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From the Seven Deadly Sins to a Risk Management Plan

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The evaluation of the safety profile of any drug in humans centres around the randomized, controlled, clinical trial; however such studies consider a relatively small sample size of patients who are observed for a short period of time. Moreover, the strict inclusion criteria, and the exclusion of special groups such as the elderly, children and pregnant women, represent additional limitations of these trials with respect to drug safety.

Once the drug is marketed, spontaneous reporting systems, along with post-approval safety studies, are put in place to obtain further data on its safety profile. Spontaneous reporting is theoretically valuable for identifying events with low frequency and 'signals' about potential safety issues that can be verified through specific surveys. Even if spontaneous reporting is sensitive, cheap and considers all marketed drugs, there might be problems and limitations because under-reporting and other biases, in many cases, are not manageable.

One of the limitations of spontaneous reporting is that doctors may fail to identify and report illnesses that they do not suspect to be induced by a drug. This realization led to the development of systems based upon 'event' reporting in which the doctor did not need to diagnose or suspect the true cause, but was merely asked to record events. An event was defined as "a particular untoward happening experienced by a patient, undesirable either generally or in the context of his disease."[1]

W.H.W. Inman, one of the fathers of modern pharmacoepidemiology, identified the following seven major reasons ('the seven deadly sins') affecting a spontaneous reporting system:[2]

- Ignorance – only severe adverse drug reactions (ADRs) need to be reported.
- Diffidence – fear of appearing ridiculous for reporting merely suspected ADRs.
- Lethargy – procrastination, lack of interest or time to find a report card, and indifference; the one case that an individual doctor might see could not contribute to medical knowledge.
- Ambition – to publish a personal case or a case series.
- Complacency – only safe drugs are allowed on the market.
- Guilt – for having caused an adverse effect.
- Fear – of possible litigation.

To overcome them, Professor Inman developed the Yellow Card scheme and Prescription Event Monitoring (PEM) in the UK. However, these reporting systems are not applicable in every country, depending mainly on the way in which the healthcare services are organized.

The Yellow Card scheme was started in 1964 as a result of the thalidomide tragedy and is run by the Medicines and Healthcare products Regulatory Agency (MHRA; formerly the Medicines Control Agency) and the Commission on Human Medicines (CHM; formerly the Committee on Safety of Medicines).

Information gathered from Yellow Card reports completed by patients and health professionals is continually assessed at the MHRA by a team of medicine safety experts made up of doctors, pharmacists and scientists who study the benefits and risks of medicines. If a new adverse effect is identified, information is carefully considered in the context of the overall adverse effect profile for the medicine, and how the adverse effect profile compares with other medicines used to treat the same condition. The MHRA takes action, whenever necessary, to ensure that medicines are used in a way that minimizes risk, while maximizing patient benefit.

In assessing the safety of medicines, the MHRA is advised by the CHM, which is the independent scientific advisory body on medicines safety for the UK Government. The CHM is made up of experts from a range of health professions and includes lay representatives.

PEM was established at the Drug Safety Research Unit of the University of Southampton in 1980 and Inman's early key objective was to recruit the first 10 000 patients who received a new drug of interest so that any adverse event that occurred in more than 1 in 1000 patients would be reliably identified.

PEM aims to complement the Yellow Card scheme and monitors drug safety by direct contact with the patient's own general practitioner (GP). All prescriptions that are written in the UK pass through the Prescription Pricing Authority (PPA), which is able to extract data for drugs of special interest and send these data to the Drug Safety Research Unit.

After a particular period (normally 6 months), the Drug Safety Research Unit sends special questionnaires (green forms) to GPs requesting information about any 'event' that was considered to be of sufficient importance to be reported by the patient.

Around 50–70% of GPs will respond to the questionnaire (green form), which is different from the Yellow Card. PEM is non-interventional, represents real-life clinical use and is relatively inexpensive to set up. If long-latency ADRs are suspected, a follow-up questionnaire can be sent and long-term safety data can be obtained.

Although the Yellow Card scheme and PEM represented a big step forward in drug safety surveillance, there are still limitations associated with their use. Any drug included in PEM must be prescribed by GPs on a scale sufficient to allow an adequate group of patients to be assembled within a reasonable time. Therefore, drugs that are mainly used in hospitals are not suitable for this kind of study. Furthermore, because the participation of GPs in PEM is voluntary, and without financial incentive, at least 30% of GPs choose not to complete the green forms. This creates a possible bias and the effect of these non-responders on the PEM study is still unknown. PEM has limited capability because it needs data from more than 10 000 questionnaires for each drug before the full analysis. This is highly labour intensive and is not a cost-effective process. Finally, because PEM takes a long time to gather information from the PPA and GPs, it is unable to respond to urgent drug safety issues.

While both schemes continue to play an important role in safety monitoring in the UK, a noteworthy step forward was made in the EU with the introduction, in 2005, of the risk management system concept and preparation of the 'so called' Risk Management Plans (RMPs). A risk management system[3] can be defined as "a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risk relating to medicinal products and the assessment of the effectiveness of those interventions."[4,5] These activities are organized as a well defined plan (the RMP) that should be submitted with the marketing authorization application for any product containing a new active substance, a similar biological medicinal product, a product for paediatric use or on a specific request from a European Competent Authority, when an unexpected new hazard is identified.

The RMP consists of two parts, the safety specification, which includes the pharmacovigilance plan, and the risk minimization plan. In the safety specification the safety profile of the product is described with data derived from clinical trials and postmarketing use. All the important identified risks, potential risks and/or missing information are discussed. The pharmacovigilance plan is focused on every identified and potential risk and can include routine pharmacovigilance activities but also specific studies and surveys.

The risk minimization part of the plan provides an evaluation of the need for risk minimization activities and the description of the measures required to manage and, if possible, minimize the identified and potential risks described in the safety specification. Sometimes routine measures are enough; the information included in the Summary of Product Characteristics and package leaflet adequately addresses any risks described in the plan. In other cases, there could be the need for additional risk minimization activities such as educational programmes or defining rules for the prescription and dispensing of a certain medicine (i.e. rules affecting the legal status of the medicine).

Last, but essential, is the good communication of data on risk for healthcare professionals and patients: "Such information should be ethically and effectively communicated in terms of both content and method."[6]

With similar goals in mind, the US Food and Drug Administration developed the Risk Minimization Action Plan (RiskMAP), which focused mainly on risk minimization activities. Currently, the draft guidance of the Risk Evaluation and Mitigation Strategy, which will be complementary and in some cases will replace the RiskMAP, is under evaluation.

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References

1. Finney DJ. The design and logic of a monitor of drug use. J Chronic Dis 1965; 18: 77-98
2. Inman WHW, editor. Monitoring of drug safety. 2nd ed. Lancaster: MTP Press Ltd., 1986: 37-8

3. European Commission. Guideline on pharmacovigilance for medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9A_2007-01.pdf [Accessed 2009 Nov 25]

4. Stather R. Risk management plans: one year on from the EMEA guidelines. Int J Pharm Med 2006; 20 (6) 385-7

5. Medicines and Healthcare products Regulatory Agency. Good pharmacovigilance practice guide. London: Pharmaceutical Press, 2009

6. Uppsala Monitoring Centre. Effective communications in pharmacovigilance: the Erice Declaration [online]. Available from URL: http://www.who-umc.org/DynPage.aspx?id=22690 [Accessed 2009 Oct 21]

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