as a trading fund. It will have some 750 staff with a broad range of regulatory responsibilities. Further, the governance of the MHRA will differ from its predecessors. MHRA has a board of 12 members both executive and non-executive, an executive chairman as well as a chief executive who is responsible for the day to day management of the Agency.

Organizational challenges facing the MHRA

Those relating to the merger of the MCA and MDA

a. At present, the medicines and devices sectors are located on different sites, but there are well-advanced plans to collocate these, which is an important aspect of creating a unified organization.
b. MCA and MDA had different IT systems. Considering the nature of the work of the MHRA it is very important that compatibility of these systems is achieved.
c. The scientific and cultural problems encountered in merging a larger organization with a smaller one, especially when their backgrounds are different, are considerable and are receiving appropriate attention.

Added value of the merger

The MHRA should not merely represent the sum of merging the activities of the MCA with the MDA; there should be extra value to the merger. Some of the aspects which are important are as follows:

Profile and communication

It was not the policy of the MCA or MDA to adopt a high public profile and few healthcare professionals, let alone members of the public, understood their role. One of the aims of the MHRA is to increase the public understanding of the concept of risk and benefit with respect to medicines and medical devices and to raise the level of public debate on matters of patient safety. This can only be carried out successfully if there is understanding of the role of the MHRA.

To achieve this we are working with a professional organization to formulate a communication strategy aimed at raising the profile of the Agency, helping it to communicate more effectively and proactively with our stakeholders – the public, healthcare professionals, industry and the Department of Health. Of equal importance is the ability to communicate in clear terms with MHRA staff who must be fully aware of the goals of the Agency.

UK public health agenda

MHRA has an important role to play in helping to shape the public health agenda of the UK. In order to do this, it must work with other newly created agencies such as the Food Standards Agency, the Health Protection Agency, the National Patient Safety Agency and the Commission for Health Audit and Inspection. There is already close contact between MHRA and some of these agencies as there is considerable overlap in responsibilities.

Working within Europe

In both the medicines and devices sector, new European regulations and directives are having profound effects in the UK.

A current major review of European Union (EU) medicines regulation (the so called 2001 review) will address how the advent of 10 new member states to the EU in May 2004 may influence the workings of the European Medicines Evaluation Agency (EMEA) and its advisory structures. These changes pose both challenges and opportunities for the UK. One challenge is to work more closely with European colleagues to make the new enlarged system function well and to give strong support to the London-based EMEA. There is an opportunity for the UK to help individual accession states to ensure they are effective partners in European regulation and MHRA is already taking on this responsibility with respect to the Czech Republic and Malta.

With respect to medical devices, expansion of the EU will obviously result in an increased number of Notified Bodies which will have the power to approve medical devices for the UK market. It is important that a uniform standard of approval is achieved across Europe. Under the so-called New Approach, a number of general and particular requirements have been listed for medical devices to conform to acceptable European standards.

Scientific challenges facing MHRA

Challenges of the new technologies

Tissue engineering

Tissue engineering is that field of medicine in which new tissue is created for individual patients for the purpose of treating disease or injury through the ability of human derived cells and a combination of mechanical support and molecular signalling processes. Such treatments are not achievable by pharmacological or medical devices means alone.

The cells may be autologous or allogeneic, the mechanical support may be natural or synthetic, i.e. a scaffold or matrix, and the molecular signalling is carried out using growth factors, cytokines and the like.

Skin, cartilage, bone, blood vessels and heart valves for use in man can be produced using tissue engineering technology; this is clearly an extremely important area of development for clinical medicine. At present, tissue engineering products are not subject to any form of regulation, although several attempts have been made to create a regulatory framework within the EU over the past 10 years. A new plan is currently at an advanced stage of debate whereby the best aspects of medicines and devices regulation will be incorporated in a new framework which will involve approval of manufacturing processes, premises and quality control systems as well as requiring assessment of clinical evidence of efficacy and safety of individual products.

Tissue engineering presents an opportunity for a merged agency such as MHRA to work closely with European colleagues in forging a new regulatory framework.

Pharmacogenetics

When a patient is given a medicine he may respond favourably to the satisfaction of both the patient and his physician, or no beneficial effect may ensue, or the patient may suffer an adverse effect to the medicine. The prescriber cannot predict which of these patterns his patient is likely to follow. Many factors determine how a patient responds to a medicine, and of these, genetic factors are among the most important not only in determining how a medicine is handled in the body, but also how the body systems respond to a drug concentration.

Pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response.

A clinical example of how pharmacogenetics will influence the work of MHRA is illustrated by abacavir toxicity. Abacavir is a nucleoside analogue, a reverse transcriptase inhibitor used in the treatment of HIV disease. Some 5% of patients given abacavir suffer a hypersensitivity reaction manifest as fever, rash or gastrointestinal upset. Such effects usually occur within 6 weeks of commencing therapy; rechallenge with the drug after a reaction can result in a more serious reaction including fatality.

Abacavir sensitivity is associated with the presence of HLA B57 histocompatibility antigen. This is present in some 2–3% of the population, but three recent studies have shown that 75, 46 and 46% of patients who were sensitive to abacavir were HLA B57-positive [1, 2].

Screening for the HLA B57 haplotype prior to starting treatment with abacavir has reduced the incidence of the hypersensitivity reaction by some 80%.

Abacavir is licensed according to medicines regulations but the tests for HLA B57, like other *in vitro* diagnostics, come under the auspices of the *In vitro* Diagnostics Directive, which came into force in December 2003 and which requires that all *in vitro* diagnostic tests are validated for sensitivity and specificity and the laboratories undertaking these tests meet approved standards.

It may be that abacavir will become an example of an increasing number of medicines which will only be utilized with an approved test to identify those who should respond or who may suffer an adverse reaction. There are already other examples in other clinical fields.

Challenges of ensuring patient safety

When a medicine is given a marketing authorization, it may have been given to less than 1000 patients in clinical trials. Serious adverse effects which may be life threatening may only occur in one in 4000 patients and may not be picked up in clinical trials, so some form of post-marketing surveillance (PMS) is needed for new medicines.

In the UK, the Yellow Card is one of the most widely used methods for PMS. Introduced in 1964 as a direct consequence of the thalidomide problem, there are now some 500 000 reports in the database, with some 20 000 being added each year. This does not account for all adverse reactions which occur, 80–90% of which are not reported. In the recent past, the MCA has been taken to task for not seeking to capture more reports for its database. In truth, MCA and now MHRA does not want a greater percentage – what it requires is better quality reports. Instructions accompanying the yellow card clearly indicate that only reactions to new drugs (designated by a black triangle in the literature) and all serious adverse reactions should be reported. Such reports are used by MHRA as signals to consult large databases using ADROIT (adverse reaction online tracking system), which gives access to national and international information and allowing further pharmacovigilance studies to be mounted.

Conclusion

There is a scientific and an organizational basis for creating MHRA from its previous constituents. Other countries in Europe, as well as the USA, have regulatory agencies in which medicines and medical devices are housed in the same organization. The UK has a real opportunity to improve the public health by forming the MHRA.

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