New horizons in pharmaceutical regulation

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A life cycle approach to pharmaceutical regulation, in which the benefit–risk balance of new drugs continues to be robustly assessed following market approval, is emerging in both the United States and Europe.

When a medicine is first marketed, much is known about its quality, pharmacology and efficacy in a selected, carefully screened group of patients involved in the clinical trial programme. However, these efficacy data may provide an incomplete, and perhaps even misleading, indication of the drug's effectiveness in the population overall. Even greater gaps in knowledge exist with regard to its safety in the wider community. Adverse effects may be too rare to detect in pre-approval clinical trials or they may occur in populations that are not represented in these trials, such as patients also taking other medicines.

These observations underscore the need for an ongoing assessment of a new drug's effectiveness and safety in the post-marketing period. Importantly, the preoccupation of the press, the public and even politicians with issues of drug safety is often misplaced, because of a focus on safety alone, even though what determines the value of a drug is its benefit–risk balance[1]. Indeed, many drugs — for example, some commonly used anticancer agents or drugs for HIV infection — have substantial toxicities but are sufficiently effective that their benefit–risk profile supports their use in treating these serious diseases, often initially under some form of supervision to maximize the health benefits for patients. Here, we discuss new directions in pharmaceutical regulation in Europe and the United States that reflect a recognition of the need for monitoring and recalibrating the benefit–risk profile during the entire life cycle of a drug.

The need for a life cycle approach

The development of innovative drugs has become more challenging and more costly in recent decades for several reasons. Regulatory authorities have heightened their requirements for evidence of efficacy and safety (in part in response to major drug safety problems), and cash-strapped payers for health care increasingly need strong evidence that new drugs represent value for money compared with existing drugs. Indeed, industry may have shifted the emphasis of its innovative drug development into areas where the bar for approval is lower owing to a lack or absence of effective drugs, but the risk of failure is higher. Nevertheless, in some disease areas there has been considerable success, such as biologics for patients with rheumatoid arthritis and molecularly targeted drugs for some cancers (such as chronic myeloid leukaemia). However, the costs of failure can be huge, particularly for indications such as Alzheimer's disease that require lengthy clinical trials and that lack validated surrogate end points.

In the United States, and some European countries, an increasingly vocal patient advocacy movement has demanded earlier access to new medicines, particularly for life-threatening diseases. This movement, which had its origins in AIDS and cancer advocacy in the 1980s, has put regulators under pressure to relax their evidentiary requirements for the approval of potentially life-saving medicines. Most regulatory agencies have responded with accelerated approval tracks and compassionate use programmes but there are some commentators who still press for a broad reversal of a regulatory trend requiring a higher level of evidence for drug approval. For example, a former commissioner of the US Food and Drug Administration (FDA) recently called for the US Congress to allow the approval of new drugs based solely on drug safety, with efficacy to be proven in post-approval trials[2]. The US Congress is currently considering legislation to speed market access of drugs for serious diseases by allowing the expanded use of surrogate end points and rapidly measurable clinical end points and thus, presumably, drug approval based on fewer, smaller and shorter trials.

Such an approach, if enacted, means that regulators must move their horizons too, focusing new attention on the post-approval period of drug development with active surveillance and post-marketing clinical trials. If standards for initial drug approval are eased — and even if they are not — regulatory agencies must have a robust process in place for the continuous evaluation of a drug's benefit–risk balance over its entire life

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cycle. In 2007, an expert committee of the Institute of Medicine (IOM) in the United States characterized the FDA's approach to benefit–risk analysis as "ad hoc, informal and qualitative", and recommended that the agency develop a more systematic evaluation as part of a life cycle approach[3].

The need for this life cycle approach again became apparent as a result of the recent controversy over the thiazolidinedione antidiabetic drug rosiglitazone (Avandia), which was granted marketing authorization in 1999 based on its ability to improve glycaemic control, as assessed by reduced levels of blood sugar and haemoglobin A1C — surrogate markers that were assumed to predict clinical benefit. However, an increased risk of cardiovascular events associated with the use of rosiglitazone — highlighted initially in 2007 — became apparent, emphasizing the need for more effective benefit–risk analysis for recently introduced medicines.

Emerging issues in drug regulation

A life cycle approach has begun to emerge in pharmaceutical regulation in Europe and the United States, although much remains to be done. In 2005, the European Commission proposed that a risk management plan become part of the required regulatory submission for new medicines. The plan should include: first, a statement of what is known about the safety of the medicines and also what is not known; second, a plan for how the unknown information should be acquired; third, what risk minimization steps, if any, should be followed (for example, allowing only specialists to prescribe the drug or launching an educational programme for patients); and last, how this information should be communicated. In 2008, the Commission proposed a new set of pharmacovigilance regulations that will take effect in July 2012. These not only reinforce the importance of risk management plans but also give regulators the authority to require post-marketing studies of effectiveness as well as of safety.

In the United States, the Food and Drug Administration Amendments Act of 2007 substantially strengthened the FDA's regulatory authority in the post-marketing period, allowing it to require specific studies in certain circumstances. The FDA was also empowered to require drug manufacturers to submit a risk evaluation mitigation strategy as a condition of drug approval.

Notwithstanding these initiatives, concerns about drug safety and the conduct of post-marketing studies remained, and were heightened by the case of rosiglitazone. Consequently, a second IOM committee was convened in 2010 at the request of the FDA and other federal agencies to offer further guidance on strategies for studying the safety of approved medicines. The final report[4], released in May 2012, acknowledges the steps that the FDA has already taken to improve drug safety but makes 23 recommendations to implement more fully a life cycle approach to drug regulation. One of the most interesting recommendations is for the development of a benefit–risk assessment management plan (BRAMP) by the sponsor of every new drug. This public document, which would be updated over the life cycle of the drug, would provide an updated assessment of its benefit–risk profile. Over time, the BRAMP would include information about any public health questions posed by the drug, a formal benefit–risk assessment (which is regularly reviewed) and a rationale for the type of any post-marketing study of effectiveness and safety. The European Commission's proposals and those encompassed in a BRAMP converge in their new attention to post-marketing drug safety and an ongoing evaluation of the drug's benefit–risk profile.

Whether the pharmaceutical industry joins in this consensus and whether companies will serve as willing or reluctant partners in an invigorated post-marketing drug regulation scheme remains unclear. Additional regulatory requirements are never welcome in the short term, and the post-marketing studies that may be required under the life cycle approach may impose substantial costs on manufacturers. However, industry has learned the hard way that inadequate responses to safety signals can have a serious detrimental impact not only on public health but also in economic and reputational terms. The long-term interests of manufacturers and regulators in well-characterized benefit–risk profiles are essentially the same.

Summary

Experts and regulators in Europe and the United States alike now recognize that a robust ongoing assessment of the benefit–risk balance of new medicines is essential. Regulatory requirements are converging in the direction of the life cycle approach. So too, we hope, will be the recognition that a fully realized vision for drug safety requires the commitment of both those who regulate medicines and those who produce them.

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Competing interests statement
The authors declare competing financial interests: see Web version for details.

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