Drug Saf 2009; 32 (12): 1105-1108
0114-5916/09/0012-1105/$49.95/0

Tomorrow's World

I. Ralph Edwards

Uppsala Monitoring Centre, Uppsala, Sweden

What is lurking in the shadows for pharmacovigilance of the future? Participants at two recent meetings have felt strongly enough about their discussions to issue statements that have the future clearly in mind.

1. Sicilian Output

Meetings in Erice, Sicily, have a track record of wide-reaching, influential communiqués on future concerns, not only in medicine but in other disciplines, notably physics, where important statements have been initiated and endorsed by eminent scientists such as Paul Dirac.

The often quoted Erice Declaration on pharmacovigilance was 12 years ago and a critical follow-up Erice Manifesto was issued in 2007.[1] They dealt with necessary pathways and activities concerning immediate future changes affecting the safety of patients. Now, in preparation, is a statement from the most recent Erice meeting of multidisciplinary stakeholders concerned with aspects of the safety of medicines (June 2009). All three Erice meetings have been about making pharmacovigilance alive and active to maximize patient safety but the challenges to achieve this goal multiply. I will attempt to summarize the mood and content of the latest Erice meeting later.

2. Challenge from Accra....

First, I want to pick up on the 10th Commonwealth Pharmacists Association Meeting in Accra in August.[2] This was a large meeting with over 1500 delegates who felt strongly enough to draw up a consensus Communiqué.[3] The theme of the meeting was 'Managing threats and crises', with a subtitle of '...The vital role of pharmacy in an unstable world...'.

Medicine must remain relevant as the world changes ever more rapidly. This Communiqué is a call to pharmacists in a world where 'Natural and man-made threats and crises and failures of systems are increasingly common features...'. It draws their attention to using their professional contacts and skills in a broader and more active sense. This involvement and commitment is true for all health professionals with any level of involvement in the better, safer use of medicines.

The call to action is clear, 'To be alert to the specific current and potential threats to the health, welfare and safety of their patients and communities' and 'To take part in collaborative planning for the reduction of risk and for the management of disasters and crises, especially those that are current and continuous, and those which can be plausibly predicted.'

What can be 'plausibly predicted' relates to:

- Major health matters: Tuberculosis, HIV/AIDS, malaria, pandemic viral infections, cancer, heart disease; lifestyle diseases (e.g. diabetes, hypertension, obesity); tobacco use; extreme weather events, natural disasters; control of counterfeit and illegal drug trafficking; unregulated use of medicines.
- Catastrophes: Flooding, wild fires, earthquakes, tsunamis, shortages of food, water, shelter; poor sanitation; lack of education; lack of access to healthcare services and medicines; unemployment.
- Vulnerable people: Pregnant women, children, the elderly. Children need access to age-appropriate dosage forms of medicines. Health systems are encouraged to remove

financial barriers limiting access to healthcare and medicines, for all children.
- Behaviour: Safe sex, compliant medication use, rational use of drugs (especially antibacterials), disease vector control.
- Pharmaceutical issues and actions: Counterfeit and sub-standard medicines, medication error, drug resistance; stockpiling of appropriate medicines, vaccines, surgical and other supplies; drills and training in disaster response; preparation of refuges and safe-havens.

Finally, the Communiqué also notes that pharmacists bear primary responsibility for meeting the medicine-related needs of populations, but the real thrust is their consideration of unmet challenges in the world today and professional willingness to confront change where they perceive they have much to offer.

3. … and from Erice

The previous Erice concerns, and the latest Erice Statement consider similar rapid changes in society and with a similar strong motivation to re-think in the face of new challenges. The pharmacovigilance focus is more limited, but pharmacovigilance can no longer be seen as limited to finding new risks with medicines, confirming them and quantifying them where possible. We cannot ignore the common knowledge that half of the serious adverse reactions taking people to hospital are avoidable. We cannot ignore some of the challenges to the safety of medicines mentioned in Accra.

The Statement recognizes three areas of major change that have happened in recent years:
- the multiplicity of stakeholders who have legitimate and active concerns about medicines;
- the dramatic expansion of information technology, which makes bad and good information available globally as well as offering new communications possibilities;
- the broadening of our concerns about the safe and effective use of medicines. A neglected problem is the need for a vigorous approach to the known harm that is caused by old medicines. An evolving problem is the leakage of medicines and their metabolites into the environment.

What does the Erice Statement say concerning these issues? The statement is due for publication soon, and should be a short summary of the points discussed below.

3.1 Stakeholders

Active research is necessary to find out about stakeholders' perceptions, requirements and interactions with each other in order to engage them as active parties with agreed roles and responsibilities. Trust is of the essence and can only be achieved through satisfactory dialogue and openness. Dialogue with patients must encourage them to be active participants, not the objects of some message, perhaps seen only once, leaving them confused and alone. Knowledge of stakeholders will enable targeted messages and dialogue to be developed, as well as encouraging active partnerships.

Blame, Trust and Legal Concerns

There is a welcome and solid move towards a no-blame culture (but maintaining accountability), understanding that many safety decisions, particularly about early signals, are based on uncertain probabilities gleaned from limited evidence. Decisions to provide information, warnings or to take other regulatory measures cannot always wait for illusory certainty: the decisions will rest on expert judgement, based on available information, which must be fully and openly explained in the context of avoiding serious harm to patients from medicines. Regulators and the pharmaceutical industry are at the forefront of knowledge concerning medicines and they have the best data and information on medicines' benefits and risks. Their resources must be used fully to support clinical practice in the changing world, and in a much more robust and imaginative way than in the past. Fear of litigation hampers open debate and transparency over judgements behind decisions.

The increasing establishment of scientifically trained reporters and researchers in the general media (including radio, television, print media

and as independent reporters) has meant that they have an increasing role as critics and interpreters of all areas of science and medicine. The media are a key partner in communication and education of the public, but they are not there for pharmacovigilance propaganda: scientific reporters will and should comment critically on information they receive; the responsibility of pharmacovigilance professionals is to ensure that they communicate openly, rationally and helpfully with competent reporters in a proactive way.

3.2 Information Technology

Information technology is an important new tool for many, but the vast amount of information available on the web may be dangerously confusing. Trusted, objective information must be made available for all the various stakeholder requirements. One impediment to clarity of information and good communication is the fear of litigation, which both encourages the over-inclusion of some items of risk (background events or very unlikely items) and the omission of all-important information on the likelihood and extent of risk as well as advice on alternative treatments available or other risk limitation strategies. In my view, this area improves all the time but there are still many situations in which *useful* information is not easily available to health professionals or the public.

Lack of trust seems to be an impediment to the collection of information on medicines safety as well. Longitudinal healthcare records, securely anonymized, have a huge potential for following the good and bad consequences of medicines in routine therapy. Continuing concerns raised about confidentiality and security of such databases threaten these vital sources of information. The concerns are based on the possibility of lapses in security or breaches of confidentiality rather than actual experience of harm from the use of anonymized patient data. Politicians, the media, and those who influence them on the balance of benefit and possible harm from the use of patient records must avoid unreasonable restrictions in the use of patient data. Pharmacovigilance and epidemiological professionals should continue to lobby for the responsible use of anonymized patient data for the benefit of the majority, but they must also make sure their practice safeguards individuals.

3.3 Ecopharmacovigilance

Drugs of all sorts and their metabolites are found in increasing quantities in effluent, with a recognized impact on the environment. The threat to humans is both direct and indirect: direct via contamination of water and indirect via environmental change. Estrogens and antimicrobials are often cited as problem areas. Already the safe disposal of medicines is encouraged, and environmental impact analyses are part of the regulatory requirement for new medicines, but more may need to be done to protect our environment and ourselves.

4. Meeting Perspectives

The world has had its fill of high level declarations of intent, and a comparison of the highlights of the two meetings is interesting. The Accra meeting Communiqué is a paradigm-shifting call to a new vision of service for all pharmacists, just as the Erice Declaration of 1997 called for a new view of pharmacovigilance.

On the other hand, the Erice Manifesto and the future Erice Statement are largely progress reports and indicate some improvements made, but mainly the lack of change, the obstacles and new horizons of challenge – we move slowly. Is our vision dimmed, our ardour cooled by bureaucracy, procedure and compromise? Where is the evidence that pharmacovigilance has led to improvements in public health?

What are the reasons why implementation of splendid intent is so slow? The safety of medicines is left behind in enthusiastic considerations of effectiveness: the urge to deliver antiretroviral medicines to those who need them was the priority, not their monitoring and safe use. The promotion of vaccines emphasizes their effectiveness, not the risk, however small.

Because the risks are indeed small for each medicinal product they are discounted, even

though the combined effect of the adverse effects of medicines is the fifth largest cause of mortality in the US.

Moreover, pharmacovigilance is stuck in its history, its concentration on finding and 'proving' novel adverse drug reactions. Almost all our effort is directed towards that area of science and technology, and little of our professional gaze is on how to measure and improve safety in therapeutics. Yes, researchers have amassed a good deal of information about what is right and wrong in choosing, prescribing and dispensing medicines but we lack the determination and the resources to apply that information to daily practice. In fact it is not even clear who would implement four changes that would make a big difference:

- better training in therapeutics and pharmacology, with the safety of medicines always being considered alongside their effectiveness in a real equipoise;
- time for health professionals to have meaningful dialogue with their patients;
- *coherent* information technology systems that are designed to support an up-to-the-minute aid to prescribing, dispensing and reporting, with the latest warnings and regulatory information as well as more extensive useful information and references included. In such systems all of the patient's medicines from whichever prescriber would be recorded. The systems would enhance clinical efficiency, not add to workloads;
- better monitoring of the effectiveness of what we do in pharmacovigilance.

The number of influential stakeholders in the effectiveness and safety of medicines grows dramatically. Our pharmacovigilance efforts in a world of limited economic growth are fractured into smaller fragments and efficiency increasingly impaired. We must cooperate, not duplicate unnecessarily and confuse, to achieve even the four changes mentioned above. Those who want to offer new ideas should consider what already works well and build on that. The global challenges considered by the Accra meeting need concerted action; perhaps this action will re-start the avalanche of development – but changing only those structures and functions that do *not* work will improve the safety of medicines, particularly when we have limited resources.

Acknowledgements

The author is very grateful to Bruce Hugman for his vivid report of the Accra meeting and for his help in editing the text.

No sources of funding were used in the preparation of this editorial. The author has no conflicts of interest that are directly relevant to the content of this editorial.

References

1. The Erice Manifesto: for global reform of the safety of medicines in patient care. Drug Saf 2007; 30 (3): 187-90
2. Around the Commonwealth: pharmacists assess global threats to health [online]. Available from URL: http://www.thecommonwealth.org/news/34580/212269/212210/120809pharmacists.htm [Accessed 2009 Sep 27]
3. Commonwealth Pharmacists Association. Pharmacists ready to meet evolving crises with concerted action [media release; online]. Available from URL: http://www.thecommonwealth.org/files/212327/FileName/CPAAccraCommunique+MediaRelease.pdf [Accessed 2009 Sep 27]

Correspondence: Professor *I. Ralph Edwards*, Uppsala Monitoring Centre, Stora Torget 3, Uppsala S-75320, Sweden.
E-mail: ralph.edwards@who-umc.org