Monitoring adverse drug reactions: An odyssey of organizing

David Demortain describes how the international regime for reporting adverse drug reactions was built from the bottom up, and considers the difficulties this creates for the agencies that often shoulder the blame.

Ensuring that medicines placed on the market do not cause adverse health events is a challenge of a particular kind. In recent years, the worldwide withdrawals of Lipobay™ and Vioxx™ have led to close scrutiny and interrogations of the work of health authorities: could there be a possibility to organize 'pharmacovigilance' – the systematic collection and evaluation of adverse drug reaction reports from doctors and other heath professionals – in a more efficient way?

Regulatory agencies in charge of pharmaceutical control, such as the UK Medicines and Healthcare products Regulatory Agency (MHRA), generally take the blame when it appears that serious adverse drug reactions were not spotted early enough or when pharmaceutical companies decide unilaterally to withdraw products from the market. However, contemporary drug scandals and obsessions of accountability create a misleading view of what drug safety is about. The 'organized' facet of pharmacovigilance – the setting up of independent regulatory agencies with responsibility for pharmaceutical control – is just the tip of the iceberg. A quick look at the history of pharmacovigilance shows that it has been organized in a decentralized and incremental way by medical experts, to improve the performance of what they characterized as an essential public health function.

Drugs can cure – can they kill?

It is nowadays evident that medicines cause adverse reactions. It is also widely recognized that these effects remain unknown until the product has been put into use. However, systematically monitoring, collecting and accessing this evidence is only a recent phenomena.

Until the 1960s, medical dictionaries had no word for naming adverse drug reactions – these were not supposed to exist in a world that valued (and still values) the discovery of new medicines above the appropriate therapeutic use of those that already exist. It is only after the sulphanilamide scandal in the US in the 1930s and, even more decisively, the thalidomide affair in 1960 that it was understood to be normal and inevitable that medicines cause adverse health events.

Subsequent high profile adverse drug reactions led to further methodological discoveries. The first of these was that the knowledge of the effects of a medicine is inevitably bounded by the limited range of patients on which it is tested. By the 1970s it was also realized that the data collected is not sufficient to assess the frequency of reactions. Reporting rates are, and remain, very low. The identification of an adverse reaction is also highly dependent on the knowledge and interpretation of the doctor of the affected patient.

Successive drug scandals thus anchored the belief that no system could ever ensure all drug effects are known. The world of pharmacovigilance is highly conscious that uncertainty is congenital to drug use. Interestingly, given this awareness, the word 'uncertainty' is not part of the standard vocabulary of drug safety experts. They are focussed on averting it, through the continuous experimentation and improvement of instruments for the collection and evaluation of drug reaction signals.

Organizing pharmacovigilance

Pharmacovigilance is a collaborative process: doctors write down their observations and a patient's history on a report. Agency-based evaluators – doctors, toxicologists or pharmacists – then review the data and encode the case in a database. The resulting record is the basis for a collegial evaluation by medical experts, who forward their conclusions to a regulatory authority, which transforms them into a modified marketing authorization and summary of product characteristics.

Medical experts started organizing this monitoring system for drug effects shortly after the thalidomide ordeal. It became clear that the extent to which thalidomide was prescribed could have been much reduced had a correlation been made earlier between the suspicions of an Australian and a German doctor. This gave weight to the belief that suspicions of drug adverse events arising from doctors' daily practice should be collected and sent to a common central office, for 'signals' of serious and rare reactions to be detected as early as possible.

In 1961, a voluntary agreement was established between the American Medical Association, the American pharmaceutical industry and the US Food and Drug Administration to organize a voluntary notification scheme. In 1962, the World Health Organisation encouraged prominent hospital doctors to organize notification schemes in their countries. In 1966, it established an international drug monitoring centre in Sweden to collect reports from each country and perform quantitative analysis on the broader sets of data.

Each country's scheme has not fundamentally changed since its creation and remains fairly simple in terms of the technologies used. Over time, the reporting of individual adverse health events has been streamlined and automated thanks to the establishment of standardized formats, operating procedures and vocabulary

by an international commission of medical experts. Networks of agents entitled to send reports have been enlarged (from just doctors to include nurses, hospital and community pharmacists and possibly patients) and methodologies to link an event to a drug and to calculate its frequency have been refined.

However, pharmacovigilance has taken different forms depending on the criteria that local or national medical communities applied to the execution of this activity. The UK school of post-marketing surveillance, inspired by epidemiology, judged its system according to its ability to assess the incidence and prevalence of adverse reactions. The French school has mostly been driven by the satisfaction of one key criteria, which is the ability to make precise causality assessments, even on single cases.

These choices were directly reflected in the collaborative protocols used by agents to organize pharmacovigilance. France has established a network of regional centres, with the specific ambition to stay as close as possible to doctors. The UK adopted a form of centralised pharmacovigilance instead, whereby signals are directly sent to a central office – originally the Committee for the Safety of Drugs, now the post-licensing division of the MHRA. The agency prides itself on having one of the most comprehensive databases of adverse events and of being able to run statistical calculations on them daily.

In the French case, particular care has been put into the design of protocols that guide the evaluation of signals in the regional centres. A decision tree guides that evaluation and attributes a score to each drug depending on the answers to specific and systematic questions (eg Was the suspected product reintroduced? Has the adverse event occurred again after re-introduction?). The entire inputting process is closely monitored; junior doctors review the data send in by regional doctors and are overseen by a senior medical officer.

Conversely, in the UK, it is the procedures and criteria used to extract the key health impact data from the central database that has become particularly sophisticated. A protocol organizes which data outcomes are to be considered by the doctors at the MHRA. In the case of significant health impacts, a whole procedure indicates who, when and how to organize the liaison with the drug's parent company, the depth of the risk/benefit assessment and the extent to which the relevant European Union authority should be involved.

This circular process, starting with the discovery of new events and ending with the development and testing of the new protocols, is a constant one. It takes place as members of the medical community – as a professional and academic group – test, develop and organize (through their practice, research and publication) techniques to avert uncertainty.

Can the organizing get organized?

There is a great deal of momentum in this process. The MHRA and other comparable agencies keep collecting series of reports, encoding them into databases, running quantitative analysis programmes and organizing 'signal detection' meetings. Further to that, much of what now constitutes official pharmacovigilance regulations is a transposition of practices and techniques slowly shaped by the medical community into the realm of law.

Can agencies do better than a professional group in developing these pragmatics of uncertainty, thereby responding to the criticism they get when adverse effects emerge? The potential difficulty lies in the power of agencies to spread organizational norms – common criteria and collaborative protocols – beyond the agency and across professional communities.

At the time when pharmacovigilance schemes were first established, agencies did not exist. They were created much later in the 1990s. The motives behind their creation typically include the necessity to authorize drugs more efficiently – ie to lower marketing times to encourage innovation and make patients benefit more quickly from new products. It was hoped that market regulation would be made more effective due to better resourced and higher quality expertize. Setting up independent agencies was also seen as a way to ensure accountability and transparency in regulation. In a nutshell, the creation of agencies to oversee pharmaceutical markets was motivated by improving marketing authorization and the setting of product standards, much more than the gathering of information on adverse effects. The parallel organization of pharmacovigilance was unexpected.

When agencies were created, national scientific committees of medical experts set up to evaluate signals were simply integrated into the new organization. But the development of independent regulatory agencies at national and European levels introduced competition into data collection as each country has asserted its need to develop a database. This has created a reluctance to share data and a duplication of analytical efforts. For example, the European Medicines Evaluation Agency has created its own central database, duplicating the efforts made by the Uppsala Monitoring Centre (Sweden) to become the international centre of reference.

Another issue affecting the development of effective agencies is the difficulty of recruiting. Specialists of pharmacovigilance have remained in hospitals and universities instead of joining agencies. Contrarily to the evaluation of marketing dossiers and of clinical trials, the evaluation of adverse drug reactions is not a highly valued medical exercise and few high profile scientists or doctors are attracted by the opportunity to work as a drug regulator.

The pace of standard-setting at the international level was also accelerated as a result of the densification of the government regulatory community. An International Conference for Harmonisation was created to harmonize guidelines related to pharmaceutical control. Originally focussed on harmonizing standards related to the testing of drugs before they get marketed, the process quickly colonized pharmacovigilance. A standard for the planning of pharmacovigilance activities by companies was thus created in this arena, despite the lack of experimentation with the tool by medical researchers and other pharmacovigilance specialists.

Pharmacovigilance teaches us a point about the relation between organization and risk. This relation may take an organized form, reflecting a deliberate attempt to create formal structures to improve accountability and enforcement. On the other hand, it is also a process of organizing activities that are dependent on a chain of heterogeneous actors. This process is incremental and decentralized; it is led by the very actors that undertake the concrete day-to-day operations.

Pharmaceutical regulatory agencies attract criticism and provide a much needed focal point, particularly for politicians and the public at large. But, in a sense, they are made responsible for the performance of systems whose development they only partly control. The actual tackling of adverse health events depends on professional groups developing norms and technologies that can be effectively adopted by agencies. Paradoxically then, supporting the research in pharmacovigilance that is done by scientists and doctors outside agency walls (eg through funding) could very well enable agencies to better fulfil their mission.

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