Off-Label Use of Medicines is an Issue for Regulators

There is a paradox at the centre of modern medical practice. Pharmaceutical regulators spend vast amounts of time examining the dossiers of proposed new medicines in order to make sure that these products meet the highest scientific standards of quality, safety and efficacy. At the same time, doctors are confronted with seriously ill patients and must decide how or even whether to prescribe these new medicines. Very often the indications for which the medicines are approved do not match the real needs of patients. Doctors may then prescribe medicines off-label because the treatments that their patients require are not available for the right indications or for the right patient population.

It is a matter of urgency that regulators, representatives of industry and healthcare professionals close the gap between what is developed and approved for the pharmaceutical market and what is needed by patients. This can be done through better communication among the parties concerned and by providing new incentives for drug development. But first, it is necessary to understand the different worlds in which regulators and medical practitioners work. For the purpose of this essay, they are described as the ‘virtual world’ and the ‘real world’.

The ‘virtual’ world

The pharmaceutical industry and drug regulatory authorities communicate extensively, and drugs must be the most regulated of any manufactured product. The amount of paperwork (soon to be replaced by the electronic dossier) that must be submitted for a marketing authorisation would cause awe and surprise to a layperson. Just the legislation and guidance documents linked to an application would fill bookshelves. The essence of all this communication is the quality, safety and efficacy of the product under evaluation.

But discussion on these very real issues takes place in a very abstract way. Trials are presented and evaluated in a statistically and scientifically sound way, but everything depends on data. A very important feature of the division of power between regulators and pharmaceutical companies is that the applicant decides what is on the agenda. Regulators only react to the information that is submitted to them.

The real world

In contrast, medical practice is not abstract at all. Patients are ill, sometimes with life-threatening diseases. Doctors frequently have to deal with patients who differ considerably from clinical trial subjects in that they have no easy diagnosis. For example, patients may suffer from more than one disease. As a consequence, patients have to use a number of different medicines to keep symptoms and adverse reactions at a distance, or even just to stay alive. The work of an average physician is therefore not just scientific; it contains a considerable amount of practical decision-making. Of course, the gold standard is Evidence Based Medicine, but in reality it is often the wet finger in the air that shows which way the wind is blowing.

Doctors have to deal with the fact that much is still unresolved in terms of the treatment of patients: many people die before their time from diseases that cannot be cured because science has not yet found the key to the problem. For some very rare conditions, there seems to be little incentive for science and industry to invest in the requisite research, so the outlook for those patients is often poor.

Communication between the two worlds: authorised product information

How does communication between the world of regulators and industry on the one hand and the world of medical practice on the other take place? The main vehicle of information sharing is the summary of product characteristics (in the USA commonly known as the Data Sheet). This document is annexed to the marketing authorisation and gives a summary of all approved information. The authorised product information is the basis for all communication between the virtual world of industry and regulators and the real world of patients and doctors. Any advertisement for a medicinal product has to be based on the authorised product information. In addition competent authorities can only inform the public, including medical practitioners, about those properties of the medicinal product that have been evaluated and have been approved. This means that communication between the two worlds is restricted to information that is authorised.

Life in the virtual world

Regulators and industry are players in a world that is ruled by legislation and guidelines. The regulatory process is used to fulfil the aim of protecting public health, but the question is how effective is this protection in practice?

The origin of the authorised product information

The summary of product characteristics is created in the virtual world. It is the product of collaboration between the applicant or holder of the authorisation and the approving competent authority, but the participants in this collaboration are not equal. The decision to include an indication or not to exclude a contra-indication or to include specific patient populations lies entirely with industry. If the applicant wants to extend the authorised uses of the medicinal product, he has to sponsor the necessary trials and submit an application. The competent authority has a passive role and can only approve or refuse the application.

This means that the official part of the application is in the control of the pharmaceutical industry. Regulatory bodies can only try to convince their counterparts of the importance of adding new indications or taking away contra-indications or including categories of patients (like children, patients with impaired liver or kidney function or pregnant or breast-feeding women) in the official information. Even in a situation where the use of a product under new conditions is well researched and the outcome...
of this research is in the public domain, competent authorities cannot unilaterally add indications or patient groups or lift contra-indications. The initiative for every change to the product information, except of course when safety issues are at stake, lies exclusively with the holder of the marketing authorisation. And there can be good reasons why a company would not want to have the widest possible application of its product.

Why some applications of a medicinal product are not authorised

Behind every action of the pharmaceutical industry lies an economic motive. Actions are rarely taken that will not lead to improvement of profit expectations, and justifiably so. After all, no one has an interest in bankrupting parts of the industry and we badly need the pharmaceutical industry to provide us with new medicinal products.

Lack of an anticipated return on investment is a good reason not to invest in the clinical research and regulatory work needed to support the widest possible range of indications for a pharmaceutical product. Concerns about intellectual property rights might be another reason. And the risks of increased product liability could be a third, particularly if a product is advertised for use in a patient population that typically has an elevated risk of serious adverse reactions.

Life in the real world

The shadow of the virtual world falls upon the world of patients and doctors. How effective are the efforts of industry and regulators to make the treatment of patients as good as possible?

Consequences of limited product information: off-label use

In medical practice, conditions have to be treated by whatever therapies are available. This means that if a medicinal product is not authorised for a certain condition or patient and there is no alternative, or the alternatives have disadvantages, prescribers have to consider using a medicinal product off-label. It has been argued that doctors should not be allowed to use medicines off-label, but this position is untenable. Every doctor has to treat his patients to the best of his ability, even if this means that he prescribes off-label. The obligations stemming from the Hippocratic Oath are of greater importance than adherence to authorised product information.

Of course, off-label prescribing should only be done after serious consideration because the evaluation of the benefit/risk balance in these cases is an enormous responsibility for the doctor. In such cases there is also a heavy obligation on the doctor to reach informed consent with the patient because the patient (or his legal representative) is entitled to know about the off-label character of the prescription. Another problem is that, even if they could give a scientifically sound opinion about off-label applications of a medicinal product, drug regulatory agencies would not be able to do so: their authority is limited to those aspects of a medicine that have been evaluated on the basis of data supplied by the manufacturer.

Connecting the two worlds

The situation where medicinal products have to be used under conditions that are not regulated is a very undesirable one. The virtual world and the real world should be connected. This is in the interest of public health because it enables mistakes in the use of a medicinal product to be avoided. The broader use of a medicinal product can also be advantageous in improving the quality of medical care. And last but not least, the position of drug regulators could benefit from connecting their work with medical practice.

How can better communication about medical needs and priorities be created?

It is urgent that a communication channel between practice and industry, in collaboration with drug regulators and policy makers, should be set up. In such an initiative it is of utmost importance to acknowledge the interests of the parties involved. If, for example, the legitimate interests of the pharmaceutical industry to act as an independent economic operator are neglected, communication is bound to fail. On the other hand, trust in the performance of the role of competent authorities is also a prerequisite for success. Through a dialogue between the two worlds, an inventory of prioritised topics could be established.

How should more complete product information be created?

The overall consideration should be a more extensive evaluation of possible uses of medicinal products in the interest of public health. If the pharmaceutical industry does not spontaneously perform clinical trials, there is probably a good reason why this is so. Analysis of these reasons and finding solutions in terms of incentives could go a long way toward closing the gap between the ‘virtual world’ of regulation and the ‘real world’ of medical practice.

John Lisman
Policy Adviser
Medicines Evaluation Board of
The Netherlands