

Post-marketing Strategies for Medicines

A Breckenridge¹

To the Editor: The medicines regulator has responsibilities to several stakeholders: first, to the general public, where he is tasked with approving only drugs with an appropriate risk benefit balance; second, to health-care professionals, where he must ensure the availability of information allowing them to prescribe medicines safely and effectively; and third, to the pharmaceutical industry, where regulations should encourage the development of innovative medicines.

It has become increasingly realized that although the efficacy of a medicine can be reasonably ascertained at the time of marketing authorization, the same cannot be said of drug safety, where only limited preclinical and clinical trial information, often from only a few patients, is available at the time a license is granted. Thus, the concept of a life-cycle approach to drug safety has gained increasing currency, whereby risk management strategies, initially formulated throughout early drug development, are refined and implemented during their subsequent use in clinical practice.

Whose responsibility is it then to design, execute, and, most importantly, fund post-marketing investigations of new and existing medicines—industry, government-funded research bodies, or the regulator?

It seems not unreasonable that industry should be charged with safeguarding the safety of the medicines that it discovers and develops. This has always been the case and it has now been recognized in law in Europe (and very likely the United States) that risk management plans should constitute

part of the agreement reached between the regulator and the pharmaceutical company when a medicine is granted a marketing authorization. It must be said, however, that in the past, the record of the pharmaceutical industry in completing post-marketing commitments, which have been given at the time of marketing approval, has been less than impressive with reports of some 70% of studies not having even been started after 5 years.¹ Hopefully, the recent legal enforcement of risk management plans, with attendant penalties for non-completion, will result in an improvement of this performance.

Government-funded research bodies such as the National Institutes of Health and the National Research Council, as well as large charitable organizations, have historically played an important role in the planning, funding, and execution of large epidemiological studies such as those on the safety and efficacy of hormone replacement therapy, antituberculous therapy, treatment of HIV disease, and the safety of childhood vaccines. Such studies have been carried out only where major public health issues have been raised and not as part of the routine surveillance process of all medicines. One interesting development in the United Kingdom is that the strategic roles of National Health Service (NHS) program of R&D and of the UK Medical Research Council, one charged with predominantly applied research and the other with more basic research, but both funded by government, have been put under the single direction of an Office for Strategic Coordination of Health Research, which will also allocate funding to the two bodies. Its task will be to formulate an overarching UK health research strategy with special reference to the translation of ideas from basic and clinical research into new products and approaches to the treatment of disease. Part of the strategy

is to facilitate the implementation of important studies on long-term studies of risks and benefits of medicines.

Implicit in the function of the medicines regulator is the encouragement of reliable and useful research on medicines, but this has rarely been clearly defined and the funding of such studies by the regulator is usually problematical.

A recent initiative by the Italian Medicines Agency (AIFA) illustrates another approach to independent research in drug usage. One of the specific tasks assigned in Italian law to AIFA is the promotion of independent research on drugs in areas of interest to the Italian National Health Service and where commercial support would normally be insufficient.

An innovative aspect of this program is its funding. Pharmaceutical companies trading in Italy are now legally required to contribute 5% of their annual expenditure, devoted to those promotional activities aimed at physicians, to an *ad hoc* fund, which has accrued some 40 million per year (\$60 million). Since it was established in 2005, this has been made available for research programs.

The mechanism of its operation is that in both 2005 and 2006, AIFA launched a call for drug-based research proposals aimed at investigators working in public organizations (*e.g.*, universities, NHS) and non-profit organizations (*e.g.*, scientific foundations, patient associations). A Research and Development Committee, chaired by the eminent scientist Professor Silvio Garattini was given the task of identifying broad research areas where financial support is needed.

For the first 2 years of the program, the following three areas were selected:

- orphan drugs for the treatment of rare diseases and drugs for non-responders;

- head-to-head comparisons of drugs and therapeutic strategies; and
- strategies to improve the appropriateness of drug use and pharmacoepidemiological studies.

The response to the call for research proposals was encouraging. Independent panels of at least 20 experts, half of whom were from abroad, evaluated the submitted proposals. In 2005, the fund was able to support some 54 studies and in 2006 51 studies. These included an assessment of the risk benefit profile of the off-label drug use for the treatment of rare diseases, the therapeutic strategies for optimizing the treatment of stroke, and the studies on the risk profile of psychopharmacological treatment for children and adolescents.

An analysis of the value of the results for Italian public health will be watched with interest by other regulatory agencies. It may be that the costs of the Italian program will merely be passed on to the consumer and this too will be carefully monitored.

So, there are several possible approaches to the conduct and funding of continuing studies of the safety and efficacy of medicines throughout their life cycle and some interesting new ideas are emerging in Europe. What is clear is that as the science of drug development continues to progress, further innovative approaches will be needed.

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CONFLICT OF INTEREST

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Response to "Post-marketing Strategies for Medicine"

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To the Editor: Alasdair Breckenridge's letter on post-marketing strategies for medicines is very timely.¹ Regulators put significant effort into the review of medicine license applications. The information and data contained in the license application are necessarily limited because of the clinical trial design and the public need to develop new medicines in a timely manner. In return, companies continue to study the medicine throughout its life cycle to maximize the benefit to the patient and better inform health-care practitioners about its use. New indications are studied, and information on potential new safety issues is acquired and added to the product information as they are validated. Key to all of these activities is the full commitment of the company to fund the relevant research.

A new national law was recently enacted in the United States to further clarify the Food and Drug Administration's (FDA) authority over post-market study requirements and also to provide the agency with increased funding to modernize its drug safety office. Breckenridge cites comments on industry's alleged less-than-impressive compliance with post-market commitments. According to FDA's analysis, only 3% of such drug studies are delayed. The time between agreement with FDA regarding the need for a post-market study and

its initiation can be significant. The protocol must be reviewed by FDA; the ethics board at the trial site must then review and approve the study, and only then can patient recruitment begin. This is why 70% of studies are listed as pending; they are not delayed but going through the normal pathway to implementation. To say that industry is not meeting its obligations in this area is a misstatement or exaggeration.

Another feature of the new US legislation is the establishment of the Reagan-Udall Foundation, designed to accelerate innovation and enhance product safety. The foundation will have an independent board of directors. Importantly, the foundation may enter into public-private partnerships to advance its goals. This will help leverage resources from both the public and private sectors. Recently, a consortium between industry, the FDA, and academia on biomarker research was entered into that holds promise for both drug development and safety assessment.

Although the model for collaboration in the US differs from the Italian and UK models outlined by Breckenridge, it holds promise, particularly because of its involvement of all stakeholders. It will be interesting to return to this issue several years from now and compare the progress that these various approaches have made in advancing our knowledge about the benefits and risks of new medicines.

CONFLICT OF INTEREST

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