Commentary

An agenda for UK clinical pharmacology

Development and delivery of clinical pharmacology in regulatory agencies

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Medicines regulation is based on a foundation of science, policy and judgement. It operates within several frameworks (scientific, legal and public health), which are interdependent. While safety, quality and efficacy remain the criteria by which medicines are assessed, the benefit-to-harm balance for any medicine or medical device is of paramount importance. While the regulator was hitherto the gatekeeper who allowed a medicine on to the market, payers now require, in addition, assessment of cost and clinical effectiveness before use. As regulatory frameworks develop, several changes will occur, as follows: (i) formal benefit-harm assessment will become an integral part of submission for marketing authorizations; (ii) there will be greater use of surveillance for adverse reactions to new medicines using methods other than voluntary reporting; (iii) risk management plans will become benefit-risk management plans; (iv) life-saving medicines will be approved earlier; and (v) regulation and health technology assessment will take place simultaneously. Clinical pharmacologists will play important roles in these developments.

Introduction

Clinical pharmacology is a central discipline linking drug usage and policy across different elements of healthcare, namely the National Health Service, academia, industry and regulatory authorities. Here I shall discuss areas of the regulation of medicines of special importance to clinical pharmacology and shall consider three related frameworks of regulation, namely scientific, public health and legal.

Scientific framework

The regulation of medicines must be based on scientific principles. One of the main responsibilities of the regulator is to ensure that the balance between the benefits and harms of medicines, both new and already on the market, is appropriate, and if this is not so to take appropriate regulatory action.

The term benefit-to-harm (or benefit-risk) balance is usually employed qualitatively, but there is an increasingly powerful argument to be more quantitative. Definition of the elements involved to express both the benefits and the harms of a medicine is useful, in that it permits a shared

understanding of the issues involved when industry and the regulator may disagree. Furthermore, it leads to greater consistency in expressing benefits and harms, and if used appropriately can make regulatory decisions more transparent. Within such a framework, several models can be used, depending on the circumstances.

It is important that the regulatory environment should support innovation, so that promising new drugs are not unnecessarily impeded in reaching patients. However, the current linear model of drug development is widely recognized to be unsustainable, both scientifically and financially. As global expenditure on pharmaceutical research and development has increased, the number of new molecular entities launched on the market has paradoxically decreased progressively. An increasing number of those medicines that have been approved are biopharmaceutical products (so-called biologics) rather than chemical ones (Figure 1). The importance of biopharmaceuticals cannot be overemphasized. Many have the potential to target underlying disease mechanisms as well as relieving symptoms. Biopharmaceutical vaccines for infectious diseases are of special importance, in that they can elicit immune responses without the risk of causing infection. Furthermore, they are stable and easy to store and can now be bioengineered to carry more than one strain of pathogen.

Figure 1

The probabilities of success of new chemical and biological entities at different stages of development. Probabilities of success to market were calculated using success rates for active substances entering phase between 2003 and 2005 and the year of assessment 2008 (redrawn, with permission, from CMR International 2010 Pharmaceutical R&D FactBook, May 2010). New biopharmaceutical entities (orange); New chemical entities (green)

Modern drug development is changing rapidly from the previous linear model, and is characterized by better understanding of the pathophysiology of the disease concerned, with early proof of concept in man followed by small, targeted clinical studies. The provision of scientific advice from the regulator at each stage of development can be of great value (Figure 2).

Drug safety is of great importance to the regulator. Only a preliminary assessment of the benefit-to-harm balance can be made when marketing approval is granted, because of the size of the population studied in clinical trials and the nature of their selection. Postmarketing information on drug safety, i.e. pharmacovigilance, is necessary. As well as documenting evidence of harm caused by medicines, using spontaneous reports, it is increasingly being realized that to extend knowledge of drug safety, surveillance using patient registers and patients' medical records should be used. Thus, a pharmacovigilance toolkit, comprising various methods, is available for use in particular circumstances (Table 1) [1].

Risk management is a powerful tool in medicines regulation. A risk management plan is a necessary part of an application to market a new medicine, and comprises risk detection and assessment, risk minimization and communication [2]. As well as specifying what is known about the safety of the medicine, the plan will indicate areas in which more information is required and how this will be obtained. In addition, measures to minimize possible risks should be indicated, such as limiting of prescribing to specialist physicians or establishing educational programmes for patients. In future, taking into account increasing

emphasis on the benefit-to-harm balance, risk management plans will become benefit-risk management plans.

Public health framework

Paradoxically, pressure from patients, politicians and the press that only 'safe' medicines should be allowed onto the market is often accompanied by requests from patients and healthcare professionals for access to promising new medicines that are still in development. This was first seen in the 1980s, with pioneering drugs being used to treat HIV/AIDS, and has been seen more recently with new biopharmaceutical anticancer drugs. These requests present sizeable problems for the regulator; to refuse makes the regulator appear unnecessarily risk averse, but to approve runs the risk of a public health problem.

A second public health issue is the relation between the regulator and those who pay for healthcare. Payers increasingly seek the advice of health technology assessors as to whether a new medicine approved by the regulator represents value for money compared with existing treatments. This is of special difficulty in the case of new biopharmaceuticals, which are expensive to produce and may cost the payer many thousands of pounds per year.

While the regulator was formerly the sole gatekeeper allowing patients access to new medicines, health technology assessment is now equally important. From an industry perspective, the value in obtaining regulatory approval is mitigated if the drug cannot be marketed for longer than it takes the health technology assessor to appraise it.

Today: Intensive all-or-nothing regulation

2020: Instant automated evolving regulation

Figure 2

The regulatory pathway in place today and a pathway that might be in place in 2020. Abbreviations: CIM, confidence in mechanism; CIS, confidence in safety; and IND, investigational new drug (redrawn, with permission, from CMR International 2010 Pharmaceutical R&D FactBook, May 2010)

Table 1

A toolkit for pharmacovigilance

Estimated exposure of patient to drug	Primary-care exposure	Safety concern identified	Missing data	Tools
High	Yes	Yes	No	Large, simple trials and observational studies (including PEM)
High	Yes	No	Yes	Observational studies
High	No	Yes	No	Large, simple trials and registry (drug or disease)
High	No	No	Yes	Registry (disease)
Low	Yes	Yes	No	Observational studies (including PEM)
Low	Yes	No	Yes	Observational studies (including PEM)
Low	No	Yes	No	Registry (drug or disease)
Low	No	No	Yes	Registry (drug or disease)

Abbreviation: PEM, prescription event monitoring.

As payers – be they governmental or insurance based – require more rapid assessment of health technology assessment advice after regulatory approval of a new medicine, attempts are now being made to synchronize the two processes when possible.

Legal framework

One of the most contentious regulatory issues, and one that is of great interest to clinical pharmacologists, is the governance

of clinical trials. In 2001, the European Clinical Trials Directive was introduced [3], in order to protect the health and safety of clinical trial participants. It also aimed to improve the ethical soundness of clinical trials across the European Union and to ensure the reliability and robustness of data generated in European clinical trials. Some 75% of clinical trials conducted in Europe are sponsored by industry, whereas 25% are non-commercial, i.e. they originate in academia or are sponsored by public health bodies and charities.

The UK implemented the Directive early (in 2004) and fully, unlike many of its European national colleagues. But

not all has gone as planned with its implementation. It has been inconsistently implemented across the European Union, which leads to difficulties in conducting multinational clinical trials. Furthermore, there is a lack of clarity in many of the definitions used in the Directive, which has led to misunderstandings and difficulties. Safety reporting has been a special difficulty, generating unnecessary data.

What is needed is a revision of the Directive and a more risk-based approach, allowing greater flexibility in how it is implemented. This review is now underway within the European Commission.

Conclusions

As regulatory frameworks develop, several changes will occur, as follows: (i) formal benefit–harm assessment will become an integral part of submission for marketing authorizations; (ii) there will be greater use of surveillance for adverse reactions to new medicines using methods other than voluntary reporting; (iii) risk management plans will become benefit–risk management plans; (vi) life-saving medicines will be approved earlier; and (v) regulation and health technology assessment will take place simultaneously.

Competing Interests

There are no competing interests to declare.

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