A New Erice Report Considering the Safety of Medicines in the 21st Century

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Abstract Pharmacovigilance policy, methods and practice require transformation at all levels to create an integrated, comprehensive, continuously improving system, fulfilling the broader remit of overall healthcare vigilance. In pursuit of this vision, energetic measures, including active engagement with patients, are needed to reduce our ignorance about many aspects of patients' experience of medical therapies and their outcomes, including the benefits, but especially the extensive harm known to be caused by medical interventions. More information and communication in this domain will help set more accurate and realistic public expectations about the benefits and harm of therapy. All aspects of medicines development, regulation and use must be characterized by openness, transparency, ethical practice and a primary focus on the benefit and self-determined choices of patients. Notwithstanding, progress has been made in medicines safety information and communication but significant gaps and deficiencies remain. Promotion of the most beneficial use of medicines and the prevention of harm have not advanced sufficiently. This paper is a report from a group of experts, following previous similar decade reviews: the Erice Declaration (1996) and the Erice Manifesto (2006).

1 Introduction

Two decades after the publication of the Erice Declaration on Communicating Drug Safety Information, a new group of experts and professionals in the science of the safety of medicines (known as pharmacovigilance), met in Erice in

September 2016. Their purpose was to review the original work and to discuss what might be needed to update and strengthen its proposals for the new century. This short report is the result of their work.

An alternative perspective from one member of the group is appended. Wording and emphasis are always personal and very important. Consensus may convey both too little or too much about any topic. Alternative statements bring life to any debate, and there are several participants who agree with some or all of the different views he takes.

2 Testing Times Ahead for the Science of Pharmacovigilance

The Erice Declaration of 1997 [1, 2], which promoted the importance of dynamic, ethical and transparent communication in all matters relating to the safety of medicines, has been recognized as a public health landmark. While the central principles of that document remain relevant and true today, significant transformations in society, driven in part by changes in technology and healthcare delivery, point to the need to revisit the original Declaration and to update it for current times and for the future. The original Declaration is still referred to as pivotal in the development of proactive, ethical, transparent, patient-centred communication in medicines safety. It came at a time when the tide of bureaucratic priorities and methods was beginning to give way to a focus on patients and their needs, and it contributed substantially to that growing movement.

In 2006, *Drug Safety* published a retrospective review of the Declaration [1], along with the original text. The Declaration was followed by an Erice Manifesto (28 June–2 July 2006) that proposed more concrete actions that could be taken after the Erice Declaration, with the reasons for them [3].

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Great progress has been made over the last two decades in monitoring the safety and effectiveness of medicinal products. Improvements in the range and quality of medicines information available have followed, but important gaps and deficiencies still remain.

For example, we know too little about the specific positive and negative effects of therapies on the lives of patients; we struggle, especially, with methods to promote the most beneficial use of medicines and to prevent the harms that medicines can cause. While advances have been significant, they have also been unintentionally held back by increasingly bureaucratic and untested regulatory requirements, and sometimes by lack of political will and therefore resources. These factors have hindered efforts to engage healthcare professionals, patients and the public more actively in ensuring safe and appropriate use of medicinal products.

To be fit for purpose in the 21st century, the field of pharmacovigilance must transform itself to be more flexible and dynamic: to support clinicians in making accurate diagnoses, both of diseases and adverse effects; to help patients, jointly with their healthcare professionals, to make informed choices about their therapeutic options; and to ensure that information about medicinal products is transparent, accurate, accessible, relevant and timely. It must help determine the best treatment options and policies within mass treatment programmes (e.g. malaria, HIV, tuberculosis) that will have maximum public health impact in resource-poor settings. It must also have broader considerations in mind, such as the interactions between drugs and the environment (with possible consequent effects on animals and humans).

To accomplish this vision, pharmacovigilance must operate in a new way, i.e. as an integrated, comprehensive, continuously improving system [4]. The following call for action is intended to help drive such a transformation.

2.1 Patient-Focused: Seamless Integration into Healthcare

- Professionals in medicines safety and healthcare in general must encourage patients to take an active part in the exchange of information about their choices, preferences, experiences and outcomes. Patients should be encouraged to ask questions and challenge assumptions; they should be encouraged to share their experiences of using medicines.
- Likewise, eliciting patients' experiences should be recognized as a vital skill and a significant element in the creation of greater knowledge for better medical practice.
- The role of medicines safety activities should be to support health professionals in informing patients about

their drug treatment options and their comparative benefits and harms, in an effort to promote patient involvement and informed, joint decision making.

2.2 The Realization of Safe and Appropriate Use of Medicines

- Appropriate and beneficial use of medicines, prevention of harm, and optimizing patients' quality of life should be priorities that are fully integrated into the planning and operation of every aspect of healthcare systems so as to improve treatment outcomes and reduce costs.
- A single and independent contact point (a toll-free phone line or a mobile application [app], for example) is required to provide easy, open lines of communication for patients to report their concerns, problems and experiences associated with using medicinal therapy, and to support the development of accurate knowledge of patient experience.
- The traditional concept of *pharmacovigilance* should evolve to embrace the broader, more encompassing remit of *healthcare vigilance* and to collaborate in environmental vigilance.

2.3 Education and Communications

- Universities and other educational institutions should promote and teach the principles of therapeutic and medicinal safety surveillance during clinical care.
- Available mobile and other technologies and communication channels, including social media, should be employed to:
 - raise awareness of medical and medicinal safety and quality issues to promote discussion and discriminating choice;
 - communicate the benefits and risks of particular or comparative therapies;
 - facilitate the best possible outcomes for patients in accordance with terms that they have defined, as a source of unique information about people's experience of healthcare.

2.4 Methodologies and Tools

- Methodologies and tools used for the surveillance of medicinal products require further development to improve how they describe benefits and harms, and to enhance understanding and analysis of treatments that fail or cause harm. Such developments should include patient reports as a major source of intelligence.

- Collaboration with research institutes is necessary to develop new tools for medicinal product safety monitoring, preventing or minimizing harm, and to generate the knowledge that would allow the effects of drugs to be more accurately predicted.
- There is a need to apply the large and increasing evidence arising from organizational and behavioural sciences on human factors that need consideration in the avoidance of medication errors.
- Application of a systematic, integrated approach to the assessment of medicines should be implemented in order to reduce the risk of products with marginal benefits or eventual excess harm from being released onto the market.
- Such an integrated system, competently and ethically managed, would also reduce the risk of unscrupulous interventions in the supply and use of medicines.

2.5 Highest Standards for Ethics, Transparency and Responsiveness

- Full disclosure of any possible conflict of interest on the part of key stakeholders, or of any professional or financial involvement in any aspect of healthcare systems or medicines supply, should be mandatory.
- A high priority, in certain parts of the world, is to address and remedy the corruption that poisons the manufacture, approval, supply, distribution, procurement, sale, prescription and use of medicines, putting the health of communities and individuals at risk.
- Active good governance practices in civil society and by all other stakeholders that are involved in bringing medicinal products to the markets must aim towards ensuring that medicinal products are produced, logistically managed, packaged, promoted, and used with a priority of minimum individual patient risk and maximum benefit.
- With all possible precautions, where ethically possible, patient data should be openly used to increase knowledge for the specific benefit of patients.
- There should be full and timely disclosure of all product safety data, that is *all* the results of clinical trials, including those that do not demonstrate expected benefit and/or are not otherwise planned to be published.
- Public health policy and practice concerning the optimal and appropriate use of medicinal products should reflect the unique needs of individuals, as well as addressing the health of the population as a whole.

2.6 An Active Policy of Prevention

- Professionals in all aspects of healthcare must ensure that useful, tailored safety information for patients is available at the point of need, and that prescribers use it in ways that are most beneficial to the specific individual.
- Medicinal product surveillance should be an integral element of clinical research and practice; it should include monitoring of how drugs are used in practice; how they are prescribed, and how these actions affect treatment outcomes. Such knowledge should be used to guide development of safer medicinal products, safer use of those products, and other improved patient outcomes.
- Information should be made available on the clinical diagnosis and management of the adverse effects that patients may suffer from medicinal therapy, so that they may be rapidly recognized and treated.

The meeting took place in Erice, Sicily, 25–29 September 2016. It was organized by Professor Giampaolo Velo, Director of the International School of Pharmacology at the Ettore Majorana Foundation and Centre for Scientific Culture, Erice, Sicily, in collaboration with Uppsala Monitoring Centre, Sweden.

Participants, in alphabetical order, were as follows.

Participants were selected by the organizing committee on the basis of their known and broad interests in medicines safety and representing global views from academia, regulatory agencies, pharmaceutical industry, and clinical practice. There were omissions of important stakeholders—broader involvement of healthcare professionals and patients. We hope they will add to the dialogue that we have had over two decades in which we have tried to make improvements, but have yet to see the active involvement of those we serve. We hope this Report will provoke broader interest and commentary.

Raja Benkirane, Morocco; Ola Caster, Sweden; Patrick Caubel, USA; Wen-Wen Chen, Taiwan; Nabarun Dasgupta, USA; Bruce Donzanti, USA; Brian Edwards, UK; Ivor Ralph Edwards, Sweden; Mick Foy, UK; Bruce Hugman, Sweden; Philip Jenkins, Switzerland; Wiltshire Johnson, Sierra Leone; Agnes Kant, The Netherlands; Juan-Ramon Laporte, Spain; Roberto Leone, Italy; Ugo Moretti, Italy; Emmanuel O. Okoro, Nigeria; Shanthi Pal, Switzerland; Jayesh Pandit, Kenya; Concetta Rafaniello, Italy; Carla Djamila Reis, Cape Verde; Meredith Smith, USA; Rachida Soulaymani Bencheikh, Morocco; Liberata Sportiello, Italy; Shirley-Ann van der Spuy, UK; Birgitta Toreheim, Sweden; Marco Tuccori, Italy; Giampaolo Velo, Italy; Mauro Venegoni, Italy.

3 An Alternative Perspective from Prof. J-R Laporte

These views do not form part of the main consensus document, although they found support among some members of the group.

3.1 Testing Times Ahead for the Science of Pharmacovigilance

Adverse drug reactions (ADRs) are a major and growing cause of illness, disability and death. They are a leading (and neglected) cause of death, ahead of diabetes, chronic obstructive pulmonary diseases and traffic accidents. A major part of this burden is caused by type A ADRs: conditions that are known, foreseeable, related to pharmacological action, dose-related, and therefore preventable—primarily by careful, individualized prescribing of medicines.

3.1.1 Medical Practice Needs to Change

Harms caused by medicines largely depend on how medicines are prescribed and used within and outside healthcare systems. Drug utilization research has consistently shown that at least half of medical prescriptions are unnecessary, or for unnecessarily long periods, often at unnecessarily high doses.

3.1.2 Risk Management Plans are Ineffective

As shown in recent reviews, observational research has often given conflicting and contradictory results. On the other hand, company-driven risk management plans, on which the US FDA and the European Medicines Agency (EMA) rely for surveillance of drug safety, are generally too small and methodologically weak, and their results are secret, thus precluding their scientific evaluation and discussion.

3.1.3 Early Surveillance of Biotechnology Products (and Other Drugs Targeted at Small Patient Groups)

Newly launched medicines should be one of the main priorities in pharmacovigilance. The new industrial paradigm for medicines regulation will imply fewer, smaller, shorter, and less rigorous clinical trials for marketing approval. This underscores the need for a critical review of the aims and methods of pharmacovigilance practice.

3.2 Patient-Focused: Seamless Integration into Healthcare

3.2.1 Good Governance

The disease burden caused by medicines depends on the prescribing patterns of medicines. These in turn depend on the successive steps of the WHO medicines chain, describing the fate of drugs in a society—development, regulation, registration, marketing, prescribing, dispensing, and use. Therefore, it would be naive to rely only on pharmacovigilance activities to guarantee the safe use of medicines.

3.3 Highest Standards for Ethics, Transparency and Responsiveness

3.3.1 More Transparency is Needed in Research

There is publication bias inherent in all observational research that cannot be lessened or avoided by compulsory registration of studies. To examine potential databases for content in advance of registering any research protocol allows the possibility of biased selection of a dataset. In addition, as long as pharmaceutical companies are the main sponsors of observational research, an industry priority bias tends to direct research to issues of commercial, rather than medical, interest.

3.3.2 More Transparency Need in Regulation and About Regulators' Decisions

Transparency in all regulatory and decision-making procedures should be the norm. The collaboration of independent academic researchers and collaborating networks free of conflicts of interest is essential to these ends.

3.4 Education and Communications

3.4.1 Public Information

The healthcare system, rather than pharmaceutical companies, should be responsible for information on medicines and therapeutics, as well as continuous medical education, and developing prescribing support tools.

3.5 An Active Policy of Prevention

3.5.1 The Value of Regional Centres in Prevention

Regional centres of pharmacovigilance are being dismantled or weakened, but they should play an active role in the

promotion of the healthier use of medicines. Their primary objective should be to prevent ADRs, not only monitor and evaluate them.

They should be close to prescribers, offer prescribing support to them and provide feedback. They should monitor local drug utilization patterns and contribute efforts to correct inadequate or suboptimal patterns of use. They should collaborate in disseminating independent information on medicines and therapeutics and participate in independent continuous medical education activities, promoting patient reporting, and collaborating with local drug and therapeutics committees.

A note on the Erice process

Giampaolo Velo was the visionary instigator and sponsor of the original Erice drug safety communications meeting in 1996; he, along with Ugo Moretti and Roberto Leone, members of his team at the University of Verona, as well as Ralph Edwards and Bruce Hugman, Uppsala Monitoring Centre, have been behind the whole series of Erice meetings leading up to and including the current meeting that resulted in the Erice Report (2017).

Compliance with Ethical Standards

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Conflicts of Interest Ivor Ralph Edwards has no conflicts of interest that are directly relevant to the content of this article. Participants attended as individuals, although coming from different professional backgrounds, as stated in the text above. None of the participants had a direct financial interest in the meeting. Further information may be obtained from: info@who-umc.org.

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