EDITORIAL

Drug Saf 2011; 34 (2): 93-96
0114-5916/11/0002-0093/$49.95/0



# Pharmacovigilance and the Null Hypothesis

## Do We do Much for Public Health?

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### 1. An Introduction

Over the past few years, the media has been replete with criticism of the failure of pharmacovigilance (PV) systems to prevent harm to people. In both the US and Europe this has resulted in calls for more effective PV. Indeed, on both sides of the Atlantic there is a flurry of funded activity to find better data sources, to use better analysis tools and to be more proactive in risk management.

It was arguably rofecoxib (Vioxx®) that instigated the activity because of the increased incidence of myocardial infarction. Because heart attack is serious and common, and the drug was very widely used, the public health impact was great and the public outcry loud; the regulators had been much too slow in taking action. Much of the above is summarized beautifully in a review by Greener.[1] Just after the Vioxx® issue became public, Edwards[2] wrote "The Vioxx® situation was not a failure of regulation itself, neither was it an issue of data collection, nor of the quality of studies performed. It was and is a complex decision-making/communication challenge in which some improvements are possible. Making wise drug safety decisions is not easy …". There was an early signal about that problem, and about 6 months after the drug was launched there were warnings in the product literature.[2] The increase in risk over background was small, even though the absolute numbers affected and the public health impact were large, and a fairly large study was needed to evaluate this. The key question was, and is, who makes the decision to do such a study, when, and who should fund and perform the study.

#### 1.1 The 'Null Hypothesis'

During the shake-up following Vioxx®, and after all previous public drug safety concerns, there has been a totally focused gaze on the harm from drugs and the defects in PV practice. There has been little or nothing on what has been achieved in improved safety over the years. It is as though there has been no significant improvement from the baseline: the unstated null hypothesis.

This is perhaps not surprising since we do not even know, either in general or for each drug, what level of safety is expected. A PubMed search on public perception of drug risk – 'public'[All Fields] AND ('perception'[MeSH Terms] OR 'perception'[All Fields]) AND 'drug'[All Fields] AND ('risk'[MeSH Terms] OR 'risk'[All Fields]) – gave only 238 hits, many of which were related to drugs of abuse and HIV/AIDS therapy, and only two were concerned with general views, which suggest that public perception of risk is unfavourably different from those of health professionals.[3,4] We do not have risk perception information for risks of different specific drugs in their different relevant patient groups, although an argument has been made for such an approach.[5]

It seems essential that those in PV should have a clear idea of what patients in particular and the public in general expect from them.

On the other hand, public health improvements related to drug safety should not be determined from lay expectation alone but take into account many other factors, such as the effectiveness of the drugs, comparisons of effectiveness and risks of other therapies for the same indication, the identification of risk-susceptible patient groups, new knowledge of drug harm, and systematic medication error, and certainly careful consideration must be given to preventable drug harm.[6]

We must be able to show that PV is an important public health function in relation to, at least, the above activities. To do this, we must be able to demonstrate that we have quality assured processes that provide, to health professions and the public, the information they need from the most comprehensive safety information feasible, and using the best tools to collect, collate and analyse safety information. We must also be able to point to the cost effectiveness of PV activities, which should be monitored and justified against public expectation. Parameters that reflect the desirable drug safety outcomes must be demonstrable as improved outcomes of therapy.

A moment's consideration of the above, makes it clear that much is missing. There is some information on drug withdrawals from the market but withdrawals differ in different jurisdictions.[7,8] There is also literature on PV communication, some of it suggesting continuous improvement, although there is still room for much improvement,[9-11] and particularly when it comes to considering four dimensions of both effectiveness and harm that often concern patients: the nature (quality, intensity, duration); probability (that it will occur); importance (to the person experiencing it); and how benefit can be maximized or harm prevented, minimized or treated.[10] We have made no attempt to make a thorough investigation of the literature on harm from treatments because the examples show that there are, at least, differences of view about whether PV is delivering adequately what the public and health professionals expect.

The main point of the above is not to show that PV may need improvements, but rather to ask the question 'where is the information to support the idea that PV activity adds anything to public health in a cost effective way?' There do not seem to be any agreed criteria that allow PV services to demonstrate their effectiveness. Some will point to measures such as the numbers of Individual Case Harm Reports (ICHR) received and processed, the number of drug withdrawals, the numbers of warnings given in summaries of product characteristics, and quality assured data management; but these are poor surrogate endpoints. We do not know whether any particular drug withdrawal has led to improved public health: what happened to the bulk of people who were doing alright on the drug? What alternative therapies were used instead? If they were older, was their effectiveness-risk profile really better? What effect do warnings have? What is the point of reporting when we do not know the effectiveness of their analysis nor the outcomes? Have we shown any impact on preventable drug harm and medication errors in clinical practice?

### 1.2 How to Show Significant Differences

Significant, in this context, has little or nothing to do with statistical significance. It is more that we understand better what health professionals want and what the public wants. Some in PV say that the public wants perfect safety, which we all know to be unattainable. We do not subscribe to the view that the majority of people are so gullible, but there must be a rapprochement between what the public in general and patients in particular want and what safety improvements are possible. This can only be done through dialogue and education.

On the other hand, there is one area that is within the control of PV professionals around the world, and that is to determine and work towards useful, measurable performance indicators. This would help inform a useful dialogue with other stakeholders, as well as give us confidence in our work, and indeed some goals to strive for.

One of the authors, Professor Ambrose Isah, has been leading and coordinating work within the WHO Programme for International Drug Monitoring to produce a list of performance indicators. That work is nearing completion, as the

final list of potential indicators comes under peer review before a final draft is agreed by the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

Professor Isah convinced me that the initial list should be as broad ranging as possible so that anything that could be seen as a measure of PV performance should be included; only with time and use will there be a core list agreed. That has not stopped the process of peer review from grouping possible contenders according to perceived value at this stage. Below we shall give a summary of the progress of the work so far.

A tripartite definition of PV indicators has been developed:

- Indicators are specific objective measures that allow the evaluation of baseline situation and progress in healthcare services and interventions.
- PV performance indicators are measures of inputs, processes, outputs, outcomes and impacts for development projects, programmes or strategies.
- They are measures that describe how well a PV programme is achieving its objectives.

The indicators themselves must have the following attributes:

- easy to measure, understand and interpret as well as inexpensive to obtain;
- not require too high a level of expertise to use;
- reproducible – irrespective of the investigator;
- sensitive enough to detect PV problems needing attention;
- sufficiently robust to serve as an efficient monitoring tool.

For each indicator it must be possible to defend their inclusion as an indicator by the following:

- Definition
  What is the content of the indicator?
- Description
  What is the purpose and scope of the indicator?
  What are the definitions of key terms?
- Uses
  What will it measure?
  Why is it important?
- Sources and methods of data collection and indicator calculation
  Main sources and methods of data collection – sample selection, sample size and methodology?
  How should the indicator be calculated?
- How can the results be interpreted?
- What are the limitations of the indicator?

A major consideration is to have some stated scope for PV. We have expressed what various stakeholders really want from PV and this consideration is important. Given the current lack of clarity, Isah and his colleagues have proposed a broad scope for those involved in PV activity to range from healthcare providers through the pharmaceutical industry, other established agencies, national PV centres, national regulatory bodies and international organizations. The overall objective is "to provide objective measures which will enable the assessment of the status of PV, the activities and its impact, globally at all levels of the healthcare system, with a view to ensuring patient safety" (Isah A, unpublished observations).

Having decided on that breadth of scope, Isah and his group set out four distinct aspects of PV where indicator information might be used to evaluate performance. These are:

- *Background information*: These define and describe the milieu where the PV activities are taking place and other factors likely to impact on PV. The information will include demographics, economics, healthcare system and pharmaceutical scenario. They provide the denominator for calculating most of the indicator values.
- *Structural indicators*: The structural indicators assess the existence of key PV structures, systems and mechanisms in any particular setting. They indicate that availability of basic infrastructure is required to enable PV operations; they assess the elements that give visibility to PV; they also assess the existence of a policy and regulatory framework that enable PV to operate. Responses will be essentially qualitative.
- *Process indicators*: These cover the entire mechanisms and degree of PV activities. They are measures that assess directly or indirectly the extent to which the system is operating efficiently.
- *Outcome (impact) indicators*: The outcome and impact indicators measure the effects (results and changes) of PV activities. They

measure the extent of realization of the PV objective which, in essence, is ensuring patient safety. The focus of the impact of PV is definitely on efficient and safe use of medicines.

Finally, there have been calls for the development of Good Pharmacovigilance Practice (GPvP), to be added to the increasing and successful guidelines for optimal performance of activities affecting drug development.[12] A recent and important contribution on this topic has been a summary of the work of a brainstorming group of experts, focusing on the important, more regulatory aspects.[13] They point out that their summary, like this editorial, does not go into details. In both instances, the main point is that that these very much related issues are works-in-progress at early stages. Whilst it may be tantalizing for many readers of this editorial, it gives the opportunity for meaningful dialogue.

Most important is to stimulate thinking about how we should justify our discipline in public health terms, and it would be exciting if dialogue on this topic could be conducted publicly through correspondence in *Drug Safety*.

## Acknowledgements

Neither author has any conflicts of interest to declare.

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