CURRENT OPINION

Drug Saf 2010; 33 (10): 811-820
0114-5916/10/0010-0811/$49.95/0

How to Apply the Human Factor to Periodic Safety Update Reports

Brian David Edwards[1] and *Giovanni Furlan*[2]

1 NDA Regulatory Science Limited, Leatherhead, Surrey, UK
2 Bracco Imaging S.p.A, Global Drug Safety and Pharmacoepidemiology, Milan, Italy

Abstract

Society has been increasingly intolerant of excuses for systems breakdown in many areas of public life. This is hardly surprising given that there is overwhelming evidence behind why processes fail and mistakes are made, and so, based on this evidence, processes should be designed to mitigate risk. The main root cause of many process failures can be attributed to the human factor, which encompasses all those factors that can influence people and their behaviour. Based on experience from other safety-conscious industries, there is a major move to manage the human factor as part of delivery of safety culture in healthcare systems. Since pharmaceutical companies are healthcare companies, it makes sense that the principles underlying a pharmaceutical safety culture are aligned with those of the healthcare sector. A good place to start applying human factor management to a pharmaceutical safety process would be the complex process required to produce a good quality Periodic Safety Update Report (PSUR) on time and to an acceptable format. This can be achieved by a process aimed at building on an ongoing learning cycle through planning, observing if execution matches expectations and learning from mistakes and through the interdependent teamwork of PSUR contributors providing mutual support. Such a framework of teamwork and communication principles can be applied to the entire process for the preparation and submission of PSURs.

1. Periodic Safety Update Reports (PSURs) and the Bad Apple Theory

Periodic Safety Update Reports (PSURs), as described in section 6 of Volume 9A of *The Rules Governing Medicinal Products in the European Union*, are important pharmacovigilance documents, providing an opportunity for Marketing Authorization Holders (MAHs) to review at designated intervals the safety profile of products and ensure that Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs) are up to date.[1] They have never been intended to replace continuous surveillance, but to act as a quality control mechanism for the MAH to reflect on the benefit-risk profile of a product over a given period in the light of new and changing information. Volume 9A also states PSURs should include a succinct summary of information from the worldwide safety experience of a product. Therefore, they remain one of the main mechanisms by which regulatory authorities can be reassured that the MAH has a functioning pharmacovigilance system and the relevant

product has an acceptable balance of benefit and risk. However, the findings of regulatory inspections conducted by authorities such as the Medicines and Healthcare products Regulatory Agency (MHRA) or on behalf of the European Medicines Agency during the last 5 years indicate that PSURs remain major areas of noncompliance.[2,3] The European Commission is concerned that MAHs treat PSURs as only 'line listings of adverse reactions' so that they are not fulfilling their essential public health function as intended.[3]

We do not know actually why MAHs fail to produce adequate PSURs or why they do not fulfil regulators' expectations. It is possible that the pharmaceutical sector, as with the healthcare system in general,[4] has fallen into the 'blame trap' by adopting the 'bad apple theory'.[5] In essence, when something goes wrong, blame is attributed to those individuals involved in producing PSURs for failing to put enough effort into or paying enough attention in preparing this document. It is all too simple to think that the responsible individuals failed to recognize the importance of the safety data they were dealing with and so have mismanaged the analysis of emerging product risks. This explanation based on a blame culture is easy to adopt and does not allow understanding of the root causes of a process failure, shifting responsibility onto individuals and away from the system. For example, one possible explanation could be that inappropriately skilled individuals have been assigned tasks they are not able to fulfil. Following a reprimand or inspection finding, it is inadequate for the 'corrective action' to consist solely of retraining some individuals on the relevant standard operating procedures (SOPs) without having identified all the root causes. If root causes to poor quality or noncompliance are not addressed, it is likely the same problem may recur, resulting in another substandard PSUR for submission. So the pharmaceutical sector should have a systemic mental model, not one based on individual fault. When a process fails, systems-based thinking is required, of which individuals are only one of the components. Using a simple model based on a model devised by one of our mentors, we visualize processes as consisting of a 'solid' component based on SOPs, rules and regulations, and a 'fluid' component reflected in decision making, leadership, cooperation and situation awareness.[6] From the huge evidence base from other industries, we know root causes are often the 'human factor' in this fluid phase. The human factor refers to all those human factors that result in errors because of a combination of varying degrees of poor knowledge, misperception, misinterpretation and poor execution. Thus, safety is ultimately all about human performance. Unfortunately, training about how to analyse errors and fix systems rarely appears in pharmacovigilance training courses and so, not surprisingly, there is little expertise. If the human factor is not fully appreciated, the corrective actions can be based on making the solid phase more complex (such as by rewriting a SOP or introducing new regulations and guidelines), thereby reducing the boundaries and freedom within which people operate, which paradoxically can increase the risk of more errors furthering noncompliance and worsening 'safety'. It is surprising that there is so little interest within the pharmaceutical sector about extrapolating from other industries' safety measures.

Although we focus mainly on PSURs prepared according to the EU requirements, the issues we have highlighted and the team-based principles for overcoming them can be applied to other forms of aggregate safety reports, such as the Annual Safety Report, the Investigational New Drug report (IND) or the forthcoming Developmental Safety Update Report (DSUR).

2. A Suggested New Way to Safety

Rather than wait for a process failure, in our opinion it is more efficient to prospectively address the human factor by planning for failure and taking the following approaches, most of which fall within the discipline of project management, an essential functional skill for the preparation of multidisciplinary documents.

- Because humans make mistakes and errors, process vigilance is essential through quality control and effective teamworking.
- SOPs will never fully describe the process for each PSUR. In practice, once a SOP is

implemented, assume that it is already out of date. Managing a process then becomes a matter of defining how far it is removed from the reality of a process.

- Processes should be implemented assuming that they will fail at some point. The aim is to capture errors when they are small and mitigate their impact on the process.
- Human errors are certainly not inevitable and on their own are never the sole 'root cause' or an excuse for process failure. Errors are as much about the process or system as the individual, so resist the temptation to perform superficial root cause analysis.
- Errors provide useful information from which others can learn; therefore, information sharing and benchmarking are important.
- Teamworking is not a substitute for individual responsibility, but each individual looks out for compliance in each other (interdependence). Indeed, the team enhances responsibility of individuals as well as holding accountable those individuals who have regulatory accountability (Qualified Person Responsible for Pharmacovigilance; senior management).
- The unpredictability of the human factor can be reduced by means of tailored documentation – such as meeting agendas and quality control checklists – which can shift more of the fluid process risk into the structured solid phase of a process. This is with the understanding that such documentation is not prescriptive and may be wrong for a particular PSUR process. Flexibility has to be retained and documentation adapted for each version of a process.

3. Evidence-Based Teamworking Principles to Deliver Safety

In the increasingly complex pharmacovigilance environment it is essential to make the best possible use of the available resources, focusing on safe human performance.[7] Currently, the pharmaceutical sector has no agreed understanding of what constitutes 'safe human performance'. Thus, we have extrapolated from the wealth of evidence used by other industries and organizations where safety and compliance is of prime importance. In particular we have turned for inspiration to a nationwide programme to implement safety culture in the US healthcare system called TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety).[7] TeamSTEPPS focuses on specific skills supporting team performance principles, including training requirements, behavioural methods, human factors and cultural change designed to improve quality and patient safety. Teamwork principles,[6-8] as described in figure 1, are introduced to provide specific tools and strategies for improving communication and teamwork, reducing the

Situational awareness	To gain or maintain an accurate awareness or understanding of the situation in which the team is functioning with the ultimate aim of a shared mental model among team members
Mutual support	Back-up behaviour allows teams to become self-correcting, distribute workload effectively and regularly provide feedback. If an individual is overloaded or excessively multitasking, the team provides support and shares work where possible. Ultimately, each team member should feel that they are part of a safety net looking out for each other
Leadership	Leaders monitor the attitude and behaviours of team members (e.g. apathy, aggression, introversion, possible conflicts) to ensure that teams perform effectively and attain desired outcomes. They apply the concepts of briefing, huddle and debrief and how these skills can be developed by the team members. A good leader plans, communicates, delegates, encourages, coaches and insists on feedback. A good leader makes every team member part of the whole
Communication	The team need to focus on how to communicate effectively. This is particularly important when giving recommendations, providing handoffs and implementing checklists. Although the leader may seek confirmation that all understand, he/she assumes that miscommunication will have occurred and so is vigilant for misunderstanding, encouraging a diligent and questioning attitude from team members

Fig. 1. Teamworking principles.

chance of error and providing safer outcomes. Implementing such principles is one of the most effective ways to manage and learn from errors, cope with stress and the impact of fatigue, deal with fluctuations in workload and ultimately obtain good quality decision making. Even in small organizations, the preparation of a PSUR is a team effort and, in every team, the more decisions are shared, the more likely every team member will feel committed and will give his/her best when it comes to making things happen.[9]

Throughout the following sections we propose a framework based on teamwork and communication principles to be applied to the entire process for the preparation and submission of good quality PSURs.

4. Planning and Preparing the Needed PSURs

We believe that the most important time in managing a PSUR is the time spent in planning. An example of an agenda for a typical PSUR planning meeting (addressing not only the specific topics and critical points for that PSUR but also who is in charge of providing the relevant information and discussing it within the PSUR) is provided in figure 2. These meetings will be characterized by the presence of representatives from all the key departments contributing to the PSUR (such as clinical research, preclinical, regulatory). Since PSURs can vary greatly in complexity even within a company, a SOP can provide only an approximate framework within which to operate, and deviations from the expected execution may occur. Therefore, whenever the process is not running as expected, the team would expect a PSUR leader to organize an *ad hoc* meeting ('a huddle') to fix the problem early, so as to avoid the risk of full-blown non-compliance. Unexpected deviations can also be avoided by encouraging overlapping quality control so that although one person is responsible for assembling the detail in certain sections, others may check it with their section to ensure that it matches each other's understanding of the facts (Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A31 provides an example of PSUR quality control checks).

Since good leadership is of paramount importance in any team effort, the SOP should clarify who is the PSUR leader and who makes decisions, so as to avoid conflict or misunderstandings while the PSUR is being prepared. To be compliant with EU regulations, the Qualified Person Responsible for Pharmacovigilance in the European Economic Area (EEA QPPV) should ultimately be accountable, although the responsibility (but not the accountability) can be delegated to the PSUR team leader. The EEA QPPV sets standards and prioritizes for PSURs using risk-based criteria such as risk management commitments, any special PSUR requirements, the product's identified or potential risks, the therapeutic margin and patient exposure in the context of how product is authorized. The QPPV should ensure the PSUR leader is empowered to coordinate a cross-functional team by applying certain teamworking principles and concepts.[10] This leader allocates responsibility for a PSUR and judges what form of meeting will suffice, i.e. face to face, teleconferences or by e-mail.

Team resourcing may or may not be the responsibility of the PSUR team leader; this is often a senior management responsibility. In any case, the number and complexity of the PSURs that have to be prepared within a certain timeframe needs to be assessed to ensure there are enough people with the required skills available for preparing them.[11] This helps to avoid finding out too late that the required skills are not available, which may lead to people having to switch unexpectedly from one task to another, leading to stress and overwork. However, the team may often have to work with what they have, recognize each others strengths and weaknesses, and accommodate accordingly. After the planning meeting, the PSUR leader should think where mistakes are likely to occur during the preparation of that specific PSUR and whether there is anything else that can be done to detect these errors or mitigate their effects should the error occur.[12]

5. PSUR Training

PSUR preparation is a highly technical activity, requiring knowledge not only of the structure

Day/month/year:	
Lead writer and host:	
Participants:	
Representative for qualified person for pharmacovigilance:	
Absent:	
Schedule	
1) Data lock date:	2) First draft for review:
3) First draft comments due:	4) Final draft for review:
5) Final draft comments due:	6) Global head PV/QPPV review and regulatory approval:
7) Signature sheet due:	8) Report due to regulatory:
9) Differences between local SPC and CSI due date:	10) Health authority due date:
PSUR topics to discuss	
Selection of case narratives:	
Signal discussion:	
Operational needs (e.g. data cleaning, recoding, listedness, change in MedDRA® version):	
Changes to SPCs for safety reasons: which need to be discussed in the PSUR? Which sections do they impact on? Only on section 3?	
Relevant changes to CSI:	
Outstanding commitments from previous PSURs:	
Ad hoc safety reports (e.g. stand-alone benefit-risk assessment or assessments of a driving risk); both voluntary and based on regulatory requests:	
Regulatory feedback from previous PSURs:	
Specific local PSUR requirements (e.g. discrepancies with local label, national post-authorization commitments):	
Risk management plans. Topics that need to be discussed within the PSUR:	
Investigator's brochure and developmental safety update report: are the safety topics in these documents consistent with those in the PSUR?	
Non-clinical studies potentially yielding relevant safety information (e.g. toxicology, carcinogenicity, primary or secondary pharmacology) planned, ongoing or for which a study report has been prepared:	
Epidemiology studies. Which are ongoing? Interim and final results:	
Clinical studies planned, ongoing or for which a study report has been prepared:	
Safety information/issues arising from studies (observational or clinical trials):	
Comments from QPPV or Deputy QPPV:	
Additional licence partners reviewers:[1]	
Holiday plans:	

Fig. 2. Example of planning meeting minutes. **1** Applicable when a licence partner contributes to the preparation of the Periodic Safety Update Report (PSUR), maybe by writing its own standalone section. **CSI** = Core Safety Information; **MedDRA®** = Medical Dictionary for Regulatory Activities; **PV** = pharmacovigilance; **QPPV** = Qualified Person Responsible for Pharmacovigilance; **SPC** = Summary of Product Characteristics.

of this document and of the information needed to compile it, but also of a variety of different fields such as pharmacology, pharmacokinetics, the risks and benefits associated with the use of the drug, the pathology for which the drug is taken and the co-morbidities of that pathology.[13]

A different level of training and understanding of the process is required according to the role each person has in the preparation of the PSUR: the person from the sales department providing the sales data needed for calculating patient exposure needs different training from the person performing

benefit-risk evaluation. However, everyone needs to understand the impact their contribution has on the overall process. Training assessment methods should verify that trainees can locate key information, they understand it and they know how to apply it.[14] For example, if the PSUR procedure states the preclinical department provides the results of 'studies' to the drug safety department, does this mean the preclinical department really knows which kind of studies are needed? Applying human factor thinking to operational sensitivity means a PSUR team leader may assume that a new preclinical representative on the team will not understand what safety information is important and so will communicate expectations clearly for a particular PSUR and follow through on whether this has been understood. Furthermore, since the level of experience of each team member may vary, some individuals will inevitably require additional training and closer monitoring than others.

6. Breaking the Dominance of the Standard Operating Procedure (SOP): SOPs do not Equal the Process

SOPs are important for describing roles and responsibilities for different individuals in a process. Ideally, they should be written by the people who actually do the job as they are the ones who best understand the nature of the work.[15] Each SOP does not reflect the detail of the way in which people work and so may not reflect the reality of a process in constant evolution each time it is implemented. However, if a company is not careful, SOPs can take on a life of their own and become the 'process' themselves rather than just a component of the process. We advise companies not to adopt the approach of 'SOP written, process sorted'. Furthermore, if the PSUR SOP is enforced by management, this will crush innovation and stifle people's sense of responsibility and team membership. More of them risk becoming mere 'passengers' and maintaining a 'silo' attitude with little motivation towards mutual oversight.[16] This can happen because different departments contribute to a PSUR and so the focus inevitably drifts towards individual contributions rather than the PSUR as a whole.

SOPs are meant to facilitate people's work by guiding who does what. Too much complexity trying to cover every scenario increases the risk of misunderstanding and non-compliance.[17] If necessary, different SOPs could be issued for PSURs prepared according to the route of authorization (e.g. a drug nationally authorized may well have a different process compared with a centrally authorized product) or complexity.

7. The Importance of a Blame-Free Culture to Deliver PSUR Compliance

Teamworking does not absolve anyone of their contribution to the PSUR or the QPPV and MAH management of their accountability for the entire process. The team performs a two-way function, holding management accountable while holding all team members responsible. Responsibility should not be an imposed burden because every mistake will be blamed and the culprit will be punished. A blame environment will only lead people to hide mistakes and to hide themselves behind rules and procedures rather than cooperating. Blame should be reserved for deliberate and egregious errors or for persistent failures to perform a task as required despite repeated training and explanations.[18]

A blame-free approach benefits management as well as the team, and no individual will be automatically blamed for the financial constraints under which they have to work. In return, everyone should feel free to speak up and say what should be improved or changed to make the process more efficient. For example, if there is an organizational problem making it difficult to collect the information needed for preparing a PSUR from a department outside drug safety, the issue might need to be escalated to a senior level as the PSUR leader might not have the authority to resolve it. Within the team, everyone should be given a certain degree of freedom to be creative, so they feel proud to have contributed to the PSUR since the document is also the result of their contribution. Divergence of thought should not be stifled: if all the team members are completely aligned and everyone says the same things, there will be no stimulus for changing and improving.

There is always room for improvement, since the zero error rate is only a myth. Therefore, the PSUR leader should protect these individuals against the group pressure, so-called groupthink. No one, starting with the leader, should have an intimidatory or authoritative attitude and think they are always right.

8. Measuring the Performance

As with any process, the team should judge the quality of the process and end-product. Collating errors and learning from them is an essential part of continuous process improvement. To measure the performance, the correct key performance indicators should be used. It is typical that intermediate process timelines or whether the PSUR was submitted within 60 days are the most usual indicators of success, ignoring whether its medical and scientific contents might be of poor quality. Risks of future failure can arise from complacency following success. If the preparation of the PSUR was a success, it is important no one, especially the PSUR leader, tries to take the credit for the success. If this happens, the other team members will be resentful and will not be willing to collaborate the next time.[19] The credit for success should always be shared among all team members: the company and team culture should be just and fair. Likewise, if there is a process failure, then the team should take responsibility and diligently identify root causes. Another dangerous attitude is to consider the PSUR a bureaucratic quality assurance exercise of all the data contained in this document.[20]

9. The Importance of the Debriefing Meeting

After every PSUR, we advise that the PSUR team leader should actively think whether or not a debrief meeting is required. In the authors' experience, this decision is rarely taken. With a busy company it is understandable if the inclination is to resist this. However, this is false logic and the best way to learn on the job and continuously improve is to critically appraise the PSUR process. For convenience, the debrief from one PSUR could be integrated into the planning team, especially if the team is similar. Before having a debrief meeting, the leader should ask all team members for their opinion of the team's performance. A written questionnaire should be sent to all team members and, if preferred, anonymous answers should be collated if that makes everyone feel able to express their ideas freely. The questionnaire should ask questions regarding communication, situational awareness, error management, personality and behaviour. Feedback (if any) from the regulatory authority assessor should also be taken into account. Figure 3 provides an example of the questions that could be asked: according to the role

Did the PSUR adequately reflect all new safety information?
Do you feel you have contributed to the PSUR and your observations have been adequately taken into account?
Did it take you more time than forecast to provide the needed information? If not, why not? Was this due to misunderstanding?
Was the correct information provided to you?
Did your participation cause undue stress?
How many mistakes, errors or lapses did you find during the PSUR review?
Was there an improvement compared with the previous PSUR?
Did the PSUR take into account all the applicable risk management plans requirements?
Were the conclusions of the PSUR in line with its content?
If the PSUR revealed different safety information from that contained in the core safety information or in a local summary of product characteristics, were these updated?
Given the authority's feedback, if any, is there anything that should have been done differently?

Fig. 3. Periodic Safety Update Report (PSUR) preparation performance questionnaire.

each member has in the preparation, not all questions may be applicable to him/her.

10. PSUR Debrief Meeting

The aim of the PSUR debrief meeting is to help the team to focus on their performance, on what went wrong, so that errors become learning opportunities. This can be done after every PSUR or periodically, maybe before amending the PSUR SOPs/working practices. During the debrief meeting the team leader should speak as little as possible, leaving the others the opportunity to talk.[21] The focus should be on analysis of team performance, not on the individual person. Therefore, personal conflict and finger pointing should be avoided. Since there is a limited amount of learning each experience can produce, the role of the leader is to understand which are the critical points on which to focus (the results of the written questionnaire may help with this) and which are the key messages that need to be taken away. To achieve this, the leader should assert an observation or an interpretation of the events and then ask open questions about why something unintended has happened. To guide the discussion while interjecting as little content as possible, the leader should use active listening techniques including non-verbal cues (such as nodding, smiling, making eye contact) as well as verbalizations (e.g. short interjections such as 'yes', 'I see', echoing, reflecting). Finally, the leader should not be afraid of silence after having encouraged the team to analyse its performance, since this requires time: leaving a few seconds after having asked questions will permit a more in-depth analysis.

11. The External Environment

The evidence base for the human factor needs to be extrapolated to suit the environment external to a PSUR team, especially in times of economic crises and scant resources, since the drug safety and regulatory environment encompassing the industry and the authorities' expectations are all intertwined. In the current environment, the profit margins of many pharmaceutical industries are shrinking, while the regulatory requirements and bureaucracy costs are increasing.[22] Therefore, there are no additional resources for drug safety (which is often perceived by the industry as an added cost), while the number of documents a drug safety department has to produce and the expectations it has to fulfil are increasing. The same people working in drug safety have to prepare more and more documents in an increasingly stressful environment and within increasingly tight timelines. The risk is that communication between departments and training will be seen as an unaffordable luxury,[23] whereas the greater these resource pressures, the more important it is to manage the human factor. From the point of view of the regulatory authority, to help companies improve PSUR quality, we would ask that regulatory requests that do not pertain to that actual PSUR do not clutter up the process. Companies can much more efficiently address a regulatory authority's *ad hoc* request for safety information separately outside the PSUR process rather than adding to a PSUR's complexity with added requests. Above all, the overriding emphasis of regulatory assessment should be on the quality of the PSUR medical content and the scientific arguments underpinning the evaluation of benefit and risk. Should a PSUR be of such poor quality that it might represent non-compliance, we advise that the senior management of a company are contacted and advised directly to fix the company-wide process for PSURs. The PSUR represents the entire MAH, not just the drug safety department.

12. Conclusions

Although we know they are not perfect, PSURs are one of the few ways a regulatory authority has to assess whether the benefit-risk of product is acceptable over a given period. In addition, the PSUR is an important way of indirectly assessing the adequacy of the MAH's pharmacovigilance system, which protects both patients and the company. Furthermore, under freedom of information legislation, PSURs have to be released on request so we must write these documents assuming they will undergo public scrutiny or, regrettably, end up in court in a

liability suit. Therefore, it is in a company's interest for companies to invest in creating a good quality PSUR process.

The aim of the process described in this article is to build an ongoing learning cycle and apply teamworking principles. The PSUR preparation process starts from its planning. During the execution phase, the team members observe how the tasks are executed in practice and if expectations match reality. They should be free to call an *ad hoc* meeting if something needs to be discussed. During the PSUR preparation and once it has been submitted, the team members are asked to find out and analyse what is going/went wrong. The analysis of mistakes may reveal ideas to improve the process and planning for the next PSUR.

The points raised in this article need to be adapted to the needs of large and small organizations. However, the principles are universal and can be applied to any drug safety activity performed by a team, and, probably, to most tasks carried out by a team where a high level of knowledge and technical or organizational skills are required. The council of despair that humans will always make errors is ludicrous: other industries have set safety standards by which the human factor can be managed and process risk adequately mitigated. It is now time for all the pharmaceutical sector stakeholders (that is, both industries and regulatory authorities) to set their own safety standards by taking into account the human factor rather than leaving every organization to adopt its own standards.

Acknowledgements

No sources of funding were used to assist in the preparation of this article. Brian Edwards is an employee of NDA Regulatory Science Limited, who provide Periodic Safety Update Report (PSUR) services for the pharmaceutical sector. Giovanni Furlan used to be an employee of Bracco Imaging S.p.A and prepared PSURs for the company. Currently he is with PrimeVigilance who provide PSUR services for the pharmaceutical sector.

References

1. Volume 9A of the rules governing medicinal products in the European Union: guidelines on pharmacovigilance for medicinal products for human use [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf [Accessed 2010 Jul 3]
2. Periodic Safety Update Reports. In: MHRA, editor. Good pharmacovigilance practice guide. London: Pharmaceutical Press, 2009: 61-71
3. Commission of the European Communities. Proposal for a regulation of the European parliament and of the council. Amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Brussels, 10.12.2008. COM (2008) 664 final [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:EN:PDF [Accessed 2010 Jul 4]
4. Carthey J, Clarke J. The 'how to guide' for implementing human factors in healthcare. NHS Institute for Innovation and Improvement. Version 1 2009. [online]. Available from URL: http://www.institute.nhs.uk/images//documents/Safer Care/Human-Factors-How-to-Guide-v1.2.pdf [Accessed 2010 Jul 4]
5. Dekker S. The field guide to understanding human error. Aldershot: Ashgate, 2008
6. Seal C, Edwards B, Morrisroe J. Aviation crew resource management (CRM): a pharmacovigilance perspective. Pipeline 2008; 20: 7-9 [online]. Available from URL: http://human-factor.no/custom/plone/hjemmeside/about [Accessed 2010 Apr 17]
7. US Department of Health & Human Services, Agency for Healthcare Research and Quality. TeamSTEPPS®: national implementation [online]. Available from URL: http://teamstepps.ahrq.gov/ [Accessed 2010 Jul 4]
8. Flinn R, O'Connor P, Crichton M. Safety at the sharp end: a guide to non-technical skills. Farnham: Ashgate, 2009
9. Adair J. Not bosses but leaders. 3rd ed. London and Philadelphia (PA): Kogan Page, 2009
10. Flin R, Patey R. Training in non-technical skills to improve patient safety. BMJ 2009; 339: 985-6
11. Klepper MJ. The periodic safety update report as a pharmacovigilance tool. Drug Saf 2004; 27 (8): 569-78
12. Provonost PJ, Goeschel CA, Olsen KL, et al. Reducing heath care hazards: lessons from the commercial aviation safety team. Health Affairs 2009; 28 (3): 479-89
13. Verpillat P, Toumi M. Periodic update reports. In: Mann R, Andrews E, editors. Pharmacovigilance. 2nd ed. Chichester: Wiley, 2007: 63-74
14. Poska R. Human error and retraining: an interview with Kevin O'Donnell Ph.D., Irish Medicines Board. Global Regul Viewp 2009; 13 (4): 47-60
15. Weick KE, Sutcliffe KM. Managing the unexpected. San Francisco (CA): Jossey-Bass, 2001
16. Garello F, Provana R. FIAT people. Bologna: Fausto Lupetti Editore, 2008
17. Institute of Medicine. To err is human. Washington, DC: National Academy Press, 2000
18. Watcher RM, Provonost PJ. Balancing "no blame" with accountability in patient safety. N Engl J Med 2009; 361 (14): 1401-6
19. Michaelson SW. Sun Tzu for execution: how to use the art of war to get results. Avon (MA): Adam Business, 2007

20. Edwards IR. The ISoP Bengt-Erik Wiholm memorial lecture. Drug Saf 2009; 32 (3): 181-5
21. Rosen MA, Salas E, Deering S, et al. Team debrief in simulation-based training: an integrative framework, strategies, and tips [poster]. Presented at the 9th Annual International Meeting on Simulation in Healthcare; 2009 Jan 11-14; Lake Buena Vista (FL)
22. Furlan G. Human factors affecting PSUR preparation. Drug Saf 2009; 32 (10): 884-5
23. Institute of Medicine. The future of drug safety: promoting and protecting public health. Washington, DC: National Academy Press, 2007

Correspondence: Dr *Brian David Edwards*, NDA Regulatory Science Limited, Prime House, Challenge Court, Barnett Wood Lane, Leatherhead, Surrey KT22 7DE, UK.
E-mail: brian.edwards@ndareg.com